Pr Rebif® 44 mcg x 3.

Interferon beta-1a

22 mcg /0.5mL and 44 mcg /0.5mL liquid formulation for injection

THERAPEUTIC CLASSIFICATION:
Immunomodulator

INDICATIONS AND CLINICAL USE:
Multiple Sclerosis: Rebif® is indicated for the treatment of relapsing forms of multiple sclerosis, to reduce the number and severity of clinical exacerbations, slow the progression of physical disability, reduce the requirement for steroids, and reduce the number of hospitalizations for treatment of multiple sclerosis and reduction in T_1-Gd enhanced and T_2 (burden of disease) as seen on MRI. Relapsing forms of multiple sclerosis include the subgroups of MS in which patients still experience recurrent attacks of neurological dysfunction including traditional RRMS but also SPMS patients still experiencing relapses. Although Rebif® did not affect progression of disability in SPMS, the clinical trial has shown that secondary progressive MS patients who still experience relapses, had a statistically significant improvement on relapse rate and on MRI measures of disease activity as compared to patients on placebo. Rebif® has not yet been investigated in patients with primary progressive multiple sclerosis and should not be administered to such patients.

CONTRAINDICATIONS:
Rebif® (Interferon beta-1a) is contraindicated in patients with a known hypersensitivity to natural or recombinant interferon beta, albumin (human), or any other component of the formulation. Rebif® is contraindicated in pregnant patients (see WARNINGS).

WARNINGS:
Rebif® (Interferon beta-1a) should be used under the supervision of a physician. The first injection should be performed under the supervision of an appropriately qualified health care professional.
Relapsing forms of Multiple Sclerosis: Depression: Depression and suicidal ideation are known to occur in increased frequency in the multiple sclerosis population and in association with interferon use, including Rebif®. Some association of increased depression has been noted with interferon use. However, clinical trial data with Rebif® has not shown an increase in depression compared to placebo-treated patients. Patients treated with Rebif® should be advised to immediately report any symptoms of depression and/or suicidal ideation to their prescribing physician. Patients exhibiting depression should be monitored closely during therapy with Rebif® and treated appropriately. Cessation of therapy with Interferon beta-1a should be considered. **Hepatic Injury:** Isolated, life-threatening cases of acute hepatic failure have been reported with Rebif® therapy. Symptomatic hepatic dysfunction, primarily presenting as jaundice, has been reported as a rare complication of Rebif® use. Several possible mechanisms may explain the effect of Rebif® on the liver (including direct toxicity, indirect toxicity via release of cytokines and/or autoimmunity). Asymptomatic elevations of transaminases (particularly ALT) is common with interferon therapy (see ADVERSE REACTIONS). Dose reduction or discontinuation should be considered if ALT rises 5 times above the ULN. **Anaphylaxis:** Anaphylaxis has been reported as a rare complication of Rebif® use. Other allergic reactions have included skin rash, angioedema, and urticaria, and have ranged from mild to severe without a clear relationship to dose or duration of exposure. Several allergic reactions, some severe, have occurred after prolonged use. **Pregnancy and Lactation:** Rebif® should not be administered in case of pregnancy and lactation. There are no adequate and well-controlled studies of Rebif® in pregnant women. In the clinical trials there were 2 spontaneous abortions observed and 5 fetuses carried to term among 7 women in the Rebif® groups. There have been cases of spontaneous abortion in the post-marketing setting. In cynomolgous monkeys administered doses approximately 2 times the cumulative weekly human dose (based on either body weight or surface area), Rebif® treatment has been associated with significant increases in embryolethal or abortifacient effects either during the period of organogenesis (gestation day 21-89) or later in pregnancy. There were no fetal malformations or other evidence of teratogenesis noted in these studies; however, it is not known if teratogenic effects exist in humans. These effects are consistent with the abortifacient effects of other type I interferons. Patients should be advised about the abortifacient potential of Rebif®. **Fertile women receiving Rebif® should be advised to take adequate contraceptive measures.** It is not known if interferons alter the efficacy of oral contraceptives. Patients planning for pregnancy and those becoming pregnant should be informed of the potential hazards of interferons to the foetus and Rebif® should be discontinued (see CONTRAINDICATIONS and also PRECAUTIONS: Information to be provided to the patient). It is not known whether Rebif® is excreted in human milk. Because of the potential for serious adverse reactions in nursing infants, a decision should be made either to discontinue nursing or to discontinue Rebif® therapy. **Cardiac Disease:** Patients with cardiac disease, such as angina, congestive heart failure or arrhythmia, should be closely monitored for worsening of their clinical condition during initiation and continued therapy with Rebif®. Symptoms of the flu-like syndrome associated with Rebif® may prove stressful to patients with cardiac conditions.

PRECAUTIONS:
General: Patients should be informed of the most common adverse reactions associated with interferon beta administration, including symptoms of the flu-like syndrome (see ADVERSE REACTIONS). These symptoms tend to be most prominent at the initiation of therapy and decrease in frequency and severity with continued treatment. Caution should be exercised when administering Rebif® (Interferon beta-1a) to patients with pre-existing seizures disorder. For patients without a pre-existing seizure disorder who develop seizures during therapy, an etiologic basis should be established and appropriate anti-convulsant therapy instituted prior to continuing treatment with Rebif®. The effect of Rebif® administration on the medical management of patients with seizure disorder is unknown. Serum neutralising antibodies against Rebif® may develop. The precise incidence and clinical significance of antibodies is as yet uncertain (see ADVERSE REACTIONS). **Pediatric use:** There is no controlled clinical experience with Rebif® in children under 16 years of age with multiple sclerosis and therefore Rebif® should not be used in this population. **Patients with Special Diseases and Conditions:** Caution should be used and close monitoring considered when administering Rebif® to patients with severe renal failure, patients with severe myelosuppression, and patients with cardiac disease (see WARNINGS). **Drug Interaction:** No formal drug interaction studies have been conducted with Rebif® in humans. Interferons have been reported to reduce the activity of hepatic cytochrome p_{450}-dependent enzymes in humans and animals. Caution should be exercised when administering Rebif® in combination with medicinal products that have a narrow therapeutic index and are largely dependent on the hepatic cytochrome p_{450} system for clearance, e.g. antiepileptics and some classes of antidepressants. The interaction of Rebif® with corticosteroids or ACTH has not been studied systematically. Clinical studies indicate that multiple sclerosis patients can receive Rebif® and corticosteroids or ACTH during relapses. Rebif® should not be mixed with other drugs in the same syringe. **Laboratory Tests: Relapsing forms of multiple sclerosis:** Laboratory abnormalities are associated with the use of interferons. Therefore, in addition to those laboratory tests normally required for monitoring patients with multiple sclerosis, liver enzymes should be monitored at baseline, every month for the first 6 months and every 6 months thereafter (see WARNINGS). Complete and differential white blood cell counts, platelet counts and blood chemistries are also recommended during Rebif® therapy. These tests should be performed at baseline, months 1, 3 and 6, and every 6 months thereafter. Patients being treated with interferon beta may occasionally develop new or worsening thyroid abnormalities. Thyroid testing should be performed at baseline and every 6 months. In case of abnormal results or in patients with a past history of thyroid dysfunction, any necessary treatment and more frequent testing should be performed as clinically indicated (see ADVERSE REACTIONS).

ADVERSE REACTIONS:
Multiple Sclerosis: As with other interferon preparations, flu-like symptoms are not uncommon. The use of interferon beta may cause flu-like syndrome, asthenia, pyrexia, chills, arthralgia, myalgia, headache, and injection site reactions. Less frequent adverse reactions include cold sores, stuffy nose, light headedness, mucosal irritation, haematological disorders (leukopenia, lymphopenia, granulocytopenia), and alterations in liver function tests such as elevated AST and ALT. These effects are usually mild and reversible. Fever and flu-like symptoms can be treated with acetaminophen or ibuprofen. Depending on the severity and persistence of the side-effects, the dose may be lowered or temporarily interrupted, at the discretion of the physician. Most injection site reactions are mild to moderate. Allergic reactions, such as pruritus, rash, erythematous rash and maculo-papular rash may occur. Cases of skin ulceration/necrosis at the site of injection have been reported with long term treatment. Anaphylaxis has also been observed with the use of Rebif® (see WARNINGS). Serious adverse hepatic reactions such as hepatitis, with or without jaundice, have been rarely reported and isolated cases of acute hepatic failure have been reported (see WARNINGS). Occasional thyroid dysfunction, generally transient and mild, may occur during the first year of treatment, particularly in patients with pre-existing thyroiditis (see PRECAUTIONS: Laboratory Tests). The adverse events experienced during the first two years of the PRISMS study are listed below, by WHOART System Organ Class. The most common amongst the injection site reactions was in the form of mild erythema. The majority of the other injection site reactions were also mild in the 2 Rebif® groups. Necrosis was reported in 8 patients treated with Rebif®. Two of these patients were in the 66 mcg weekly and six in the 132 mcg weekly groups. All patients completed the planned treatment period, with only 1 requiring temporary dose reductions and another patient stopping treatment for 2 weeks. Those that required treatment, received antibiotics.

Proportion of Patients Enrolled in the PRISMS study Reporting Adverse Events During Years 1 and 2 of Treatment

Body System	Preferred term	Placebo	Rebif® 66 mcg weekly	Rebif® 132 mcg weekly
Application site disorders	Injection site inflammation (a)(b)	15.0%	65.6%	65.8%
	Injection site reaction (a)(b)	13.4%	31.2%	34.8%
	Injection site pain (b)	14.4%	20.1%	22.8%
Body as a whole - general disorders	Influenza-like symptoms	51.3%	56.1%	58.7%
	Fatigue	35.8%	32.8%	41.3%
	Fever (a)(b)	15.5%	24.9%	27.7%
	Leg pain	14.4%	10.1%	13.0%
	Rigors(b)(c)	5.3%	6.3%	13.0%
Centr. & periph. nervous system disorders	Headache	62.6%	64.6%	70.1%
	Dizziness	17.6%	14.3%	16.3%
	Paraesthesia	18.7%	19.6%	16.3%
	Hypoaesthesia	12.8%	12.2%	7.6%
Respiratory system disorders	Rhinitis	59.9%	52.4%	50.5%
	Upper Resp Tract Infection	32.6%	36.0%	29.3%
	Pharyngitis (b)	38.5%	34.9%	28.3%
	Coughing	21.4%	14.8%	19.0%
	Bronchitis	9.6%	10.6%	9.2%
Gastro-intestinal system disorders	Nausea	23.0%	24.9%	24.5%
	Abdominal pain	17.1%	22.2%	19.6%
	Diarrhoea	18.7%	17.5%	19.0%
	Vomiting	12.3%	12.7%	12.0%
Musculo-skeletal system disorders	Back pain	19.8%	23.3%	24.5%
	Myalgia	19.8%	24.9%	25.0%
	Arthralgia	17.1%	15.3%	19.0%
	Skeletal pain	10.2%	14.8%	9.8%
Psychiatric disorders	Depression	27.8%	20.6%	23.9%
	Insomnia	21.4%	19.6%	23.4%
White cell & res. disorders	Lymphopenia (a)(b)	11.2%	20.1%	28.8%
	Leucopenia (a)(b)(c)	3.7%	12.7%	22.3%
	Granulocytopenia (a)(b)	3.7%	11.6%	15.2%
	Lymphadenopathy	8.0%	11.1%	12.0%
Skin & appendages disorders	Pruritus	11.8%	9.0%	12.5%
Liver & biliary system disorders	ALT increased (a)(b)	4.3%	19.6%	27.2%
	AST increased (a)(b)(c)	3.7%	10.1%	17.4%
Urinary system disorders	Urinary tract infection	18.7%	18.0%	16.8%
Vision disorders	Vision abnormal	7.0%	7.4%	13.0%
Secondary terms	Fall	16.0%	16.9%	15.8%

(a) Significant difference between placebo and Rebif® 66 mcg weekly groups ($p \leq 0.05$)
(b) Significant difference between placebo and Rebif® 132 mcg weekly groups ($p \leq 0.05$)
(c) Significant difference between Rebif® 66 mcg and Rebif® 132 mcg weekly groups ($p \leq 0.05$)

In addition to the above listed adverse events, the following events have been experienced less frequently, in one or both of the relapsing-remitting multiple sclerosis studies: asthenia, fluid retention, anorexia, gastroenteritis, heartburn, paradentium affections, dental abcess or extraction, stomatitis, glossitis, sleepiness, anxiety, irritability, confusion, lymphadenopathy, weight gain, bone fracture, dyspnoea, cold sores, fissure at the angle of the mouth, menstrual disorders, cystitis, vaginitis. After 2 years, the placebo patients were switched to Rebif®, and along with the patients for the Rebif® treatment groups, they were treated for an additional two years. Listed below by WHOART System Organ Class, are the proportion of patients reporting the most common adverse events during years 3 and 4 of treatment. The results are similar to those obtained in the original phase of the study. The findings indicate that the incidence of interferon-related adverse events diminishes somewhat with continued exposure to the medication. Cases of necrosis were rare and not a cause of drop-out. For Rebif® 66 mcg weekly, there was one episode of skin necrosis per 92 years of exposure or per 14,100 injections. The comparable figures for Rebif® 132 mcg weekly are 1 episode of necrosis per 61 years of exposure or per 9,300 injections.

Proportion of Patients Reporting the Most Common Adverse Events During Years 3 and 4 of Treatment

Body system	Preferred term	Placebo/66 (n=85)	Placebo/132 (n=87)	Rebif® 66 mcg weekly (n=167)	Rebif® 132 mcg weekly (n=167)
Application site disorders	Injection site inflammation	65.9%	65.5%	56.9%	66.5%
	Injection site reaction	28.2%	37.9%	29.9%	31.7%
	Injection site pain	18.8%	21.8%	15.0%	13.8%
Body as a whole - general disorders	Influenza-like symptoms	42.4%	60.9%	50.3%	42.5%
	Fatigue	34.1%	36.8%	24.6%	27.5%
	Fever	14.1%	14.9%	15.6%	12.0%
	Leg pain	8.2%	12.6%	6.6%	7.8%
	Trauma	15.3%	5.7%	14.4%	11.4%
	Hypertonia	14.1%	11.5%	10.8%	9.6%
	Pain	4.7%	14.9%	4.2%	4.2%
Centr. & periph. nervous system disorders	Headache	44.7%	55.2%	46.7%	46.7%
	Dizziness	4.7%	11.5%	13.2%	12.6%
	Paraesthesia	15.3%	13.8%	10.2%	7.8%
	Hypoaesthesia	7.1%	13.8%	7.2%	9.0%
Respiratory system disorders	Rhinitis	38.8%	29.9%	39.5%	33.5%
	Upper Resp Tract Infection	18.8%	14.9%	22.8%	20.4%
	Pharyngitis	23.5%	12.6%	19.8%	15.0%
	Coughing	5.9%	11.5%	8.4%	13.8%
	Sinusitis	8.2%	11.5%	5.4%	10.2%
Gastro-intestinal system disorders	Nausea	12.9%	19.5%	10.8%	11.4%
	Abdominal pain	8.2%	16.1%	13.2%	10.8%
	Diarrhoea	5.9%	8.0%	12.0%	9.0%
	Constipation	14.1%	9.2%	6.0%	7.2%
Musculo-skeletal system disorders	Back pain	14.1%	20.7%	20.4%	22.2%
	Myalgia	21.2%	23.0%	15.6%	14.4%
	Arthralgia	16.5%	18.4%	12.6%	18.0%
	Muscle weakness	12.9%	17.2%	7.2%	9.6%
	Skeletal pain	8.2%	11.5%	7.2%	6.6%
Psychiatric disorders	Depression	29.4%	27.6%	23.4%	25.1%
	Insomnia	22.4%	21.8%	16.2%	21.6%
White cell & res. disorders	Lymphopenia	22.4%	23.0%	19.8%	25.7%
	Leucopenia	16.5%	14.9%	12.0%	13.8%
	Granulocytopenia	9.4%	10.3%	7.8%	12.0%
	Lymphadenopathy	2.4%	14.9%	8.4%	10.2%
Liver & biliary system disorders	ALT increased	11.8%	14.9%	13.8%	12.6%
Urinary system disorders	Urinary tract infection	8.2%	14.9%	16.2%	13.8%

Asymptomatic laboratory abnormalities were reported frequently with interferon dosing over the 4 years. Of the abnormalities noted, the cytopenias and abnormalities of liver function showed dose-related differences. Lymphopenia occurred in 35% of high-dose patients and 27% of low-dose patients. Thrombocytopenia was seen in 2.6% of patients on low-dose, and 8.2% of patients on high dose. Differences in the frequency of abnormal liver enzymes were seen which included elevated ALT (24% for low dose vs. 30% for high dose, p=0.07) and elevated AST (11% vs. 20%, p=0.03). Severe elevations are uncommon and not different between dose groups. These data suggest that there is only minimal evidence of significant dose-dependent lab abnormalities with interferon therapy in MS patients. After 4 years of therapy, 23.7% of the low dose and 14.3% of the high-dose patients had developed persistent neutralising antibodies (p=0.024, 44 mcg vs. 22 mcg), the vast majority of which (91%) developed within 24 months. The lower incidence in the high dose group may be due to the phenomenon of high-zone tolerance. While continuing interferon treatment, 20.0% of low-dose Nab+ patients reverted, while 25.7% of high-dose Nab+ patients reverted. The neutralising antibodies were associated with reduced clinical efficacy during years 3 and 4 and reduced MRI efficacy over 4 years. The table below presents adverse events that were reported in at least 10% of the patients in any treatment group of the SPECTRIMS study; the AEs are listed by WHOART System Organ Class and preferred term (sorted by preferred term in order of frequency). The most frequently reported adverse event was injection site inflammation, which occurred in 67% of both treated groups compared to 16% for placebo. Lower frequencies of the closely associated but more symptomatic injection site reactions were reported in 3 to 4 times as many treated patients as placebo patients. Injection site necrosis was seen in 3.3% and 8.8% of patients in the 22 mcg and 44 mcg groups respectively, but almost always as a single event per patient. The rate of necrosis was 1/3800 injections for high-dose and 1/9600 for low-dose therapy. Liver function abnormalities were also reported 3 to 4 times more commonly with active therapy. The haematopoietic system was also affected, with increased reports of leucopenia, granulocytopenia and lymphopenia associated with active therapy and most prominently with the higher dose. These haematopoietic abnormalities are expected side-effects of interferon therapy. Increased reports of anaemia and thrombocytopenia were noted with treatment, but these events occurred in less than 10% of patients.

Adverse Events Experienced by Patients Enrolled in the SPECTRIMS Study

Body System	Preferred term	Placebo	Rebif® 66 mcg weekly	Rebif® 132 mcg weekly
Application site disorders	Injection site inflammation (a)(b)	15.6%	66.5%	67.2%
	Injection site reaction (a)(b)(c)	7.8%	21.1%	31.9%
	Injection site pain	18.0%	17.2%	22.5%
	Injection site bruising (a)	16.1%	8.1%	9.8%
Body as a whole - general disorders	Influenza-like symptoms	52.2%	50.7%	49.5%
	Headache (c)	56.6%	52.2%	63.2%
	Fatigue (b)(c)	32.2%	33.0%	43.1%
	Fever (c)	11.7%	14.4%	19.1%
	Leg pain	9.3%	11.5%	12.3%
	Asthenia (c)	9.8%	5.7%	12.3%
Centr. & periph. nervous system disorders	Hypertonia	26.8%	24.4%	30.4%
	Dizziness	18.0%	16.3%	17.2%
	Paraesthesia	13.2%	8.1%	9.3%
	Hypoaesthesia	9.3%	10.0%	8.3%
Respiratory system disorders	Rhinitis	41.5%	38.3%	33.3%
	Upper Resp Tract Infection	33.2%	31.1%	26.0%
	Pharyngitis	20.0%	19.6%	17.2%
Gastro-intestinal system disorders	Nausea (b)	26.3%	23.9%	17.6%
	Abdominal pain	18.0%	14.8%	15.2%
	Diarrhoea	15.6%	18.7%	13.7%
	Constipation	19.0%	14.8%	13.2%
Musculo-skeletal system disorders	Myalgia	23.9%	24.9%	27.9%
	Arthralgia	25.4%	24.4%	23.0%
	Back pain	22.4%	21.5%	22.1%
	Muscle weakness	18.0%	17.2%	16.7%
Psychiatric disorders	Depression	28.8%	32.1%	34.8%
	Insomnia	22.0%	20.6%	23.5%
White cell & res. disorders	Lymphopenia (b)	15.1%	21.5%	26.0%
	Leucopenia (a)(b)(c)	4.9%	11.0%	21.1%
	Granulocytopenia (a)(b)	2.0%	9.1%	13.2%
Liver & biliary system disorders	ALT increased (a)(b)	7.3%	21.1%	23.0%
	AST increased (a)(b)	3.4%	11.5%	13.2%
Urinary system disorders	Urinary tract infection	26.3%	34.4%	27.0%
	Cystitis	12.7%	17.2%	10.8%
Vision disorders	Vision abnormal (a)(b)	11.7%	10.5%	4.9%
Secondary terms	Traumas Nos	28.3%	24.9%	23.0%

(a) Significant difference between placebo and Rebif® 66 mcg weekly groups (p=0.05)
(b) Significant difference between placebo and Rebif® 132 mcg weekly groups (p=0.05)
(c) Significant difference between Rebif® 66 mcg and Rebif® 132 mcg weekly groups (p=0.05)

The data indicate that Rebif® is safe when administered chronically even at high dose. Furthermore, studies with Rebif® have included patients with disability ranging from none to severe, age ranging from 18 to 55 at study start and in the forms of MS (SPMS, RRMS) that comprise over 80% of all MS patients. In the ETOMS study adverse events were reported more frequently in patients assigned Rebif® than in those assigned placebo. These events included injection-site inflammation (60% vs. 12%), fever (28% vs. 12%), myalgia (17% vs. 9%) and chills (11% vs. 5%). Serious adverse events were reported in five patients in the placebo group and six in the Interferon beta-1a group.

DOSAGE AND ADMINISTRATION:

Relapsing Forms of Multiple Sclerosis: Before initiating a patient on Rebif® therapy, please review completely the CONTRAINDICATIONS section of this Product Monograph. The recommended dose is 44 mcg given 3 times per week by subcutaneous injection. The dose can be reduced to 22 mcg tiw if the patient is not able to tolerate the higher dose. Treatment should be initiated under supervision of a physician experienced in the treatment of the disease. When first starting treatment with Rebif®, in order to allow tachyphylaxis to develop thus reducing adverse events, it is recommended that 20% of the total dose be administered during the initial 2 weeks of therapy, 50% of total dose be administered in weeks 3 and 4, and the full dose from the fifth week onwards. Please also review the WARNINGS and PRECAUTIONS sections and ensure appropriate monitoring of patients with depression, hepatic dysfunction, a history of seizures, cardiac disease, renal dysfunction, thyroid dysfunction, myelosuppression, and female patients of child-bearing potential. Patients should be advised of Rebif®'s side-effects and instructed on the use of aseptic technique when administering Rebif®. The Rebif® Patient Leaflet should be carefully reviewed with all patients, and patients should be educated on self-care and advised to keep the Leaflet for continued reference during Rebif® therapy. At the present time, it is not known for how long patients should be treated. Safety and efficacy with Rebif® have been demonstrated following 4 years of treatment. Therefore, it is recommended that patients should be evaluated after 4 years of treatment with Rebif® and a decision for longer-term treatment be made on an individual basis by the treating physician.

Preparation of Solution: Liquid formulation: The liquid formulation in a pre-filled syringe is ready for use. These syringes are graduated to facilitate therapy initiation. The pre-filled syringes contain 22 mcg and 44 mcg of Rebif® respectively. The pre-filled syringes are ready for subcutaneous use only.

STABILITY AND STORAGE RECOMMENDATIONS: Liquid formulation: Refer to the date indicated on the labels for the expiry date. Rebif® liquid in a pre-filled syringe should be stored at 2-8°C. Rebif® syringes may be stored for a limited period at room temperature (up to 25°C), but not more than 1 month. Do not freeze.

AVAILABILITY OF DOSAGE FORM:

Rebif® is available as a liquid formulation, in pre-filled syringes. Two package strengths are available: 22 mcg /0.5mL and 44 mcg /0.5mL. The pre-filled syringes are supplied as single units, 3-packs and 12-packs. The pre-filled syringes are ready for subcutaneous use only.

The route of administration for Relapsing forms of Multiple Sclerosis is subcutaneous.

The Product Monograph is available upon request.

Serono Canada Inc., Oakville, Ontario, Canada L6M 2G2

If you have any questions, call:
The Multiple Support Program at 1-888-MS-REBIF® (1-888-677-3243)

References:

1. Rebif® product monograph. Serono Canada. November 2003
2. The PRISMS Study Group and University of British Columbia MS/MRI Analysis Group. PRISMS 4: long-term efficacy of interferon-beta-1a in relapsing MS. *Neurology* 2001; 56: 1628-1636.

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See IFC

IMITREX DF™
SUMATRIPTAN SUCCINATE

25mg, 50mg and 100 mg Tablet

IMITREX®

(sumatriptan succinate)

6 mg Subcutaneous Injection and Autoinjector

IMITREX®

(sumatriptan)

5 mg and 20 mg Nasal Spray

THERAPEUTIC CLASSIFICATION
Migraine Therapy

PHARMACOLOGIC CLASSIFICATION
5-HT_1 Receptor Agonist

Pharmacokinetics
Pharmacokinetic parameters following subcutaneous, oral or intranasal administration are shown in Table 1. Sumatriptan is rapidly absorbed after oral, subcutaneous and intranasal administration. The low oral and intranasal bioavailability is primarily due to metabolism (hepatic and presystemic) and partly due to incomplete absorption. The oral absorption of sumatriptan is not significantly affected either during migraine attacks or by food. Inter-patient and intra-patient variability was noted in most pharmacokinetic parameters assessed.

Table 1: Summary of Pharmacokinetic Parameters

Parameter	Subcutaneous	Oral	Intranasal
Bioavailability	96%	14%	16%
C_{max} (ng/mL)	6mg: 72 ng/mL	100mg: 50-60ng/mL 25mg: 18ng/mL	5mg: 4.7ng/mL 10mg: 8.5ng/mL 20mg: 14.4ng/mL
T_{max}	6mg: 15min	100mg: 0.5-5hr*	1-1.5hr
$T_{1/2}$	2hr (1.7-2.3hr)	2hr (1.9-2.2hr)	2hr (1.3-5.4hr)
Protein Binding	14-21%		
Volume of Distribution	170L		
Total Plasma Clearance	1160mL/min		
Renal Plasma Clearance	260mL/min		

* 70% to 80% of C_{max} values were attained within 30-45 minutes of dosing

In vitro studies with human microsomes suggest that sumatriptan is metabolized by monoamine oxidase (MAO), predominantly the A isoenzyme. In studies conducted in a limited number of patients, MAO inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure.
Non-renal clearance of sumatriptan accounts for about 80% of the total clearance. The major metabolite, the indole acetic acid analogue of sumatriptan is mainly excreted in the urine where it is present as a free acid (35%) and the glucuronide conjugate (11%). It has no known 5-HT_1 or 5- HT_2 activity. Minor metabolites have not been identified.
No differences have been observed between the pharmacokinetic parameters in healthy elderly volunteers compared with younger volunteers (less than 65 years old). Significant relief begins about 10-15 minutes following subcutaneous injection, 15 minutes following intranasal administration and 30 minutes following oral administration.

INDICATIONS AND CLINICAL USES
IMITREX DF™ (sumatriptan succinate) and IMITREX® (sumatriptan succinate/sumatriptan) is indicated for the acute treatment of migraine attacks with or without aura.
IMITREX DF™ and IMITREX® is not for use in the management of hemiplegic, basilar, or ophthalmoplegic migraine (see CONTRAINDICATIONS). Safety and efficacy have not been established for cluster headache which is present in an older, predominantly male population.

CONTRAINDICATIONS
IMITREX DF™ (sumatriptan succinate) and IMITREX® (sumatriptan succinate/sumatriptan) is contraindicated in patients with history, symptoms, or signs of ischemic cardiac, cerebrovascular, or peripheral vascular syndromes, valvular heart disease or cardiac arrhythmias (especially tachycardias). In addition, patients with other significant underlying cardiovascular diseases (e.g., atherosclerotic disease, congenital heart disease) should not receive IMITREX DF™ and IMITREX® . Ischemic cardiac syndromes include, but are not limited to, angina pectoris of any type (e.g., stable angina of effort and vasospastic forms of angina such as the Prinzmetal's variant), all forms of myocardial infarction, and silent myocardial ischemia. Cerebrovascular syndromes include, but are not limited to, strokes of any type as well as transient ischemic attacks (TIAs). Peripheral vascular disease includes, but is not limited to, ischemic bowel disease, or Raynaud's syndrome (see WARNINGS).
Because IMITREX DF™ and IMITREX® may increase blood pressure, it is contraindicated in patients with uncontrolled or severe hypertension.
Concurrent administration of MAO inhibitors or use within 2 weeks of discontinuation of MAO inhibitor therapy is contraindicated (see CLINICAL PHARMACOLOGY AND PRECAUTIONS: Drug Interactions).
Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because IMITREX DF™ and IMITREX® may also cause coronary vasospasm and these effects may be additive, the use of IMITREX DF™ and IMITREX® within 24 hours before or after treatment with other 5-HT_1 receptor agonists, or ergotamine-containing drugs or their derivatives (eg. dihydroergotamine, methysergide) is contraindicated.
IMITREX DF™ and IMITREX® should not be administered to patients with severe hepatic impairment.
IMITREX DF™ and IMITREX® is contraindicated in patients with hemiplegic, basilar, or ophthalmoplegic migraine.
IMITREX DF™ and IMITREX® is contraindicated in patients with hypersensitivity to sumatriptan or any of the ingredients of the formulations.
IMITREX® Injection should not be given intravenously because of its potential to cause coronary vasospasm.

WARNINGS
IMITREX DF™ (sumatriptan succinate) and IMITREX® (sumatriptan succinate/sumatriptan) should only be used where a clear diagnosis of migraine has been established.
***Risk of Myocardial Ischemia and/or Infarction and Other Adverse Cardiac Events:* IMITREX DF™ and IMITREX® has been associated with transient chest and/or neck pain and tightness which may resemble angina pectoris. In rare cases, the symptoms have been identified as being the likely result of coronary vasospasm or myocardial ischemia. Rare cases of serious coronary events or arrhythmia have occurred following use of IMITREX DF™ and IMITREX® . IMITREX DF™ and IMITREX® should not be given to patients who have documented ischemic or vasospastic coronary artery disease (CAD) (see CONTRAINDICATIONS). It is strongly recommended that IMITREX DF™ and IMITREX® not be given to patients in whom unrecognized CAD is predicted by the presence of risk factors (e.g., *hypertension, hypercholesterolemia, smoking, obesity, diabetes, strong* family history of CAD, female who is surgically or physiologically postmenopausal, or male who is over 40 years of age) unless a cardiovascular evaluation provides satisfactory clinical evidence that the patient is reasonably free of coronary artery and ischemic myocardial disease or other significant underlying cardiovascular disease. The sensitivity of cardiac diagnostic procedures to detect cardiovascular disease or predisposition to coronary artery vasospasm is unknown. If, during the cardiovascular evaluation, the patient's medical history or electrocardiographic investigations reveal findings indicative of, or consistent with, coronary artery vasospasm or myocardial ischemia, IMITREX DF™ and IMITREX® should not be administered (see CONTRAINDICATIONS).**
For patients with risk factors predictive of CAD, who are considered to have a satisfactory cardiovascular evaluation, the first dose of IMITREX DF™ and IMITREX® should be administered in the setting of a physician's office or similar medically staffed and equipped facility. Because cardiac ischemia can occur in the absence of clinical symptoms, consideration should be given to obtaining electrocardiograms in patients with risk factors during the interval immediately following IMITREX DF™ and IMITREX® administration on the first occasion of use. However, an absence of drug-induced cardiovascular effects on the occasion of the initial dose does not preclude the possibility of such effects occurring with subsequent administrations. Intermittent long term users of IMITREX DF™ and IMITREX® who have or acquire risk factors predictive of CAD, as described above, should receive periodic interval cardiovascular evaluations over the course of treatment. If symptoms consistent with angina occur after the use of IMITREX DF™ and IMITREX®, ECG evaluation should be carried out to look for ischemic changes.
The systematic approach described above is intended to reduce the likelihood that patients with unrecognized cardiovascular disease will be inadvertently exposed to IMITREX DF™ and IMITREX® .
Cardiac Events and Fatalities Associated with 5-HT_1 Agonists: IMITREX DF™ and IMITREX® can cause coronary artery vasospasm. Serious adverse cardiac events, including acute myocardial infarction, life threatening disturbances of cardiac rhythm, and death have been reported within a few hours following the administration of 5-HT_1 agonists. Considering the extent of use of 5-HT_1 agonists in patients with migraine, the incidence of these events is extremely low. The fact that some of these events have occurred in patients with no prior cardiac disease history and with documented absence of CAD, and the close proximity of the events to IMITREX DF™ and IMITREX® use support the conclusion that some of these cases were caused by the drug. In many cases, however, where there has been known underlying coronary artery disease, the relationship is uncertain.
Premarketing Experience With IMITREX DF™ and IMITREX® : Of 6348 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of oral IMITREX DF™ and IMITREX®, two experienced clinical adverse events shortly after receiving oral IMITREX DF™ and IMITREX® that may have reflected coronary vasospasm. Neither of these adverse events was associated with a serious clinical outcome.
Among the more than 1900 patients with migraine who participated in premarketing controlled clinical trials of subcutaneous IMITREX DF™ and IMITREX®, there were eight patients who sustained clinical events during or shortly after receiving IMITREX DF™ and IMITREX® that may have reflected coronary artery vasospasm. Six of these eight patients had ECG changes consistent with transient ischemia, but without accompanying clinical symptoms or signs. Of these eight patients, four had either findings suggestive of CAD or risk factors predictive of CAD prior to study enrollment.
Among approximately 4,000 patients with migraine who participated in premarketing controlled and uncontrolled clinical trials of IMITREX® nasal spray, one patient experienced an asymptomatic subendocardial infarction possibly subsequent to a coronary vasospastic event.
Postmarketing Experience With IMITREX DF™ and IMITREX® : Serious cardiovascular events, some resulting in death, have been reported in association with the use of IMITREX® Injection or IMITREX DF™ and IMITREX® Tablets. The uncontrolled nature of postmarketing surveillance, however, makes it impossible to determine definitively the proportion of the reported cases that were actually caused by IMITREX DF™ and IMITREX® or to reliably assess causation in individual cases. On clinical grounds, the longer the latency between the administration of IMITREX DF™ and IMITREX® and the onset of the clinical event, the less likely the association is to be causative. Accordingly, interest has focused on events beginning within 1 hour of the administration of IMITREX DF™ and IMITREX® .
Cardiac events that have been observed to have onset within 1 hour of IMITREX DF™ and IMITREX® administration include: coronary artery vasospasm, transient ischemia, myocardial infarction, ventricular tachycardia and ventricular fibrillation, cardiac arrest, and death.
Some of these events occurred in patients who had no findings of CAD and appear to represent consequences of coronary artery vasospasm. However, among reports from the USA of serious cardiac events occurring within 1 hour of IMITREX DF™ and IMITREX® administration, almost all of the patients had risk factors predictive of CAD and the presence of significant underlying CAD was established in most cases (see CONTRAINDICATIONS).
Cerebrovascular Events and Fatalities with 5-HT_1 Agonists: Cerebral hemorrhage, subarachnoid hemorrhage, stroke, and other cerebrovascular events have been reported in patients treated with oral or subcutaneous IMITREX DF™ and IMITREX®, and some have resulted in fatalities. The relationship of IMITREX DF™ and IMITREX® to these events is uncertain. In a number of cases, it appears possible that the cerebrovascular events were primary. IMITREX DF™ and IMITREX® having been administered in the incorrect belief that the symptoms experienced were a consequence of migraine when they were not. IMITREX DF™ and IMITREX® should not be administered if the headache being experienced is atypical for the patient. It should also be noted that patients with migraine may be at increased risk of certain cerebrovascular events (e.g., stroke, hemorrhage, TIA). If a patient does not respond to the first dose, the opportunity should be taken to review the diagnosis before a second dose is given.
Special Cardiovascular Pharmacology Studies: In subjects (n=10) with suspected coronary artery disease undergoing angiography, a 5-HT_1 agonist at a subcutaneous dose of 1.5mg produced an 8% increase in aortic blood pressure, an 18% increase in pulmonary artery blood pressure, and an 8% increase in systemic vascular resistance. In addition, mild chest pain or tightness was reported by four subjects. Clinically significant increases in blood pressure were experienced by three of the subjects (two of whom also had chest pain/discomfort). Diagnostic angiogram results revealed that 9 subjects had normal coronary arteries and 1 had insignificant coronary artery disease.
In an additional study with this same drug, migraine patients (n=35) free of cardiovascular disease were subjected to assessments of myocardial perfusion by positron emission tomography while receiving a subcutaneous 1.5mg dose in the absence of a migraine attack. Reduced coronary vasodilatory reserve (~10%), increase in coronary resistance (~20%), and decrease in hyperemic myocardial blood flow (~10%) were noted. The relevance of these finding to the use of the recommended oral doses of this 5-HT_1 agonist is not known.
Similar studies have not been done with IMITREX DF™ and IMITREX®. However, owing to the common pharmacodynamic actions of 5-HT_1 agonists, the possibility of cardiovascular effects of the nature described above should be considered for any agent of this pharmacological class.
Hypersensitivity: Rare hypersensitivity (anaphylaxis/anaphylactoid) reactions may occur in patients receiving 5-HT_1 agonists such as IMITREX DF™ and IMITREX®. Such reactions can be life threatening or fatal. In general, hypersensitivity reactions to drugs are more likely to occur in individuals with a history of sensitivity to multiple allergens (see CONTRAINDICATIONS). Owing to the possibility of cross-reactive hypersensitivity *reactions, IMITREX DF™ and IMITREX® should not be used in patients having a history* of hypersensitivity to chemically-related 5-HT_1 receptor agonists. There have been reports of patients with known hypersensitivity to sulphonamides exhibiting an allergic reaction following administration of IMITREX DF™ and IMITREX®. Reactions ranged from cutaneous hypersensitivity to anaphylaxis.
Other Vasospasm Related Events: 5-HT_1 agonists may cause vasospastic reactions other than coronary artery vasospasm. Extensive post-market experience has shown the use of IMITREX DF™ and IMITREX® to be associated with rare occurrences of peripheral vascular ischemia and colonic ischemia with abdominal pain and bloody diarrhea.
Increase in Blood Pressure: Significant elevation in blood pressure, including hypertensive crisis, has been reported on rare occasions in patients with and without a history of hypertension. IMITREX DF™ and IMITREX® is contraindicated in patients with uncontrolled or severe hypertension (see CONTRAINDICATIONS). In patients with controlled hypertension, IMITREX DF™ and IMITREX® should be administered with caution, as transient increases in blood pressure and peripheral vascular resistance have been observed in a small portion of patients.

PRECAUTIONS
Cluster Headache: There is insufficient information on the efficacy and safety of IMITREX DF™ (sumatriptan succinate) and IMITREX® (sumatriptan succinate/sumatriptan) in the treatment of cluster headache, which is present in an older, predominantly male population. The need for prolonged use and the demand for repeated medication in this condition renders the dosing information inapplicable for cluster headache.
Cardiovascular: Discomfort in the chest, neck, throat and jaw (including pain, pressure, heaviness and tightness) has been reported after administration of IMITREX DF™ and IMITREX®. Because 5-HT_1 agonists may cause coronary artery vasospasm, patients who experience signs or symptoms suggestive of angina following IMITREX DF™ and IMITREX® should be evaluated for the presence of CAD or a predisposition to variant angina before receiving additional doses, and should be monitored electrocardiographically if dosing is resumed and similar symptoms recur. Similarly, patients who experience other symptoms or signs suggestive of decreased arterial flow, such as ischemic bowel syndrome or Raynaud's syndrome following IMITREX DF™ and IMITREX® should be evaluated for atherosclerosis or predisposition to vasospasm (see CONTRAINDICATIONS AND WARNINGS).
Neurological Conditions: Care should be taken to exclude other potentially serious neurologic conditions before treating headache in patients not previously diagnosed with migraine headache or who experience a headache that is atypical for them. There have been rare reports where patients received 5-HT_1 agonists for severe headaches that were subsequently shown to have been secondary to an evolving neurologic lesion. For newly diagnosed patients or patients presenting with atypical symptoms, the diagnosis of migraine should be reconsidered if no response is seen after the first dose of IMITREX DF™ and IMITREX®.
Seizures: Caution should be observed if IMITREX DF™ and IMITREX® is to be used in patients with a history of epilepsy or structural brain lesions which lower the convulsion threshold.
Psychomotor Impairment: Patients should be cautioned that drowsiness may occur as a result of treatment with IMITREX DF™ and IMITREX®. They should be advised not to perform skilled tasks (e.g. driving or operating machinery) if drowsiness occurs.
Renal Impairment: The effects of renal impairment on the efficacy and safety of IMITREX DF™ and IMITREX® have not been evaluated. Therefore IMITREX DF™ and IMITREX® is not recommended in this patient population.
Hepatic Impairment: The effect of hepatic impairment on the efficacy and safety of IMITREX DF™ and IMITREX® has not been evaluated, however, the pharmacokinetic profile of sumatriptan in patients with moderate hepatic impairment shows that these patients, following an oral dose of 50mg, have much higher plasma sumatriptan concentrations than healthy subjects (Table 2). Therefore, an oral dose of 25 mg may be considered in patients with hepatic impairment.
Assessed by aminopyrine breath test (~0.2-0.4 scaling units)

Table 2: Pharmacokinetic Parameters After Oral Administration of IMITREX® 50 mg to Healthy Volunteers and Moderately Hepatically Impaired Patients

Parameter	Mean Ratio (hepatic impaired/healthy) n=8	90% CI	p-value
AUC_∞	181%	130 to 252%	0.009*
C_{max}	176%	129 to 240%	0.007*

* Statistically significant

The pharmacokinetic parameters of 6 mg subcutaneous sumatriptan do not differ statistically between normal volunteers and moderately hepatically impaired subjects. However, sumatriptan should not be administered to patients with severe hepatic impairment (see CONTRAINDICATIONS).
Drug Interactions: Single dose pharmacokinetic drug interaction studies have not shown evidence of interactions with propranolol, flunarizine, pizotifen or alcohol. Multiple dose interaction studies have not been performed. The pharmacokinetics of sumatriptan nasal spray were unaltered when preceded by a single clinical dose of the nasal decongestant xylometazoline (Otrivin™ *).
* Trademark Ciba Self Medication

Ergot-Containing Drugs: Ergot-containing drugs have been reported to cause prolonged vasospastic reactions. Because there is a theoretical basis for these effects being additive, ergot-containing or ergot-type medications (like dihydroergotamine or methysergide) are contraindicated within 24 hours of IMITREX DF™ and IMITREX® administration (see CONTRAINDICATIONS).
MAO Inhibitors: In studies conducted in a limited number of patients, MAO inhibitors reduce sumatriptan clearance, significantly increasing systemic exposure. Therefore, the use of IMITREX DF™ and IMITREX® in patients receiving MAO inhibitors is contraindicated (see CONTRAINDICATIONS, AND CLINICAL PHARMACOLOGY).
Other Serotonergic Drugs: Rare postmarketing reports describe patients with weakness, hyperreflexia, and incoordination following the combined use of a selective serotonin reuptake inhibitor (SSRI) and 5-HT_1 agonists. If concomitant treatment with IMITREX DF™/ IMITREX® and an SSRI (e.g., fluoxetine, fluvoxamine, paroxetine, sertraline), tricyclic antidepressant, or other drug with serotonergic activity is clinically warranted, appropriate observation of the patient for acute and long-term adverse events is advised.

Other 5-HT_1 agonists: The administration of IMITREX DF™ and IMITREX® with other 5-HT_1 agonists has not been evaluated in migraine patients. As an increased risk of coronary vasospasm is a theoretical possibility with co-administration of 5-HT_1 agonists, use of these drugs within 24 hours of each other is contraindicated.

Drug/Laboratory Test Interactions: IMITREX DF™ and IMITREX® are not known to interfere with commonly employed clinical laboratory tests.

Use in Elderly (>65 years): Experience of the use of IMITREX DF™ and IMITREX® in patients aged over 65 years is limited. Therefore the use of IMITREX DF™ and IMITREX® in patients over 65 years is not recommended.

Use in Children (<18 years): The safety and efficacy of IMITREX DF™ and IMITREX® in children has not been established and its use in this age group is not recommended.

Use in Pregnancy: Reproduction studies, performed in rats, have not revealed any evidence of impaired fertility, teratogenicity, or post-natal development due to IMITREX DF™ and IMITREX®. Reproduction studies, performed in rabbits by the oral route, have shown increased incidence of variations in cervico-thoracic blood vessel configuration in the foetuses. These effects were only seen at the highest dose tested, which affected weight gain in the dams, and at which blood levels were in excess of 50 times those seen in humans after therapeutic doses. A direct association with IMITREX DF™ and IMITREX® treatment is considered unlikely but cannot be excluded. Therefore, the use of IMITREX DF™ and IMITREX® is not recommended in pregnancy. In a rat fertility study, oral doses of IMITREX DF™ and IMITREX® resulting in plasma levels approximately 150 times those seen in humans after a 6 mg subcutaneous dose and approximately 200 times those seen in humans after a 100 mg oral dose were associated with a reduction in the success of insemination. This effect did not occur during a subcutaneous study where maximum plasma levels achieved approximately 100 times those in humans by the subcutaneous route and approximately 150 times those in humans by the oral route.

To monitor maternal-foetal outcomes of pregnant women exposed to sumatriptan, a Pregnancy Registry has been established. Physicians are encouraged to register patients by calling 1-800-336-2176.

Lactation: Sumatriptan is excreted in human breast milk. Therefore, caution is advised when administering IMITREX DF™ and IMITREX® to nursing women. Infant exposure can be minimised by avoiding breast feeding for 24 hours after treatment.

Binding to Melanin Containing Tissues: In rats treated with a single subcutaneous dose (0.5 mg/kg) or oral dose (2 mg/kg) of radiolabeled sumatriptan, the elimination half life of radioactivity from the eye was 15 and 23 days, respectively, suggesting that sumatriptan and/or its metabolites bind to the melanin of the eye. Because there could be an accumulation in melanin rich tissues over time, this raises the possibility that sumatriptan could cause toxicity in these tissues after extended use. However, no effects on the retina related to treatment with sumatriptan were noted in any of the oral or subcutaneous toxicity studies. Although no systematic monitoring of ophthalmologic function was undertaken in clinical trials, and no specific recommendations for ophthalmologic monitoring are offered, prescribers should be aware of the possibility of long term ophthalmologic effects.

Laboratory Tests: No specific laboratory tests are recommended for monitoring patients prior to and/or after treatment with IMITREX DF™ and IMITREX®.

ADVERSE REACTIONS

Serious cardiac events, including some that have been fatal, have occurred following the use of 5-HT_1 agonists. These events are extremely rare and most have been reported in patients with risk factors predictive of CAD. Events reported have included coronary artery vasospasm, transient myocardial ischemia, myocardial infarction, ventricular tachycardia, and ventricular fibrillation (see CONTRAINDICATIONS, WARNINGS, and PRECAUTIONS).

Experience in Controlled Clinical Trials with IMITREX DF™ and IMITREX®

Typical 5-HT_1 Agonist Adverse Reactions: As with other 5-HT_1 agonists, IMITREX DF™ (sumatriptan succinate) and IMITREX® (sumatriptan succinate/sumatriptan) has been associated with sensations of heaviness, pressure, tightness or pain which may be intense. These may occur in any part of the body including the chest, throat, neck, jaw and upper limb.

Acute Safety: In placebo-controlled migraine trials, 7,668 patients received at least one dose of IMITREX DF™ and IMITREX® (3095 oral, 1432 subcutaneous, 3141 intranasal). The following tables (Tables 3-5) list adverse events occurring in these trials at an incidence of 1% or more in any of the IMITREX DF™ and IMITREX® dose groups and that occurred at a higher incidence than in the placebo groups.

Table 3: Treatment-Emergent Adverse Events in Oral Placebo-Controlled Clinical Trials Reported by at Least 1% of Patients with Migraine

	Placebo	IMITREX® 25 mg	IMITREX® 50 mg	IMITREX® 100 mg
Number of Migraine Attacks Treated	1187	945	1889	14750
Symptoms of Potentially Cardiac Origin				
• Chest Sensations*	0.6%	2.3%	2.6%	3.2%
• Neck/Throat/Jaw Sensations*	1.4%	2.3%	3.5%	5.2%
• Upper Limb Sensations*	1.2%	1.4%	2.5%	3.6%
• Palpitations	0.6%	0.3%	1.0%	1.1%
Neurological				
• Head/Face Sensations*	1.3%	2.3%	2.5%	4.7%
• Dizziness	2.5%	3.1%	3.3%	6.2%
• Headache	3.3%	4.0%	2.2%	3.3%
• Vertigo	0.6%	1.1%	1.1%	1.0%
• Drowsiness	1.6%	1.1%	1.2%	2.1%
• Tremor	0.4%	0.9%	0.4%	1.1%
Gastrointestinal				
• Nausea	5.8%	2.8%	4.4%	11.0%
• Hyposalivation	1.2%	1.4%	1.1%	1.2%
• Vomiting	2.9%	4.3%	1.1%	4.4%
• Gastrointestinal Discomfort & Pain	1.4%	1.1%	0.8%	2.0%
• Abdominal Discomfort & Pain	0.3%	NR	0.4%	1.2%
• Diarrhea	0.9%	0.3%	0.6%	1.1%
Musculoskeletal				
• Musculoskeletal Pain	0.7%	2.3%	0.4%	1.4%
• Muscle Pain	0.3%	0.9%	0.1%	1.0%
• Muscle Atrophy Weakness & Tiredness	NR	0.6%	0.4%	1.4%
Ear, Nose & Throat				
• Infections	0.6%	0.6%	1.1%	1.4%
• Nasal Signs & Symptoms	0.7%	1.4%	0.8%	1.0%
• Throat & Tonsil Symptoms	0.6%	NR	0.4%	2.3%
Respiratory				
• Viral Infection	0.3%	1.1%	0.1%	1.0%
Non-Site Specific				
• Limb Sensations*	0.4%	1.1%	0.4%	1.5%
• Sensations* (body region unspecified)	4.5%	5.7%	8.0%	9.0%
• Malaise/Fatigue	5.1%	3.7%	2.6%	9.5%
• Sweating	0.4%	0.6%	0.6%	1.6%

* The term "sensations" encompasses adverse events described as pain & discomfort, pressure, heaviness, constriction, tightness, heat/burning sensation, paresthesia, numbness, tingling, and strange sensations.
** Includes patients receiving up to 3 doses of 100mg
NR = Not Reported

Table 4: Treatment-Emergent Adverse Events in Subcutaneous Placebo-Controlled Clinical Trials Reported by at Least 1% of Patients with Migraine

	Placebo	IMITREX® 6 mg
Number of Patients	615	1432
Number of Migraine Attacks Treated	742	2540
Symptoms of Potentially Cardiac Origin		
• Chest Sensations*	1.6%	5.7%
• Neck/Throat/Jaw Sensations*	1.3%	12.0%
• Upper Limb Sensations*	2.0%	6.8%
Neurological		
• Head/Face Sensations*	3.7%	16.6%
• Dizziness	3.7%	7.9%
• Headache	0.7%	3.4%
• Drowsiness	1.8%	2.9%
Gastrointestinal		
• Nausea	5.9%	9.4%
• Hyposalivation	2.8%	3.3%
Musculoskeletal		
• Muscle Atrophy Weakness & Tiredness	NR	1.7%
Ear / Nose and Throat		
• Throat & Tonsil Symptoms	0.3%	1.0%
Respiratory		
• Breathing Disorders	0.8%	1.3%
Non-Site Specific		
• Sensations* (body region unspecified)	15.9%	39.0%
• Injection Site Reactions	10.4%	24.7%
• Limb Sensations*	1.5%	6.0%
• Malaise/Fatigue	2.3%	4.7%
• Sweating	1.1%	1.7%
• Trunk Symptoms*	0.5%	1.4%

* The term "sensations" encompasses adverse events described as pain & discomfort, pressure, heaviness, constriction, tightness, heat/burning sensation, paresthesia, numbness, tingling, and strange sensations.
NR = Not Reported

Table 5: Treatment-Emergent Adverse Events in Intranasal Placebo-Controlled Clinical Trials Reported by at Least 1% of Patients with Migraine

	Placebo	IMITREX® 5 mg	IMITREX® 10 mg	IMITREX® 20 mg**
Number of Patients	741	496	1007	1638
Number of Migraine Attacks Treated	1047	933	1434	2070
Symptoms of Potentially Cardiac Origin				
• Chest Sensations*	0.3%	1.0%	0.7%	0.6%
• Neck/Throat/Jaw Sensations*	1.2%	0.6%	1.6%	2.3%
Neurological				
• Head/Face Sensations*	0.8%	1.4%	2.4%	2.4%
• Dizziness	1.2%	1.6%	1.5%	1.2%
• Headache	0.7%	1.4%	0.9%	0.8%
• Migraine	2.6%	3.2%	2.4%	1.8%
Gastrointestinal				
• Nausea	10.4%	14.3%	9.6%	8.3%
• Vomiting	7.6%	11.1%	9.6%	6.8%
Ear, Nose & Throat				
• Sensitivity to Noise	3.1%	4.4%	2.5%	1.5%
• Nasal Signs & Symptoms	1.3%	3.0%	1.6%	1.8%
• Infections	0.9%	1.8%	1.3%	0.5%
• Upper Respiratory Inflammation	0.5%	1.0%	0.6%	0.7%
• Throat & Tonsil Symptoms	0.8%	0.2%	1.0%	0.7%
Non-Site Specific				
• Sensations* (body region unspecified)	1.8%	2.4%	2.7%	2.4%
• Malaise/Fatigue	1.3%	1.8%	1.3%	0.8%
• Descriptions of odor or taste	1.8%	15.3%	20.2%	20.8%

* The term "sensations" encompasses adverse events described as pain & discomfort, pressure, heaviness, constriction, tightness, heat/burning sensation, paresthesia, numbness, tingling, and strange sensations.
** Includes patients receiving up to 3 doses of 20mg

IMITREX DF™ and IMITREX® is generally well tolerated. Most of the events were transient in nature and resolved within 45 minutes of subcutaneous administration and within 2 hours of oral or intranasal administration.

Of the 3630 patients treated with IMITREX® Nasal Spray in clinical trials, there was one report of a coronary vasospasm related to IMITREX® administration.

Minor disturbances of liver function tests have occasionally been observed with sumatriptan treatment. There is no evidence that clinically significant abnormalities occurred more frequently with sumatriptan than with placebo. Patients treated with IMITREX DF™ and IMITREX® rarely exhibit visual disorders like flickering and diplopia. Additionally cases of nystagmus, scotoma and reduced vision have been observed. Very rarely a transient loss of vision has been reported. However, visual disorders may also occur during a migraine attack itself.

DOSAGE AND ADMINISTRATION

General:

IMITREX DF™ (sumatriptan succinate) and IMITREX® (sumatriptan succinate/sumatriptan) is indicated for the acute treatment of migraine headache with or without aura. Sumatriptan should not be used prophylactically. Sumatriptan may be given orally, subcutaneously or as a nasal spray. The safety of treating an average of more than four headaches in a 30 day period has not been established.

In selecting the appropriate formulation for individual patients, consideration should be given to the patient's preference for formulation and the patient's requirement for rapid onset of relief. Significant relief begins about 10-15 minutes following subcutaneous injection, 15 minutes following intranasal administration and 30 minutes following oral administration.

In addition to relieving the pain of migraine, sumatriptan (all formulations) has also been shown to be effective in relieving associated symptoms of migraine (nausea, vomiting, phonophobia, photophobia). Sumatriptan is equally effective when administered at any stage of a migraine attack. Long term (12-24 months) clinical studies with maximum recommended doses of sumatriptan indicate that there is no evidence of the development of tachyphylaxis, or medication-induced (rebound) headache.

Tablets:

The minimal effective single adult dose of IMITREX DF™ Tablets is 25mg. The maximum recommended single dose is 100 mg.

The optimal dose is a single 50mg tablet. However, depending on individual patient's needs and response to treatment, some patients may require 100mg.

Clinical trials have shown that approximately 50 - 75% of patients have headache relief within two hours after oral dosing with 100mg, and that a further 15 - 25% have headache relief by 4 hours. Comparator studies have shown similar efficacy rates with the 50mg and 100mg tablets. There is evidence that doses of 50 and 100mg may provide greater effect than 25mg.

If the migraine headache returns, or if a patient has a partial response to the initial dose, the dose may be repeated after 2 hours. Not more than 200mg should be taken in any 24 hour period.

If a patient does not respond to the first dose of IMITREX DF™ Tablets, a second dose should not be taken for the same attack, as it is unlikely to be of clinical benefit. IMITREX DF™ and IMITREX® may be taken to treat subsequent migraine attacks.

The tablet should be swallowed whole with water, not crushed, chewed or split.

Hepatic Impairment

In patients with mild or moderate hepatic impairment, plasma sumatriptan concentrations up to two times those seen in healthy subjects have been observed. Therefore, a 25 mg dose (single tablet) may be considered in these patients (see PRECAUTIONS). Sumatriptan should not be administered to patients with severe hepatic impairment (see CONTRAINDICATIONS).

Injection

IMITREX® Injection should be injected subcutaneously (on the outside of the thigh or in the upper arm) using an autoinjector.

The recommended adult dose of sumatriptan is a single 6 mg subcutaneous injection.

Clinical trials have shown that approximately 70-72% of patients have headache relief within one hour after a single subcutaneous injection. This number increases to 82% by 2 hours.

If the migraine headache returns, or if a patient has a partial response to the initial dose, the dose may be repeated after 1 hour. Not more than 12 mg (two 6 mg injections) should be taken in any 24 hour period.

If a patient does not respond to the first dose of IMITREX® Injection, a second dose should not be taken for the same attack, as it is unlikely to be of clinical benefit. IMITREX® may be taken for subsequent attacks.

Administration during migraine aura prior to other symptoms occurring may not prevent the development of a headache.

Patients should be advised to read the patient instruction leaflet regarding the safe disposal of syringes and needles.

Nasal Spray

The minimal effective single adult dose of sumatriptan nasal spray is 5mg. The maximum recommended single dose is 20mg.

If the migraine headache returns, or if a patient has a partial response to the initial dose, the dose may be repeated after 2 hours. Not more than 40mg should be taken in any 24 hour period.

In clinical studies totalling 3693 patients, optimal rates of headache relief were seen with the 20mg dose. Single doses above 20mg should not be used due to limited safety data and lack of increased efficacy relative to the 20mg single dose. Within the range of 5-20 mg, an increase in dose was not associated with any significant increase in the incidence or severity of adverse events other than taste disturbance (See ADVERSE REACTIONS).

The nasal spray should be administered into one nostril **only**. The device is a ready to use single dose unit and **must not** be primed before administration. Patients should be advised to read the patient instruction leaflet regarding the use of the nasal spray device before administration.

COMPOSITION

IMITREX DF™ Tablets contain 100 mg, 50 mg or 25 mg sumatriptan (base) as the succinate salt. IMITREX DF™ Tablets also contain croscarmellose sodium, iron oxide red (100mg only), dibasic calcium phosphate anhydrous, sodium bicarbonate, magnesium stearate, methylhydroxypropyl cellulose, microcrystalline cellulose, titanium dioxide, and triacetin.

IMITREX® Injection contains 6 mg sumatriptan (base) as the succinate salt in an isotonic sodium chloride solution containing water for injection.

IMITREX® Nasal Spray contains 5 mg, or 20 mg of sumatriptan base (as the hemisulphate salt formed *in situ*) in an aqueous buffered solution containing anhydrous dibasic sodium phosphate, monobasic potassium phosphate, purified water, sodium hydroxide and sulphuric acid.

AVAILABILITY OF DOSAGE FORMS

IMITREX DF™ Tablets are available as pink 100mg, white 50mg, or white 25mg film-coated tablets in blister packs containing 6 tablets.

IMITREX® Injection (6mg; total volume = 0.5 mL) is available in prefilled syringes placed in a tamper-evident carrying/disposal case. Two pre-filled syringes plus an IMITREX STATdose Pen™ autoinjector are packed in an IMITREX STATdose System™ autoinjector kit. A refill pack is available containing 2 pre-filled syringes in a carton.

IMITREX® Injection is also available to physicians or hospitals in a single dose vial (6mg; total volume = 0.5 mL). There are 5 vials per carton.

IMITREX® Nasal Spray 5 mg and 20 mg are each supplied in boxes of 6 nasal spray devices (3 X 2 devices). Each unit dose spray supplies 5 and 20 mg, respectively.

Product Monograph available to physicians and pharmacists upon request.

Please contact GlaxoSmithKline Inc., 7333 Mississauga Road N., Mississauga, Ontario L5N 6L4.

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Date of preparation: January 17, 1992
Date of revision: May 07, 2004

References: 1. Walls C *et al.* Pharmacokinetic profile of a new form of sumatriptan tablets in healthy volunteers. *Current Medical Research and Opinion* 2004;20(6):803-809. **2.** Carpay J *et al.* Efficacy and tolerability of sumatriptan tablets in a fast-disintegrating, rapid-release formulation for the acute treatment of migraine: results of a multicenter, randomized, placebo-controlled study. *Clin Therapeutics* 2004;26(2):214-223. **3.** Product Monograph "IMITREX DF™/IMITREX® (sumatriptan succinate/sumatriptan) GlaxoSmithKline Inc. May 2004.

GlaxoSmithKline
GlaxoSmithKline
7333 Mississauga Road North
Mississauga, Ontario L5N 6L4

See IBC

NEW

Pr **Keppra®**

levetiracetam

CONNECTING EXCELLENT PROFILES IN EFFICACY AND TOLERABILITY

PRESCRIBING INFORMATION

Tablets of 250 mg, 500 mg, and 750 mg
Therapeutic classification: Antiepileptic

ACTIONS AND CLINICAL PHARMACOLOGY

Mechanism of Action

Levetiracetam is a drug of the pyrrolidine class chemically unrelated to existing antiepileptic drugs (AEDs). Levetiracetam exhibits anti-seizure and antiepileptogenic activity in several models of chronic epilepsy in both mice and rats, while being devoid of anticonvulsant activity in the classical screening models of acute seizures.

The mechanism of action of levetiracetam has not yet been fully established, however, it appears to be unlike that of the commonly used AEDs. *In vitro* studies show that levetiracetam, at concentrations of up to 10 μM did not result in significant ligand displacement at known receptor sites such as benzodiazepine, GABA (gamma-aminobutyric acid), glycine, NMDA (N-methyl-D-aspartate), re-uptake sites or second messenger systems. Furthermore, levetiracetam does not modulate neuronal voltage-gated sodium and T-type calcium currents and does not induce conventional facilitation of the GABAergic system.

Pharmacokinetics

Summary: Single- and multiple-dose pharmacokinetics of levetiracetam have included healthy volunteers, adult and pediatric patients with epilepsy, elderly subjects, and subjects with renal and hepatic impairment. Results of these studies indicate that levetiracetam is rapidly and almost completely absorbed after oral administration. The pharmacokinetic profile is linear with low intra- and inter-subject variability. There is no modification of the clearance after repeated administration. Food does not affect the extent of absorption of levetiracetam, although the rate is decreased. Levetiracetam is not protein-bound (< 10% bound) and its volume of distribution is close to the volume of intracellular and extracellular water. Sixty-six percent (66%) of the dose is renally excreted unchanged. The major metabolic pathway of levetiracetam (24% of the dose) is an enzymatic hydrolysis of the acetamide group. It is not liver cytochrome P450 dependent. The metabolites have no known pharmacodynamic activity and are renally excreted. Plasma half-life of levetiracetam across studies is 6-8 hours. Plasma half-life is increased in subjects with renal impairment, and in the elderly primarily due to impaired renal clearance.

Based on its pharmacokinetic characteristics, levetiracetam is unlikely to produce or to be subject to metabolic interactions.

The pharmacokinetic profile is comparable in healthy volunteers and in patients with epilepsy.

Due to its complete and linear absorption, plasma levels can be predicted from the oral dose of levetiracetam expressed as mg/kg bodyweight. Therefore, there is no need for plasma level monitoring of levetiracetam.

Human Pharmacology

Pharmacokinetics: The pharmacokinetics of levetiracetam have been characterized in single and multiple dose PK studies, with doses up to 5000 mg; these studies included healthy volunteers (n = 98), patients with epilepsy (n = 58 adult patients and n = 24 pediatric patients), elderly subjects (n = 16) and subjects with renal and hepatic impairment (n = 36 and 16, respectively).

Absorption and Distribution: Levetiracetam is rapidly and almost completely absorbed after oral administration. The oral bioavailability of levetiracetam tablets is 100%. Plasma peak concentrations (C_{max}) are achieved at 1.3 hours after dosing. The extent of absorption is independent of both dose and the presence of food, but the latter delays T_{max} by 1.5 hours and decreases C_{max} by 20%. The pharmacokinetics of levetiracetam are linear over the dose range of 500 – 5000 mg. Steady-state is achieved after two days of a twice daily administration schedule. Mean peak concentrations (C_{max}) are 31 and 43 μg/mL, respectively, following a single 1000 mg dose, and a repeated 1000 mg twice daily dose.

Neither levetiracetam nor its primary metabolite is significantly bound to plasma proteins (< 10%). The volume of distribution of levetiracetam is approximately 0.5 to 0.7 L/kg, a value that is close to the total body water volume. No tissue distribution data for humans are available.

Metabolism: Levetiracetam is not extensively metabolized in humans. The major metabolic pathway is the enzymatic hydrolysis of the acetamide group, which produces the pharmacologically inactive carboxylic acid metabolite, ucb L057 (24% of dose). The production of this metabolite is not dependent on any liver cytochrome P450 isoenzymes and is mediated by serine esterase(s) in various tissues, including blood cells. Two minor metabolites were identified as the product of hydroxylation of the 2-oxo-pyrrolidine ring (2% of dose) and opening of the 2-oxo-pyrrolidine ring in position 5 (1% of dose). There is no evidence for enantiomeric interconversion of levetiracetam or its major metabolite.

Elimination: Levetiracetam plasma half-life in adults is 7 ± 1 hours and was unaffected by dose, route of administration or repeated administration. Levetiracetam is eliminated from the systemic circulation by renal excretion as unchanged drug, which represents 66% of administered dose. The total body clearance is 0.96 mL/min/kg and the renal clearance is 0.6 mL/min/kg. Approximately 93% of the dose was excreted within 48 hours. The mechanism of excretion is glomerular filtration with subsequent partial tubular reabsorption. The primary metabolite, ucb L057, is excreted by glomerular filtration and active tubular secretion with a renal clearance of 4 mL/min/kg. Levetiracetam elimination is correlated to creatinine clearance and clearance is thus reduced in patients with impaired renal function (See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Special Populations: *Elderly:* Pharmacokinetics of levetiracetam were evaluated in 16 elderly patients, ranging in age from 61-88 years, with 11 of the 16 patients aged 75 years of age or over with creatinine clearance ranging from 30 to 74 mL/min. Following oral administration of 500 mg bid for 10 days, total body clearance decreased by 38% and the half-life was increased about 40% (10 to 11 hours) when compared to healthy adults. This is most likely due to the decrease in renal function in these subjects. *Pediatrics (6 to 12 years):* Pharmacokinetics of levetiracetam were evaluated in 24 pediatric patients (age 6-12 years) after a single dose. The apparent clearance of levetiracetam adjusted to body weight was approximately 40% higher than in epileptic adults. *Gender:* Levetiracetam C_{max} and AUC were 20% higher in women (n = 11) compared to men (n = 12). However, clearances adjusted for body weight were comparable. *Race:* Formal pharmacokinetic studies of the effects of race have not been conducted. Because levetiracetam is primarily renally excreted and there are no known important racial differences in creatinine clearance, significant pharmacokinetic differences due to race are not expected.

Renal Impairment: Single dose pharmacokinetics were performed in 20 subjects with renal impairment (n = 7 mild/CL_{cr} of 50-79 mL/min; n = 8 moderate/CL_{cr} of 30-49 mL/min; n = 5 severe/CL_{cr} <30 mL/min), and n = 11 matching healthy volunteers. Clearance of levetiracetam is correlated with creatinine clearance and levetiracetam pharmacokinetics following repeat administration were well predicted from single dose data. The apparent body clearance of the parent drug levetiracetam is reduced in patients with impaired renal function by approximately 40% in the mild group, 50% in the moderate group, and 60% in the severe renal impairment group. For the primary metabolite ucb L057, the decrease in clearance values from baseline was greater than that seen for the parent drug in all subject groups.

In anuric (end stage renal disease) patients, the apparent body clearance was approximately 30% compared to that of normal subjects. Approximately 50% of the pool of levetiracetam in the body is removed during a standard 4-hour hemodialysis procedure.

Dosage should be reduced in patients with impaired renal function receiving levetiracetam, and supplemental doses should be given to patients after dialysis (see **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Hepatic Impairment: A single-dose pharmacokinetic study was performed in 16 subjects with hepatic impairment (n = 5 mild/Child-Pugh Grade A; n = 6 moderate/Grade B; n = 5 severe/Grade C vs 5 healthy controls). For the mild and moderate subgroups neither mean nor individual pharmacokinetic values were clinically different from those of controls. In patients with severe hepatic impairment, mean apparent body clearance was 50% that of normal subjects, with decreased renal clearance accounting for most of the decrease. Patients with severe hepatic impairment thus require a reduced dosage of Keppra® (See **PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

INDICATIONS AND CLINICAL USE

Keppra® (levetiracetam) is indicated as adjunctive therapy in the management of patients with epilepsy who are not satisfactorily controlled by conventional therapy.

CONTRAINDICATIONS

This product should not be administered to patients who have previously exhibited hypersensitivity to levetiracetam or any of the inactive ingredients in Keppra® (levetiracetam) tablets.

WARNINGS

Central Nervous System Adverse Events

Keppra® (levetiracetam) use is associated with the occurrence of central nervous system (CNS) adverse events; the most significant of these can be classified into the following categories: 1) somnolence and fatigue, 2) behavioral/psychiatric symptoms and 3) coordination difficulties.

There was no clear dose response relationship for any of the three categories of CNS adverse events, within the recommended dose range of up to 3000 mg/day. Somnolence/asthenia and coordination difficulties occurred most frequently within the first four weeks of treatment and usually resolved while patients remained on treatment. In the case of behavioral/psychiatric symptoms (including such adverse events as aggression, agitation, anger, anxiety, emotional lability, hostility, irritability), approximately half of the patients reported these events within the first four weeks, with the remaining events occurring throughout the duration of the trials. See also **PRECAUTIONS, *Central Nervous System Adverse Events***.

Withdrawal of Anti-Epileptic Drugs

As with all antiepileptic drugs, Keppra® should be withdrawn gradually to minimize the potential of increased seizure frequency.

PRECAUTIONS

General

Hematological Abnormalities: Minor but statistically significant decreases compared to placebo were seen in total mean RBC count, mean hemoglobin, and mean hematocrit in Keppra®-treated patients in controlled trials. For hemoglobin values, the percentage of Keppra® or placebo treated patients with possibly clinically significant abnormalities were less than 0.5% each. For hematocrit values, a total of 5.1% of Keppra® treated versus 3.2% of placebo patients had at least one possibly significant decrease in hematocrit (≤ 37% in males and 32% in females).

For white blood cells (WBC), 2.9% of treated versus 2.3% of placebo patients had at least one possibly clinically significant decrease in WBC count (≤ 2.8 x 10^9/L), while 2.6% of treated vs. 1.7% of placebo patients had at least one possibly significant decrease in neutrophil count (≤ 1.0 x 10^9/L). Of the Keppra®-treated patients with a low neutrophil count, all but one rose towards or reached baseline with continued treatment. No patient was discontinued secondary to low neutrophil counts.

Central Nervous System Adverse Events **(See WARNINGS):** Keppra® (levetiracetam) use is associated with the occurrence of central nervous system (CNS) adverse events; the most significant of these can be classified into the following categories: 1) somnolence and fatigue, 2) behavioral/psychiatric symptoms and 3) coordination difficulties.

The following CNS adverse events were observed in controlled clinical trials.

Table 1:
Total Combined Incidence Rate for Each of the Three Categories of CNS Adverse Events in Placebo-controlled Add-on Clinical Trials.

Category of CNS adverse event	Keppra®* + AED therapy (n = 672)	Placebo + AED therapy (n = 351)
Somnolence and fatigue		
Somnolence	15%	10%
Asthenia	14%	10%
Behavioral/psychiatric symptoms		
Nonpsychotic[1]	14%	6%
Psychotic[2]	1%	0%
Coordination difficulties[3]	3%	2%

* Reflects Keppra® doses of 1000 mg, 2000 mg, 3000 mg, and 4000 mg per day.

[1] "Non-psychotic behavioral/psychiatric symptoms" encompasses the following terms: agitation, antisocial reaction, anxiety, apathy, depersonalization, depression, emotional lability, euphoria, hostility, nervousness, neurosis, personality disorder and suicide attempt.

[2] "Psychotic behavioral/psychiatric symptoms" encompasses the following terms: hallucinations, paranoid reaction, psychosis and psychotic depression.

[3] "Coordination difficulties" encompasses the following terms: ataxia, abnormal gait, incoordination.

See **ADVERSE EVENTS, Table 2,** for incidence rate of individual AEs contained within the categories.

Behavioral/psychiatric symptoms (including agitation, emotional lability, hostility, anxiety, etc.) have been reported approximately equally in patients with and without a psychiatric history.

There was no clear dose response relationship for any of the three categories of CNS adverse events, within the recommended dose range of up to 3000 mg/day. In a controlled study including a dose of 4000 mg, administered without titration, the incidence rate of somnolence during the first four weeks of treatment for patients receiving the high dose was 42%, compared to 21% for patients receiving 2000 mg/day.

Special Populations

Patients with Renal Impairment: Renal excretion of unchanged drug accounts for approximately 66% of administered levetiracetam dose. Consistent with this, pharmacokinetic studies in renally-impaired patients indicate that apparent clearance is significantly reduced in subjects with renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY, *Special Populations***).

In patients with renal impairment Keppra® dosage should be appropriately reduced. Patients with end stage renal disease, i.e. those undergoing dialysis, should be given supplemental doses after dialysis (See **DOSAGE AND ADMINISTRATION**).

Pregnancy and Nursing: There are no adequate and well-controlled studies on the use of Keppra® in pregnant women. Levetiracetam and/or its metabolites cross the placental barrier in animal species. In reproductive toxicity studies in rats and rabbits, levetiracetam induced developmental toxicity at exposure levels similar to or greater than the human exposure. There was evidence of increased skeletal variations/minor anomalies, retarded growth, embryonic death, and increased pup mortality. In the rat, fetal abnormalities occurred in the absence of overt maternal toxicity. The systemic exposure at the observed no effect level in the rabbit was about 4 to 5 times the human exposure. The potential risk for humans is unknown. Keppra® should not be used during pregnancy unless potential benefits to mother and fetus are considered to outweigh potential risks to both. Discontinuation of antiepileptic treatments may result in disease worsening, which can be harmful to the mother and the fetus.

Pregnancy Exposure Registry: To facilitate monitoring of fetal outcomes of pregnant women exposed to Keppra®, physicians should encourage patients to register, before fetal outcome is known (e.g., ultrasound, results of amniocentesis, etc.), in the Antiepileptic Drug Pregnancy Registry by calling (888) 233-2334 (toll free).

Nursing Mothers: Levetiracetam is excreted in breast milk. Therefore, there is a potential for serious adverse reactions from Keppra® in nursing infants. Recommendations regarding nursing and epilepsy medication should take into account the importance of the drug to the mother, and the as yet uncharacterized risks to the infant. Typically, recommendations are made in the context of the necessary prior risk-benefit judgement, regarding pregnancy and epilepsy medication.

Use in Pediatric Patients: Safety and efficacy in patients below the age of 18 have not been established.

Use in the Elderly: Renal function can be decreased in the elderly and levetiracetam is known to be substantially excreted by the kidney, the risk of adverse reactions to the drug may be greater in patients with impaired renal function. A pharmacokinetic study in 16 elderly subjects (age 61-88 years) showed a decrease in clearance by about 40% with oral administration of both single dose and 10 days of multiple twice-daily dosing. This decrease is most likely due to the expected decrease in renal function in these elderly subjects. Care should therefore be taken in dose selection for elderly patients, and it may be useful to monitor renal function.

There were insufficient numbers of elderly patients in controlled trials of epilepsy to adequately assess the efficacy or safety of Keppra® in these patients. Nine of 672 patients treated with Keppra® were 65 or over.

Drug Interactions

***In Vitro* Studies on Metabolic Interaction Potential** *In vitro*, levetiracetam and its primary metabolite have been shown not to inhibit the major human liver cytochrome P450 isoforms (CYP3A4, 2A6, 2C8/9/10, 2C19, 2D6, 2E1 and 1A2), glucuronyl transferase (paracetamol UGT, i.e. UGT1A6, ethinyl estradiol UGT, i.e.UGT1A1, and *p*-nitrophenol UGT, i.e.UGT [pI6.2]) and epoxide hydrolase activities. In addition, levetiracetam does not affect the *in vitro* glucuronidation of valproic acid. In human hepatocytes in culture, levetiracetam did not cause enzyme induction.

Levetiracetam circulates largely unbound (< 10% bound) to plasma proteins; therefore clinically significant interactions with other drugs through competition for protein binding sites are unlikely.

Thus *in-vitro* data, in combination with the pharmacokinetic characteristics of the drug, indicate that Keppra® is unlikely to produce, or be subject to, pharmacokinetic interactions.

Clinical Pharmacokinetic Data

Other Antiepileptic Drugs (AEDs): Potential drug interactions between Keppra® and other AEDs (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine, gabapentin and primidone) were assessed by evaluating the serum concentrations of levetiracetam and these AEDs during placebo-controlled clinical studies. These data suggest that levetiracetam may not significantly influence the plasma concentrations of these other AEDs, and that the other AEDs may not significantly influence the plasma concentrations of levetiracetam.

For two of these AEDs — phenytoin and valproate — formal pharmacokinetic interaction studies with Keppra® were performed. Keppra® was co-administered with either phenytoin or valproate at doses of 3000 mg/day and 1000 mg/day respectively. No clinically significant interactions were observed.

Other Drug Interactions

Oral Contraceptives: A pharmacokinetic clinical interaction study has been performed in healthy subjects between the oral contraceptive containing 0.03 mg ethinyl estradiol and 0.15 mg levonorgesterol, and the lowest therapeutic dose of Keppra® (500 mg bid). No clinically significant pharmacokinetic interactions were observed.

However, pharmacokinetic interaction studies using Keppra® as adjunctive therapy and covering the recommended dosage range, have not been conducted. Therefore, physicians should advise their female patients to be alert to any irregular vaginal bleeding or spotting, and to immediately report to them any occurrences.

Digoxin: Keppra® (1000 mg bid) did not influence the pharmacokinetics and pharmacodynamics (ECG) of digoxin given as a 0.25 mg dose every day. Coadministration of digoxin did not influence the pharmacokinetics of levetiracetam.

Warfarin: Keppra® (1000 mg bid) did not influence the pharmacokinetics of R and S warfarin (2.5 mg, 5 mg, or 7.5 mg daily). Prothrombin time was not affected by levetiracetam. Coadministration of warfarin did not affect the pharmacokinetics of levetiracetam.

Probenecid: Probenecid, a renal tubular secretion blocking agent, administered at a dose of 500 mg four times a day, did not change the pharmacokinetics of levetiracetam 1000 mg bid. C_{ssmax} of the metabolite, ucb L057, was approximately doubled in the presence of probenecid and the renal clearance of the metabolite ucb L057 was decreased by 60%; this alteration is likely related to competitive inhibition of tubular secretion of ucb L057. The effect of Keppra® on probenecid was not studied.

ADVERSE EVENTS

Commonly Observed

In well-controlled clinical studies, the most frequently reported adverse events associated with the use of Keppra® in combination with other AEDs, not seen at an equivalent frequency among placebo-treated patients, were somnolence, asthenia, dizziness and infection. Of the most frequently reported adverse events, asthenia, somnolence and dizziness appeared to occur predominantly during the first four weeks of treatment with Keppra®.

Incidence of AEs in Controlled Clinical Trials

Table 2:

Incidence (%) of Treatment-emergent Adverse Events in Placebo-controlled, Add-on Studies by Body System. (Adverse Events Occurred in at least 1% of Keppra®-treated Patients and Occurred More Frequently than Placebo-treated Patients.) (Studies N051, N052, N132 and N138)

Body system/ adverse event	Keppra®+ AED therapy (n = 672) (%)	Placebo + AED therapy (n = 351) (%)
Body as a whole		
Asthenia	14	10
Infection*	13	7
Digestive system		
Tooth disorders	2	1
Hemic and lymphatic system		
Ecchymosis	2	1
Nervous system		
Amnesia	2	0
Anxiety	2	1
Ataxia	3	1
Depression	4	2
Dizziness	9	4
Emotional lability	2	0
Hostility	2	1
Nervousness	4	2
Personality disorders	1	0
Somnolence	15	10
Thinking abnormal	2	1
Vertigo	3	1
Respiratory system		
Pharyngitis	6	4
Rhinitis	4	3
Sinusitis	2	1

* In levetiracetam-treated patients, the majority of "infection" events (93%) were coded to reported terms of "common cold" or "infection upper respiratory".

Additional Events Observed in Placebo Controlled Trials

Lack of Dose-related Incidence within Therapeutic Range: Based on the data from the controlled clinical trials, there was no evidence of dose relationship within the recommended dose range of 1000 to 3000 mg/day.

Discontinuation or Dose Reduction in Well-controlled Clinical Studies: In well-controlled clinical studies, 14.3% of patients receiving Keppra® and 11.7% receiving placebo either discontinued or had a dose reduction as a result of an adverse event. The adverse events most commonly associated (>1%) with discontinuation or dose reduction in either treatment group are presented in **Table 3.**

Table 3:

Adverse Events Most Commonly Associated with Discontinuation or Dose Reduction in Placebo-controlled Studies in Patients with Epilepsy

	Keppra® (n = 672)	Placebo (n = 351)
Asthenia	9 (1.3%)	3 (0.9%)
Headache	8 (1.2%)	2 (0.6%)
Convulsion	16 (2.4%)	10 (2.8%)
Dizziness	11 (1.6%)	0
Somnolence	31 (4.6%)	6 (1.7%)
Rash	0	5 (1.4%)

The overall adverse experience profile of Keppra® was similar between females and males. There are insufficient data to support a statement regarding the distribution of adverse experience reports by age and race.

Post-marketing Experience

In post-marketing experience, nervous system and psychiatric disorders have most frequently been reported. In addition to adverse reactions during clinical studies, and listed above, the following adverse reactions have been reported in post-marketing experience. Data are insufficient to support an estimate of their incidence in the population to be treated.

Blood and lymphatic disorders: leukopenia, neutropenia, pancytopenia, thrombocytopenia.

SYMPTOMS AND TREATMENT OF OVERDOSE

Symptoms

The highest reported Keppra® overdose is approximately 10 times the therapeutic dose. In the majority of overdose cases, multiple drugs were involved. Somnolence, agitation, aggression, depressed level of consciousness, respiratory depression, and coma were observed with Keppra® overdoses. The minimal lethal oral dose in rodents is at least 233 times the maximum clinically studied dose.

Treatment

There is no antidote for overdose with Keppra®; treatment is symptomatic and may include hemodialysis. If indicated, elimination of unabsorbed drug should be attempted by emesis or gastric lavage; usual precautions should be observed to maintain airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient.

Standard hemodialysis procedures result in significant removal of levetiracetam (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

DOSAGE AND ADMINISTRATION

General

Renal excretion of unchanged drug accounts for approximately 66% of administered levetiracetam dose. Consistent with this, reduced doses are recommended for patients with renal impairment.

Keppra® is given orally with or without food.

Adults

Treatment should be initiated at a dose of 1000 mg/day, given as twice daily dosing (500 mg bid). Depending on clinical response and tolerability, the daily dose may be increased every two weeks by increments of 1000 mg, to a maximum recommended daily dose of 3000 mg.

In clinical trials, daily doses of 1000 mg, 2000 mg, and 3000 mg, given as twice a day dosing, were shown to be effective. Although there was a tendency toward greater response rate with higher dose, a consistent statistically significant increase in response with increased dose has not been shown. There are limited safety data from controlled clinical trials at doses higher than 3000 mg/day (approximately 40 patients), therefore these doses are not recommended.

Patients with Impaired Renal Function

Keppra® dosage should be reduced in patients with impaired renal function (see **Table 4** below). Patients with end stage renal disease should receive supplemental doses following dialysis. To use this dosing table, an estimate of the patient's CL_{cr} in mL/min is needed. CL_{cr} in mL/min may be estimated from serum creatinine (mg/dL) determination using the following formula:

$$CL_{cr} = \frac{[140\text{-age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for female patients})$$

Table 4:

Dosing Adjustment for Patients with Impaired Renal Function

Group	Creatinine clearance (mL/min)	Dosage and frequency
Normal	≥ 80	500 to 1500 mg twice daily
Mild	50-79	500 to 1000 mg twice daily
Moderate	30-49	250 to 750 mg twice daily
Severe*	< 30	250 to 500 mg twice daily
End-stage renal disease patients undergoing dialysis†	—	500 to 1000 mg once daily

† Following dialysis, a 250 to 500 mg supplemental dose is recommended.
* or according to best clinical judgement

Patients with Impaired Hepatic Function

No dose adjustment is needed in patients with mild-to-moderate hepatic impairment. In patients with severe hepatic impairment, the creatinine clearance may underestimate the renal insufficiency. Therefore a 50% reduction of the daily maintenance dose is recommended when the creatinine clearance is < 70 mL/min.

Elderly Patients

Dose selection and titration should proceed cautiously in elderly patients, as renal function decreases with age.

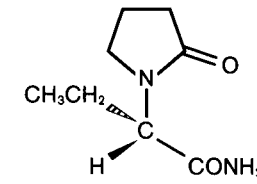
PHARMACEUTICAL INFORMATION

Drug Substance

U.S.A.N: levetiracetam

Chemical Name: (-)-(S)-α-ethyl-2-oxo-1-pyrrolidine acetamide

Structural Formula:



Molecular Formula: $C_8H_{14}N_2O_2$

Molecular Weight: 170.21

Physical Form: A white to off-white crystalline powder with a faint odor and a bitter taste.

Solubility: It is very soluble in water (104.0 g/100 mL). It is freely soluble in chloroform (65.3 g/100 mL) and in methanol (53.6 g/100 mL), soluble in ethanol (16.5 g/100 mL), sparingly soluble in acetonitrile (5.7 g/100 mL) and practically insoluble in n-hexane.

pKa and pH values: The pKa of levetiracetam is < -2 and cannot be determined with accuracy due to the chemical instability of the protonated form.

The protonation of ucb L059 starts at H_0 values between -1 and -2.

Partition Co-efficient: Δ log P (log $P_{octanol}$ - Log $P_{cyclohexane}$) was calculated at pH 7.4 using phosphate buffered saline and at pH 1.0 using KCl/HCl. The Δ log P at pH 7.4 is 3.65 and at pH 1.0 is 3.10.

Melting Range: 115-119°C

Composition: Keppra® tablets contain the labeled amount of levetiracetam. Inactive ingredients include colloidal silicon dioxide, corn starch, hydroxypropyl methylcellulose, magnesium stearate, polyethylene glycol 4000, povidone, talc, titanium dioxide and coloring agents.

The individual tablets contain the following coloring agents:
250 mg tablets: FD&C Blue No. 2,
500 mg tablets: FD&C Blue No. 2 and yellow iron oxide,
750 mg tablets: FD&C Blue No. 2, FD&C Yellow No. 6 and red iron oxide.

Stability and Storage Recommendations

Store between 15-30°C (59-86°F).

AVAILABILITY OF DOSAGE FORMS

Keppra® (levetiracetam) tablets, 250 mg are blue, oblong-shaped, film-coated tablets debossed with "ucb" and "250" on one side. They are supplied in bottles of 120 tablets.

Keppra® (levetiracetam) tablets, 500 mg are yellow, oblong-shaped, film-coated tablets debossed with "ucb" and "500" on one side. They are supplied in bottles of 120 tablets.

Keppra® (levetiracetam) tablets, 750 mg are orange, oblong-shaped, film-coated tablets debossed with "ucb" and "750" on one side. They are supplied in bottles of 120 tablets.

For more information, please refer to the complete Keppra® Product Monograph.

References: 1. Cereghino JJ, Biton V, Abou-Khalil B, et al. Levetiracetam for partial seizures: results of a double-blind, randomized clinical trial. *Neurology* 2000;55:236-4. **2.** Keppra Product Monograph. UCB Pharma, Inc.

Lundbeck

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See pages A-12, A-13

PrCOPAXONE®
(glatiramer acetate injection)

20 mg, single use vials and 20 mg/1.0 mL, pre-filled syringes for Subcutaneous Injection

THERAPEUTIC CLASSIFICATION Immunomodulator

ACTION AND CLINICAL PHARMACOLOGY

COPAXONE® [glatiramer acetate for injection (formerly known as copolymer-1)] is a sterile, lyophilized mixture of synthetic polypeptides containing four naturally occurring amino acids: L-glutamic acid, L-alanine, L-tyrosine and L-lysine with an average molar fraction of 0.141, 0.427, 0.095 and 0.338, respectively.

The mechanism(s) by which glatiramer acetate exerts its effect on Multiple Sclerosis (MS) is (are) not fully elucidated. However, it is thought to act by modifying immune processes that are currently believed to be responsible for the pathogenesis of MS. This hypothesis is supported by findings of studies that have been carried out to explore the pathogenesis of experimental allergic encephalomyelitis (EAE), a condition induced in animals that is generally accepted as an experimental model of MS.

Studies in animals and *in vitro* systems suggest that upon its administration glatiramer acetate specific suppressor T cells are induced and activated in the periphery.

Because the immunological profile of glatiramer acetate remains to be fully elucidated, concerns exist about its potential to alter naturally occurring immune responses (see **PRECAUTIONS**).

Pharmacokinetics: Results obtained in pharmacokinetic studies performed in humans (healthy volunteers) and animals support the assumption that a substantial fraction of the therapeutic dose delivered to patients subcutaneously is hydrolyzed locally. Nevertheless, larger fragments of glatiramer acetate can be recognized by glatiramer acetate reactive antibodies. Some fraction of the injected material, either intact or partially hydrolyzed, is presumed to enter the lymphatic circulation, enabling it to reach regional lymph nodes, and some, may enter the systemic circulation intact.

Clinical Studies: The efficacy of COPAXONE® (glatiramer acetate for injection) was evaluated in two placebo-controlled trials in patients with Relapsing-Remitting MS (RR-MS). In a third placebo-controlled study the effects of glatiramer acetate on MRI parameters were assessed. In these studies, a dose of 20 mg/day was used. No other dose or dosing regimen has been studied in placebo-controlled trials of RR-MS.

The first trial was a pilot study Trial 1 (Trial BR-I) which was conducted at a single-center and was a double-blind, randomized, matched-pair, parallel group placebo-controlled trial. Fifty patients with RR-MS were randomized to receive 20 mg/day glatiramer acetate (n=25) or placebo (n=25) subcutaneously. The protocol-specified primary outcome measure was the proportion of patients who were relapse free during the 2-year duration of the trial, but two additional relevant outcomes were also specified as endpoints: frequency of attacks during the trial, and the change in the number of attacks compared to the rate of attacks in the 2 years prior to study entry. Results from this study (see Table 1) show that there was a statistically significant effect of glatiramer acetate on number of relapses.

TABLE 1 – Trial BR-1: Efficacy Results

Outcome	Trial I[a]		
	Glatiramer acetate n=25	Placebo n=25	p-Value
% Relapse Free Patients	14/25 (56%)	7/25 (28%)	0.085
Mean Relapse Frequency	0.6/2 years	2.4/2 years	0.005
Reduction in Relapse Rate compared to pre-study	3.2	1.6	0.025
Median Time to First Relapse (days)	>700	150	0.03
% of Progression-Free* Patients	20/25 (80%)	13/25 (52%)	0.07

[a] The primary efficacy measure for **Trial I** was the proportion of patients who were relapse free during the 2 year duration of the trial (**% Relapse Free**). Analyses were based on the intent-to-treat population.

* Progression defined as an increase of at least 1 point on the DSS that persists for at least 3 consecutive months.

Trial II (01-9001) was a multicenter double-blind, randomized, placebo-controlled trial. Two hundred and fifty-one patients with RR-MS were randomized to receive 20 mg/day glatiramer acetate (n=125) or placebo (n=126) subcutaneously. Patients were diagnosed with RR-MS by standard criteria, and had at least 2 exacerbations during the 2 years immediately preceding enrollment. Patients had a score of no more than 5 on the Kurtzke Expanded Disability Scale Score (EDSS), a standard scale ranging from 0 (normal) to 10 (death due to MS). A score of 5 is defined as one at which a patient is still ambulatory but for whom full daily activities are impaired due to disability, a score of 6 is defined as one at which the patient is still ambulatory but requires assistance and a score of 7 on this scale means that the patient requires a wheelchair.

Patients were seen every 3 months for 2 years, as well as within several days of a presumed exacerbation. In order for an exacerbation to be confirmed, a blinded neurologist had to document objective neurologic signs, as well as document the existence of other criteria (e.g., the persistence of the lesion for at least 48 hours).

The protocol-specified primary outcome measure was the mean number of relapses during treatment. Table 2 shows results of the analysis of primary as well as several secondary outcome measures at two years based on the intent-to-treat population.

TABLE 2 – Core (24-month) Double-Blind Study: Effect on Relapse Rate

Outcome	Trial II[a]		
	Glatiramer acetate n=125	Placebo n=126	p-Value
Mean No. of Relapses/2 years[b]	1.19	1.68	0.055
% Relapse Free Patients	42/125 (34%)	34/126 (27%)	0.25
Median Time to First Relapse (days)	287	198	0.23
% of Patients Progression Free[c]	98/125 (78%)	95/126 (75%)	0.48
Mean Change in EDSS	-0.05	+0.21	0.023

[a] The primary efficacy measure for **Trial II** was the number of relapses during treatment. Analyses were based on the intent-to-treat population.

[b] Baseline adjusted mean.

[c] Progression defined as an increase of at least 1 point on the EDSS that persists for at least 3 consecutive months.

The effects of glatiramer acetate on relapse severity were not evaluated in either trial.

Both studies showed a beneficial effect of glatiramer acetate on relapse rate, and on this basis glatiramer acetate is considered effective.

The third study (9003) was a multi-national, multi-center, MRI-monitored study. A total of 239 patients with RR-MS (119 on glatiramer acetate and 120 on placebo) were randomized. Inclusion criteria were similar to those in Trial II (Study 01-9001) with the additional criteria that patients had to have at least one Gd-enhancing lesion on the screening MRI. The patients were treated initially in a double-blind manner for nine months, during which they underwent monthly MRI scanning. The primary endpoint for the double-blind phase was the total cumulative number of T1 Gd-enhancing lesions over nine months. Other MRI parameters were assessed as secondary endpoints. Table 3 summarizes the results for the parameters monitored during the nine-month double-blind phase for the intent-to-treat cohort. Because the link between MRI findings and the clinical status of patients is contentious, the prognostic value of the following statistically significant findings is unknown.

TABLE 3 – Nine-Month Double-Blind Phase: MRI Endpoints – Results

No.	Outcome	Glatiramer acetate n=113	Placebo n=115	p-Value
Primary Endpoint				
1.	Medians of the Cumulative Number of T1 Gd-Enhancing Lesions	12	17	0.0037
Secondary Endpoints				
2.	Medians of the Cumulative Number of New T1 Gd-Enhancing Lesions	9	14	0.0347
3.	Medians of the Cumulative Number of New T2 Lesions	5	8	0.01
4.	Medians of the Cumulative Change from Baseline in volumes (mL) of T1 Gd-Enhancing Lesions	-0.309	0	0.0248
5.	Medians of the Cumulative Change from Baseline in volumes (mL) of T2 Lesions	8.852	13.566	0.0229
6.	Medians of the Cumulative Change from Baseline in volumes (mL) of T1 Hypointense Lesions	1.642	1.829	0.7311
7.	Proportion of T1 Gd-Enhancing Lesion-Free Patients	46.4%	32.2%	0.0653

The mean number of relapses in this 9-month study was 0.50 for the COPAXONE® group and 0.77 for the placebo group (p=0.0077).

INDICATIONS AND CLINICAL USE

For use in ambulatory patients with Relapsing-Remitting Multiple Sclerosis to reduce the frequency of relapses.

The safety and efficacy of COPAXONE® in chronic progressive MS have not been established.

CONTRAINDICATIONS

COPAXONE® (glatiramer acetate for injection) is contraindicated in patients with known hypersensitivity to glatiramer acetate or mannitol.

WARNINGS

The only recommended route of administration of COPAXONE® (glatiramer acetate for injection) injection is the subcutaneous route. COPAXONE® should not be administered by the intravenous route.

Symptoms of Potentially Cardiac Origin: Approximately 26% of COPAXONE® patients in the pre-marketing multicenter controlled trial (compared to 10% of placebo patients) experienced at least one episode of what was described as transient chest pain (see **ADVERSE REACTIONS: Chest Pain**). While some of these episodes occurred in the context of the Immediate Post-Injection Reaction (see **ADVERSE REACTIONS: Immediate Post-Injection Reaction**), many did not. The pathogenesis of this symptom is unknown. Patients in controlled clinical trials were free of significant cardiovascular problems (New York Heart Association Class I and II) and thus the risks associated with COPAXONE® treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown.

COPAXONE® has been associated with an Immediate Post-Injection Reaction consisting of a constellation of symptoms appearing immediately after injection that could include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria (see **ADVERSE REACTIONS: Immediate Post-Injection Reaction**).

COPAXONE® has not been studied in patients with a history of severe anaphylactoid reactions, obstructive pulmonary disease or asthma, nor in patients under treatment for either of these two latter conditions. Particular caution is therefore advised regarding the use of COPAXONE® in such patients.

Anaphylactoid reactions associated with the use of COPAXONE® have been reported in rare instances (<1/1000) during the post-marketing period. Some cases required treatment with epinephrine and other appropriate medical treatment.

PRECAUTIONS

General: Patients should be instructed in aseptic reconstitution and self-injection techniques to assure the safe administration of COPAXONE® (glatiramer acetate for injection) (see **INFORMATION FOR THE PATIENT**). The first injection should be performed under the supervision of an appropriately qualified health care professional. Patient understanding and use of aseptic self-injection techniques and procedures should be periodically re-evaluated. Patients should be cautioned against the re-use of needles or syringes and instructed in safe disposal procedures. A puncture-resistant container for disposal of used needles and syringes should be used by the patient. Patients should be instructed on the safe disposal of full containers.

Considerations Involving the Use of a Product Capable of Modifying Immune Responses: COPAXONE® is an antigenic substance and thus it is possible that detrimental host responses can occur with its use. Whether COPAXONE® can alter normal human immune responses, such as the recognition of foreign antigens is unknown. It is therefore possible that treatment with COPAXONE® may undermine the body's defenses against infections and tumor surveillance. Systematic assessments of these risks have not been done. Continued alteration of cellular immunity due to chronic treatment with glatiramer acetate might result in untoward effects.

Glatiramer acetate-reactive antibodies are formed in practically all patients exposed to daily treatment with the recommended dose. Studies in both the rat and monkey have suggested that immune complexes are deposited in the renal glomeruli. Furthermore, in a controlled clinical trial of 125 RR-MS patients given glatiramer acetate 20 mg for 2 years, serum IgG levels reached at least 3 times baseline values in 80% of patients by 3 months of initiation of treatment. By 12 months of treatment, however, 30% of patients still had IgG levels at least 3 times baseline values, and 90% had levels above baseline by 12 months. The antibodies are exclusively of the IgG subtype – and predominantly of the IgG-1 subtype. No IgE type antibodies could be detected in any of the 94 sera tested. Nevertheless, anaphylaxis can be associated with the administration of almost any foreign substance and, therefore, this risk cannot be excluded.

Preclinical studies to assess the carcinogenic potential of glatiramer acetate in mice and rats do not suggest any evidence of carcinogenic potential related to glatiramer acetate administered subcutaneously at dose levels of up to 30 mg/kg/day in rats and 60 mg/kg/day in mice (see **TOXICOLOGY: Carcinogenicity**). The relevance of these findings for humans is unknown (see **PRECAUTIONS: Considerations Involving the Use of a Product Capable of Modifying Immune Responses**).

Drug Interactions: Interactions between COPAXONE® and other drugs have not been fully evaluated. Results from existing clinical trials do not suggest any significant interactions of COPAXONE® with therapies commonly used in MS patients. This includes the concurrent use of corticosteroids for up to 28 days. COPAXONE® has not been formally evaluated in combination with Interferon beta. However, 246 patients who failed on or who did not tolerate therapy with Interferon beta and were later treated with COPAXONE® within the framework of an open clinical trial did not report any serious or unexpected adverse events thought to be related to treatment.

Use in Pregnancy: There are no adequate and well-controlled studies in pregnant women. No evidence of reproductive toxicity was observed in preclinical studies (see **TOXICOLOGY: Reproduction and Teratology**). Because animal reproduction studies are not always predictive of human response, this drug should be used during pregnancy only if clearly needed. During pre-marketing clinical trials with COPAXONE®, seven women conceived while being treated with the active drug. One case was lost to follow-up. Three of the patients electively discontinued pregnancy. Three patients stopped treatment 1, 1.5 and 2 months after learning they were pregnant; all delivered healthy babies.

Nursing Mothers: It is not known whether this drug is excreted in human milk. Because many drugs are excreted in human milk, treating a nursing woman with COPAXONE® should only be considered after careful risk/benefit assessment and be used with caution.

Use in Children: The safety and effectiveness of COPAXONE® have not been established in individuals below 18 years of age.

Use in the Elderly: COPAXONE® has not been studied in the elderly (>65 years old).

Use in Patients with Impaired Renal Function: The pharmacokinetics of COPAXONE® in patients with impaired renal function have not been determined.

ADVERSE REACTIONS

In the pre-marketing clinical trials, approximately 900 individuals have received at least one dose of COPAXONE® (glatiramer acetate for injection) in controlled and uncontrolled clinical trials. Total patient exposure to COPAXONE® in clinical trials ranged from 6 months (693 patients) to 2 years (306 patients), and to over 7 years (69 patients) at a daily dose of 20 mg.

In controlled clinical trials, the most commonly observed adverse events associated with the use of COPAXONE® which occurred at a higher frequency than in placebo treated patients were: injection site reactions, vasodilation, chest pain, asthenia, infection, pain, nausea, arthralgia, anxiety and hypertonia.

Of a total of 844 patients who could be evaluated for safety, approximately 8% discontinued treatment due to an adverse event. The adverse events most commonly associated with discontinuation were: injection site reaction (6.5%), vasodilation, unintended pregnancy, depression, dyspnea, urticaria, tachycardia, dizziness and tremor. Treatment discontinuation due to a serious adverse event considered by investigators to be related to COPAXONE® treatment included a case of life-threatening serum sickness.

Immediate Post-Injection Reaction: Approximately 10% of Multiple Sclerosis patients exposed to COPAXONE® in pre-marketing studies reported a post-injection reaction immediately following subcutaneous injection of COPAXONE®. Symptoms experienced could include flushing, chest pain, palpitations, anxiety, dyspnea, constriction of the throat and urticaria. These symptoms were invariably transient, self-limited, did not require specific treatment and in general, arose several months after initiation of treatment, although they may occur earlier in the course of treatment. A given patient may experience one or several episodes of these symptoms during treatment with COPAXONE®. Whether these episodes are mediated by an immunologic or non-immunologic mechanism, and whether several similar episodes seen in a given patient have identical mechanisms is unknown. In fact, whether or not this constellation of symptoms actually represents a specific syndrome is unknown. During the post-marketing period, there have been reports of patients with similar symptoms who received emergency medical care (see **WARNINGS**).

Chest Pain: Approximately 26% of glatiramer acetate patients in the multicenter pre-marketing controlled trial (compared to 10% of placebo patients) experienced at least one episode of what was described as transient chest pain. While some of these episodes occurred in the context of the Immediate Post-Injection Reaction described above, many did not. The temporal relationship of the chest pain to an injection of glatiramer acetate was not always known, although the pain was transient (usually lasting only a few minutes), often unassociated with other symptoms, and appeared to have no important clinical sequelae. Some patients experienced more than one such episode, and episodes usually began at least 1 month after the initiation of treatment. The pathogenesis of this symptom is unknown. There has been only one episode of chest pain during which a full ECG was performed; the ECG showed no evidence of ischemia. Patients in clinical trials were free of significant cardiovascular disease (New York Heart Association Class I or II); therefore, the risks associated with glatiramer acetate treatment for Multiple Sclerosis patients with comorbid cardiovascular disease are unknown (see **WARNINGS: Symptoms of Potentially Cardiac Origin**).

Table 4 lists the adverse experiences after up to 35 months of treatment (>27-33 months: COPAXONE®, n=84; Placebo, n=75; >33 months: COPAXONE®, n=12; Placebo, n=24) in the pre-marketing multicenter placebo-controlled study (Trial II) in relapsing-remitting Multiple Sclerosis patients that occurred at an incidence of at least 2% among patients who received COPAXONE® and at an incidence that was at least 2% more than that observed in the same trial for placebo patients regardless of their causal relationship to treatment. No laboratory adverse experiences that met these criteria were reported.

It should be noted that the figures cited in Table 4 cannot be used to predict the incidence of side effects during the course of usual medical practice, where patient characteristics and other factors differ from those that prevailed in the clinical trials. However, the cited figures do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

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TABLE 4
Pre-marketing Controlled Trial in Patients with Multiple Sclerosis
Adverse Experiences ≥ 2% Incidence and ≥ 2% Above Placebo

	COPAXONE® n=125		Placebo n=126	
Adverse Experience	**n**	**%**	**n**	**%**
Body as a Whole				
Injection Site Pain	83	66.4	46	36.5
Asthenia	81	64.8	78	61.9
Injection Site Erythema	73	58.4	17	13.5
Injection Site Pruritus	48	38.4	5	4.0
Flu syndrome	38	30.4	34	27.0
Injection Site Inflammation	35	28.0	9	7.1
Back pain	33	26.4	28	22.2
Chest pain	33	26.4	13	10.3
Injection Site Mass	33	26.4	10	7.9
Injection Site Induration	25	20.0	1	0.8
Injection Site Welt	19	15.2	5	4.0
Neck pain	16	12.8	9	7.1
Face Edema	11	8.8	2	1.6
Injection Site Urticaria	9	7.2	0	0
Injection Site Hemorrhage	8	6.4	4	3.2
Chills	5	4.0	1	0.8
Cyst	5	4.0	1	0.8
Injection Site Reaction	4	3.2	1	0.8
Injection Site Atrophy	3	2.4	0	0
Abscess	3	2.4	0	0
Cardiovascular				
Vasodilatation	34	27.2	14	11.1
Palpitation	14	11.2	6	4.8
Migraine	9	7.2	5	4.0
Syncope	8	6.4	4	3.2
Digestive				
Nausea	29	23.2	22	17.5
Vomiting	13	10.4	7	5.6
Anorexia	6	4.8	3	2.4
Gastroenteritis	6	4.8	2	1.6
Oral Moniliasis	3	2.4	0	0
Tooth Caries	3	2.4	0	0
Hemic and Lymphatic				
Lymphadenopathy	23	18.4	12	9.5
Ecchymosis	15	12.0	12	9.5
Metabolic and Nutritional				
Peripheral Edema	14	11.2	7	5.6
Weight gain	7	5.6	0	0
Edema	5	4.0	1	0.8
Musculo-Skeletal				
Arthralgia	31	24.8	22	17.5
Nervous System				
Hypertonia	44	35.2	37	29.4
Tremor	14	11.2	7	5.6
Agitation	7	5.6	4	3.2
Confusion	5	4.0	1	0.8
Nystagmus	5	4.0	2	1.6
Respiratory				
Rhinitis	29	23.2	26	20.6
Dyspnea	23	18.4	8	6.4
Bronchitis	18	14.4	12	9.5
Skin and Appendages				
Sweating	15	12.0	10	7.9
Erythema	8	6.4	4	3.2
Skin Disorder	5	4.0	2	1.6
Skin Nodule	4	3.2	1	0.8
Wart	3	2.4	0	0
Special Senses				
Ear Pain	15	12.0	12	9.5
Eye Disorder	8	6.4	1	0.8
Urogenital System				
Urinary Urgency	20	16.0	17	13.5
Vaginal Moniliasis	16	12.8	9	7.1
Dysmenorrhea	12	9.6	9	7.1
Unintended Pregnancy	4	3.2	0	0
Impotence	3	2.4	0	0

Other events which occurred in at least 2% of patients but were present at equal or greater rates in the placebo group included: *Body as a whole:* Headache, injection site ecchymosis, accidental injury, abdominal pain, allergic rhinitis and malaise. *Digestive System:* Dyspepsia, constipation, dysphagia, fecal incontinence, flatulence, nausea and vomiting, gastritis, gingivitis, periodontal abscess, and dry mouth. *Musculo-Skeletal:* Myasthenia and myalgia. *Nervous System:* Dizziness, hypesthesia, paresthesia, insomnia, depression, dysesthesia, incoordination, somnolence, abnormal gait, amnesia, emotional lability, Lhermitte's sign, abnormal thinking, twitching, euphoria, and sleep disorder. *Respiratory System:* Pharyngitis, sinusitis, increased cough and laryngitis. *Skin and Appendages:* Acne, alopecia, and nail disorder. *Special Senses:* Abnormal vision, diplopia, amblyopia, eye pain, conjunctivitis, tinnitus, taste perversion, and deafness. *Urogenital System:* Urinary tract infection, urinary frequency, urinary incontinence, urinary retention, dysuria, cystitis, metrorrhagia, breast pain, and vaginitis.

Data on adverse events occurring in the controlled clinical trials were analyzed to evaluate gender related differences. No clinically significant differences were identified. In these clinical trials 92% of patients were Caucasian, which is representative of the population of patients with Multiple Sclerosis. In addition, the vast majority of patients treated with COPAXONE® were between the ages of 18 and 45. Consequently, inadequate data are available to perform an analysis of the incidence of adverse events related to clinically relevant age subgroups.

Laboratory analyses were performed on all patients participating in the clinical program for COPAXONE®. Clinically significant changes in laboratory values for hematology, chemistry, and urinalysis were similar for both COPAXONE® and placebo groups in blinded clinical trials. No patient receiving COPAXONE® withdrew from any trial due to abnormal laboratory findings.

Other Adverse Events Observed During All Clinical Trials

COPAXONE® has been administered to approximately 900 individuals during clinical trials, only some of which were placebo-controlled. During these trials, all adverse events were recorded by clinical investigators using terminology of their own choosing. To provide a meaningful estimate of the proportion of individuals having adverse events, similar types of events were grouped into a smaller number of standardized categories using COSTART II dictionary terminology. All reported events that occurred at least twice and potentially important events occurring once, are included except those already listed in the previous table, those too general to be informative, trivial events, and other events which occurred in at least 2% of treated patients and were present at equal or greater rates in the placebo group.

Events are further classified within body system categories and enumerated in order of decreasing frequency using the following definitions: *Frequent* adverse events are defined as those occurring in at least 1/100 patients; *infrequent* adverse events are those occurring in 1/100 to 1/1000 patients. **Body as a whole:** *Frequent:* Injection site edema, injection site atrophy, abscess and injection site hypersensitivity. *Infrequent:* Injection site hematoma, injection site fibrosis, moon face, cellulitis, generalized edema, hernia, injection site abscess, serum sickness, suicide attempt, injection site hypertrophy, injection site melanosis, lipoma and photosensitivity reaction. **Cardiovascular:** *Frequent:* Hypertension. *Infrequent:* Hypotension, midsystolic click, systolic murmur, atrial fibrillation, bradycardia, fourth heart sound, postural hypotension and varicose veins. **Digestive:** *Infrequent:* Dry mouth, stomatitis, burning sensation on tongue, cholecystitis, colitis, esophageal ulcer, esophagitis, gastrointestinal carcinoma, gum hemorrhage, hepatomegaly, increased appetite, melena, mouth ulceration, pancreas disorder, pancreatitis, rectal hemorrhage, tenesmus, tongue discolouration and duodenal ulcer. **Endocrine:** *Infrequent:* Goiter, hyperthyroidism, and hypothyroidism. **Gastrointestinal:** *Frequent:* Bowel urgency, oral moniliasis, salivary gland enlargement, tooth caries, and ulcerative stomatitis. **Hemic and Lymphatic:** *Infrequent:* Leukopenia, anemia, cyanosis, eosinophilia, hematemesis, lymphedema, pancytopenia, and splenomegaly. **Metabolic and Nutritional:** *Infrequent:* Weight loss, alcohol intolerance, Cushing's syndrome, gout, abnormal healing, and xanthoma. **Musculoskeletal:** *Infrequent:* Arthritis, muscle atrophy, bone pain, bursitis, kidney pain, muscle disorder, myopathy, osteomyelitis, tendon pain, and tenosynovitis. **Nervous:** *Frequent:* Abnormal dreams, emotional lability, and stupor. *Infrequent:* Aphasia, ataxia, convulsion, circumoral paresthesia, depersonalization, hallucinations, hostility, hypokinesia, coma, concentration disorder, facial paralysis, decreased libido, manic reaction, memory impairment, myoclonus, neuralgia, paranoid reaction, paraplegia, psychotic depression and transient stupor. **Respiratory:** *Frequent:* Hyperventilation, hay-fever. *Infrequent:* Asthma, pneumonia, epistaxis, hypoventilation, and voice alteration. **Skin and Appendages:** *Frequent:* Eczema, herpes zoster, pustular rash, skin atrophy and warts. *Infrequent:* Dry skin, skin hypertrophy, dermatitis, furunculosis, psoriasis, angioedema, contact dermatitis, erythema nodosum, fungal dermatitis, maculopapular rash, pigmentation, benign skin neoplasm, skin carcinoma, skin striae, and vesiculobullous rash. **Special Senses:** *Frequent:* Visual field defect. *Infrequent:* Dry eyes, otitis externa, ptosis, cataract, corneal ulcer, mydriasis, optic neuritis, photophobia, and taste loss. **Urogenital:** *Frequent:* Amenorrhea, hematuria, impotence, menorrhagia, suspicious Papanicolaou smear, urinary frequency and vaginal hemorrhage. *Infrequent:* Vaginitis, flank pain (kidney), abortion, breast engorgement, breast enlargement, breast pain, carcinoma cervix *in situ*, fibrocystic breast, kidney calculus, nocturia, ovarian cyst, priapism, pyelonephritis, abnormal sexual function, and urethritis.

Adverse Events Reported Post-Marketing and Not Previously Noted in Clinical Trials

Post-marketing experience has shown an adverse event profile similar to that presented above. Reports of adverse reactions occurring under treatment with COPAXONE® (glatiramer acetate for injection) not mentioned above, that have been received since market introduction and that may have or not have causal relationship to the drug include the following:

Body as a whole: Sepsis, LE syndrome, hydrocephalus, enlarged abdomen, injection site hypersensitivity, allergic reaction, anaphylactoid reaction, bacterial infection, fever, infection. **Cardiovascular:** Thrombosis, peripheral vascular disease, pericardial effusion, myocardial infarct, deep thrombophlebitis, coronary occlusion, congestive heart failure, cardiomyopathy cardiomegaly, arrhythmia, angina pectoris, tachycardia. **Digestive:** Tongue edema, stomach ulcer hemorrhage, liver function abnormality, liver damage, hepatitis, eructation, cirrhosis of the liver, cholelithiasis, diarrhea, gastrointestinal disorder. **Hemic and Lymphatic:** Thrombocytopenia, lymphoma-like reaction, acute leukemia. **Metabolic and Nutritional:** Hypercholesteremia. **Musculoskeletal:** Rheumatoid arthritis, generalized spasm. **Nervous:** Myelitis, meningitis, CNS neoplasm, cerebrovascular accident, brain edema, abnormal dreams, aphasia, convulsion, neuralgia, anxiety, foot drop, nervousness, speech disorder, vertigo. **Respiratory:** Pulmonary embolus, pleural effusion, carcinoma of lung, hay fever, laryngismus. **Skin and Appendages:** Herpes simplex, pruritis, rash, urticaria. **Special Senses:** Glaucoma, blindness, visual field defect. **Urogenital:** Urogenital neoplasm, urine abnormality, ovarian carcinoma, nephrosis, kidney failure, breast carcinoma, bladder carcinoma, urinary frequency.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

Overdose with COPAXONE® has been reported in three patients. One patient injected four doses (80 mg total) of COPAXONE® at once. No sequelae were noted. Two other patients, a 28-year old male and a 37-year old female, were given 3 injections of 20 mg of COPAXONE® at one half hour intervals by error. Neither patient evidenced any change in blood pressure, heart rate, or temperature. Telephone follow-up several hours later produced no report of adverse experiences from either patient.

DOSAGE AND ADMINISTRATION

COPAXONE® should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Multiple Sclerosis.

The recommended dose of COPAXONE® (glatiramer acetate for injection or glatiramer acetate injection) for the treatment of relapsing-remitting MS is a daily injection of 20 mg given subcutaneously.

Instructions for Use: To reconstitute lyophilized COPAXONE® for injection, use a sterile syringe and adapter to transfer 1.1 mL of the diluent supplied, Sterile Water for Injection, into the COPAXONE® vial. Gently swirl the vial of COPAXONE® and let stand at room temperature until the solid material is completely dissolved. Inspect the reconstituted product visually and discard or return the product to the pharmacist before use if it contains particulate matter. Use within 8 hours after reconstitution. Withdraw 1.0 mL of the solution into a sterile syringe. Remove the adapter, connect a 27-gauge needle and inject the solution subcutaneously. Sites for self-injection include arms, stomach (abdomen), buttocks, and thighs. A vial is suitable for single use only; unused portions should be discarded (see **INFORMATION FOR THE PATIENT: Reconstituted product**).

For the pre-filled syringe of COPAXONE®, please see the **INFORMATION FOR THE PATIENT: pre-filled syringe** for instructions on the preparation and injection of COPAXONE®.

PHARMACEUTICAL INFORMATION

Drug Substance:

Proper Name: Glatiramer acetate

Chemical Name: Glatiramer acetate is the acetate salt of synthetic polypeptides.

Description: Glatiramer acetate is prepared by chemically reacting the activated derivatives of four amino acids: L-glutamic acid (L-Glu), L-alanine (L-Ala), L-tyrosine (L-Tyr), and L-lysine (L-Lys) in a specified ratio. The molar fraction of each amino acid residue ranges as follows: L-Glu 0.129-0.153, L-Ala 0.392-0.462, L-Tyr 0.086-0.100 and L-Lys 0.300-0.374.

Structural Formula: Poly[L-Glu$^{13-15}$, L-Ala$^{39-46}$, L-Tyr$^{8.6-10}$, L-Lys$^{30-37}$]•nCH$_3$CO$_2$H (n=15-24)

Molecular Weight: The average molecular weight of the polypeptide is between 4,700 and 11,000 daltons, with at least 68 percent of the material within the range of 2,500 to 22,500 daltons.

Physical Form: White to slightly yellowish lyophilized material.

Solubility: Sparingly soluble in water, insoluble in acetone.

pH: The pH of a 0.5% w/v solution of glatiramer acetate in water is in the range of 5.5-8.0.

Composition: COPAXONE® (glatiramer acetate for injection) is a sterile, lyophilized drug product, intended for subcutaneous injection following reconstitution with Sterile Water for Injection. Each vial of lyophilized drug product contains 20 mg glatiramer acetate, plus a 2 mg overage to allow for losses in reconstitution and transfer, and 40 mg mannitol. Each vial of Sterile Water for Injection contains 1.1 mL of Sterile Water for Injection plus a 0.35 mL overage to allow for losses in reconstitution and transfer.

COPAXONE® (glatiramer acetate injection) is a single-use 20 mg/1.0 mL pre-filled syringe containing a sterile solution equivalent with the COPAXONE® reconstituted solution (i.e., 20 mg/mL glatiramer acetate and 40 mg mannitol in sterile water for injection).

Stability and Storage Recommendations: Vials of lyophilized COPAXONE® should be stored under refrigeration (2° - 8°C). COPAXONE® may also be stored at room temperature (15° - 30°C) for up to 14 days. The vials of diluent (Sterile Water for Injection) should be stored at room temperature.

The pre-filled syringes of COPAXONE® should be refrigerated immediately upon receipt (between 2° - 8°C). DO NOT FREEZE. If you cannot have refrigerator storage, pre-filled syringes of COPAXONE® can be stored at room temperature (15° - 30°C) for up to one week. Do not store pre-filled syringes at room temperature for longer than one week. Note: this drug is light sensitive, do not expose to light when not injecting. Each pre-filled syringe is for single use only.

Reconstituted Solutions: To reconstitute lyophilized COPAXONE®, prior to injection, use a sterile syringe and adapter to transfer the diluent supplied, Sterile Water for Injection, into the COPAXONE® vial. Gently swirl the vial of COPAXONE® and let stand at room temperature until the solid material is completely dissolved. Inspect the reconstituted product visually and discard or return the product to the pharmacist if it contains particulate matter. Soon after the product is completely dissolved, withdraw 1.0 mL of the solution into a sterile syringe. Remove the adapter, connect a 27-gauge needle and inject the solution subcutaneously. A vial is suitable for single use only; unused portions should be discarded. The reconstituted solution should not be left longer than 8 hours at room temperature.

Parenteral Products: COPAXONE® should be reconstituted only with the provided diluent, Sterile Water for Injection.

Vial Size	Volume of Diluent to be Added	Volume to be Injected	Nominal Concentration per mL
2 mL	1.1 mL	1.0 mL	20 mg

AVAILABILITY OF DOSAGE FORMS

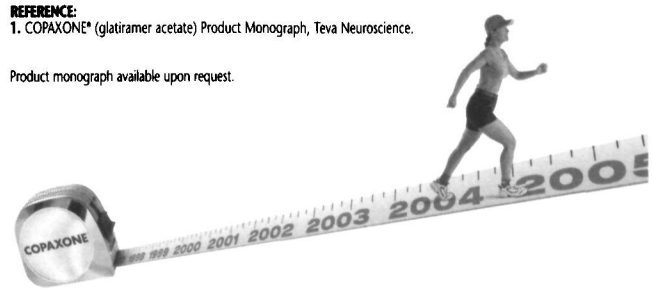
COPAXONE® (glatiramer acetate for injection) is supplied as a 20 mg dose of sterile lyophilized glatiramer acetate with mannitol, packaged in single use 2 mL amber vials. A separate vial, containing 1.1 mL of diluent (Sterile Water for Injection) plus 0.35 mL of overage of diluent is included in the Self Injection Administration Package for each vial of drug. COPAXONE® (glatiramer acetate for injection) is available in packs of 32 amber vials of sterile lyophilized material for subcutaneous injection. The diluent (Sterile Water for Injection) for COPAXONE® is supplied in packs of 32 clear vials and is located in the Self Injection Administration Package.

COPAXONE® (glatiramer acetate injection) is a single-use 20 mg/1.0 mL pre-filled syringe containing a sterile solution equivalent with the COPAXONE® reconstituted solution (i.e., 20 mg/mL glatiramer acetate and 40 mg mannitol in sterile water for injection). COPAXONE® (glatiramer acetate injection) is available in packs of 30 single-use 20 mg/1.0 mL pre-filled glass syringes with 33 alcohol preps (swabs).

REFERENCE:

1. COPAXONE® (glatiramer acetate) Product Monograph, Teva Neuroscience.

Product monograph available upon request.



TEVA NEUROSCIENCE
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PAAB

See page A-5

PrLYRICA* PREGABALIN

SUMMARY PRODUCT

Classification

Analgesic Agent

Route of Administration	Dosage Form / Strength	Clinically Relevant Nonmedicinal Ingredients
Oral	Capsules, 25 mg, 50 mg, 75 mg, 150 mg, 300 mg	Lactose monohydrate For a complete listing, see Dosage Forms, Composition and Packaging section.

INDICATIONS AND CLINICAL USE

Adults: LYRICA (pregabalin) is indicated for the management of neuropathic pain associated with:

- Diabetic peripheral neuropathy and
- Postherpetic neuralgia

Geriatrics (>65 years of age): Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function. (see **WARNINGS AND PRECAUTIONS,** Geriatrics [>65 years of age])

Pediatrics (<18 years of age): The safety and efficacy of pregabalin in pediatric patients (<18 years of age) have not been established and its use in this patient population is not recommended (see **WARNINGS AND PRECAUTIONS,** Pediatrics).

CONTRAINDICATIONS

Patients who are hypersensitive to pregabalin or to any ingredient in the formulation or component of the container.

WARNINGS AND PRECAUTIONS

Tumorigenic Potential

In standard preclinical in vivo lifetime carcinogenicity studies of pregabalin, a high incidence of hemangiosarcoma was identified in two different strains of mice (see **Preclinical Toxicology**). The clinical significance of this finding is uncertain. Clinical experience during pregabalin's premarketing development provides no direct means to assess its potential for inducing tumors in humans.

In clinical studies across various patient populations, comprising 6396 patient-years of exposure in 8666 patients ranging in age from 12 to 100 years, new or worsening-preexisting tumors were reported in 57 patients. The most common malignant tumor diagnosed was skin carcinoma (17 patients) followed by breast carcinoma (8 patients), prostatic carcinoma (6 patients), carcinoma not otherwise specified (6 patients) and bladder carcinoma (4 patients). Without knowledge of the background incidence and recurrence in similar populations not treated with LYRICA (pregabalin), it is impossible to know whether the incidence seen in these cohorts is or is not affected by treatment.

Ophthalmological Effects

In controlled studies, pregabalin treatment was associated with vision-related adverse events such as blurred vision (amblyopia) (6% pregabalin and 2% placebo) and diplopia (2% pregabalin and 0.5% placebo). Approximately 1% of pregabalin-treated patients discontinued treatment due to vision-related adverse events (primarily blurred vision). Of the patients who did not withdraw, the blurred vision resolved with continued dosing in approximately half of the cases (see **Post-Marketing Adverse Drug Reactions**).

Prospectively planned ophthalmologic testing, including visual acuity testing, formal visual field testing and dilated funduscopic examination, was performed in over 3600 patients. In these patients, visual acuity was reduced in 7% of patients treated with pregabalin, and 5% of placebo-treated patients. Visual field changes were detected in 13% of pregabalin-treated, and 12% of placebo-treated patients. Funduscopic changes were observed in 2% of pregabalin-treated, and 2% of placebo-treated patients. At this time, clinical significance of the ophthalmologic findings is unknown.

Patients should be informed that if changes in vision occur, they should notify their physician. If visual disturbance persists, further assessment, including discontinuation of pregabalin, should be considered. More frequent assessments should be considered for patients who are already routinely monitored for ocular conditions.

Peripheral Edema

In controlled clinical trials pregabalin treatment caused peripheral edema in 6% of patients (336/5608) compared with 2% of patients (42/2384) in the placebo group. In these studies, 0.5% (28/5508) of pregabalin patients and 0.2% (4/2384) of placebo patients withdrew due to peripheral edema (see **ADVERSE REACTIONS**, Peripheral Edema).

In controlled clinical trials of up to 13 weeks in duration of patients without clinically significant heart or peripheral vascular disease, there was no apparent association between peripheral edema and cardiovascular complications such as hypertension or congestive heart failure. In the same trials, peripheral edema was not associated with laboratory changes suggestive of deterioration in renal or hepatic function.

Higher frequencies of weight gain and peripheral edema were observed in patients taking both LYRICA (pregabalin) and a thiazolidinedione antidiabetic agent compared to patients taking either drug alone. The majority of patients using thiazolidinedione antidiabetic agents in the overall safety database were participants in studies of pain associated with diabetic peripheral neuropathy. In this population, peripheral edema was reported in 3% (2/60) of patients who were using thiazolidinedione antidiabetic agents only, 8% (69/859) of patients who were treated with pregabalin only, and 15% (23/120) of patients who were on both pregabalin and thiazolidinedione antidiabetic agents. Similarly, weight gain was reported in 0% (0/60) of patients on thiazolidinediones only; 4% (35/859) of patients on pregabalin only; and 7.5% (9/120) of patients on both drugs.

As the thiazolidinedione class of antidiabetic drugs can cause weight gain and/or fluid retention, possibly exacerbating or leading to heart failure, care should be taken when co-administering LYRICA and these agents.

Because there are limited data on congestive heart failure patients with New York Heart Association (NYHA) Class III or IV cardiac status, LYRICA should be used with caution in these patients.

Weight Gain

Pregabalin treatment was associated with weight gain. In pregabalin controlled clinical trials of up to 13 weeks, a gain of 7% or more over baseline weight was observed in 8% of pregabalin-treated patients and 2% of placebo-treated patients. Few patients treated with pregabalin (0.2%) withdrew from controlled trials due to weight gain (see **ADVERSE REACTIONS**, **Weight Gain**). Pregabalin associated weight gain was related to dose and duration of exposure, but did not appear to be associated with baseline BMI, gender or age. Weight gain was not limited to patients with edema (see **WARNINGS AND PRECAUTIONS, Peripheral Edema**).

Although weight gain was not associated with clinically important changes in blood pressure in short-term controlled studies, the long-term cardiovascular effects of pregabalin-associated weight gain are unknown.

Among diabetic patients, pregabalin-treated patients gained an average of 1.6 kg (range: -16 to 16 kg), compared to an average 0.3 kg (range: -10 to 9 kg) weight gain in placebo patients. In a cohort of 333 diabetic patients who received pregabalin for at least 2 years, the average weight gain was 5.2 kg.

While the effects of pregabalin-associated weight gain on glycemic control have not been systematically assessed, in controlled and longer-term open label clinical trials with diabetic patients, pregabalin treatment did not appear to be associated with loss of glycemic control (as measured by HbA_{1c}).

Dizziness and Somnolence

In controlled neuropathic pain studies, pregabalin caused dizziness in 23% of patients (424/1831) compared to 7% in placebo (58/857). Somnolence was experienced by 14% (256/1831) and 4% (33/857) of the patients treated with pregabalin and placebo, respectively. These events begin shortly after the initiation of therapy and generally occur more frequently at higher doses. In these studies, dizziness and somnolence led to withdrawal of 3.5% and 2.6% of the pregabalin-treated patients, respectively. For the remaining patients (359 and 208, respectively) who experienced these events, dizziness and somnolence persisted until the last dose of pregabalin in 43% and 58% of the patients, respectively (see **ADVERSE REACTIONS**, Tables 2 and 4, and **Post-Marketing Adverse Drug Reactions**).

Accordingly, patients should be advised not to drive or operate complex machinery or engage in other hazardous activities until they have gained sufficient experience on pregabalin to gauge whether or not it affects their mental and/or motor performance adversely (see **CONSUMER INFORMATION**).

Abrupt or Rapid Discontinuation

Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache and diarrhea. Pregabalin should be tapered gradually over a minimum of one week rather than discontinued abruptly (see **ADVERSE REACTIONS**, Adverse Events Following Abrupt or Rapid Discontinuation).

Sexual Function/Reproduction

Impairment of Male Fertility

Preclinical Data

In fertility studies in which male rats were orally administered pregabalin (50 to 2500 mg/kg) prior to and during mating with untreated females, a number of adverse reproductive and developmental effects were observed. These included decreased sperm counts and sperm motility, increased sperm abnormalities, reduced fertility, increased preimplantation embryo loss, decreased litter size, decreased fetal body weights and an increased incidence of fetal abnormalities. Effects on sperm and fertility parameters were reversible in studies of this duration (3-4 months). The no-effect dose for male reproductive toxicity in these studies (100 mg/kg) was associated with a plasma pregabalin exposure (AUC) approximately 3 times human exposure at the maximum recommended dose (MRD) of 600 mg/day.

In addition, adverse effects on reproductive organ (testes, epididymides) histopathology were observed in male rats exposed to pregabalin (500 to 1250 mg/kg) in general toxicology studies of four weeks or greater duration. The no-effect dose for male reproductive organ histopathology in rats (250 mg/kg) was associated with a plasma exposure approximately 8 times human exposure at the MRD.

In a fertility study in which female rats were given pregabalin (500, 1250 or 2500 mg/kg) orally prior to and during mating and early gestation, disrupted estrous cyclicity and an increased number of days to mating were seen at all doses and embryolethality occurred at the highest dose. The low dose in this study produced a plasma exposure approximately 9 times that in humans receiving the MRD. A no-effect dose for female reproductive toxicity in rats was not established. The clinical significance of female fertility findings in animals is unknown.

Human Data

In a double-blind, placebo-controlled clinical trial to assess the effect of pregabalin on sperm motility, 30 healthy male subjects were exposed to pregabalin 600 mg/day for 3 months (one complete sperm cycle). Pregabalin did not exhibit significant detrimental effects on the reproductive function of healthy male subjects, as measured by semen analysis, when compared with placebo (n=16). However, due to the small sample size and short-term exposure to pregabalin (only one complete sperm cycle), no conclusions can be made regarding possible reproductive effects of pregabalin during long-term exposure. Effects on other male reproductive parameters in humans have not been adequately studied.

Special Populations

Renal

Because pregabalin is eliminated primarily by renal excretion, the dose of pregabalin should be adjusted as noted for elderly patients with renal impairment (see **ACTION AND CLINICAL PHARMACOLOGY** and **DOSAGE AND ADMINISTRATION**).

Adjustment of Dose in Renally-Impaired Patients

In patients with a medical history of significant renal insufficiency, daily dosages should be reduced accordingly (see Table in **DOSAGE AND ADMINISTRATION, Dosing Considerations**).

Preclinical Data

Pregabalin was not teratogenic in mice, rats or rabbits. Pregabalin induced fetal toxicity in rats and rabbits at ≥39 times the mean human exposure at the maximum recommended clinical dose of 600 mg/day [$AUC_{0\text{-}24}$ of 123 µg•hr/mL]. In the prenatal-postnatal toxicity study, pregabalin induced offspring developmental toxicity in rats at ≥5 times the maximum recommended human exposure. No developmental effects occurred at 2 times the maximum recommended human exposure (see **PRODUCT MONOGRAPH**).

Human Data

Pregnant Women

There are no adequate and well-controlled studies in pregnant women. Pregabalin should be used during pregnancy only if the potential benefit justifies the potential risk to the fetus.

Labour and Delivery

The effects of pregabalin on labour and delivery in pregnant women are unknown. In the prenatal-postnatal study in rats, pregabalin prolonged gestation and induced dystocia at exposures ≥47 times the mean human exposure [$AUC_{0\text{-}24}$ of 123 µg•hr/mL] at the maximum recommended clinical dose of 600 mg/day (see **PRODUCT MONOGRAPH**).

Nursing Women

It is not known if pregabalin is excreted in human breast milk; however, it is present in the milk of rats. Because of the potential for adverse reactions in nursing infants from pregabalin, a decision should be made whether to discontinue nursing or to discontinue the drug, taking into account the importance of the drug to the mother (see **PRODUCT MONOGRAPH**).

Pediatrics (<18 years of age)

The safety and efficacy of pregabalin in pediatric patients (<18 years of age) have not been established.

Geriatrics (>65 years of age)

Of the 1831 patients who received pregabalin in neuropathic pain studies, 528 were 65 to 74 years of age, and 452 were 75 years of age or older. No significant differences in efficacy were observed between these patients and younger patients. Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function. In general, the incidence of adverse events did not increase with age.

Creatine Kinase Elevations

Pregabalin treatment was associated with creatine kinase elevations. Mean changes in creatine kinase from baseline to the maximum value were 60 U/L for pregabalin-treated patients and 28 U/L for the placebo patients. In all controlled trials across multiple patient populations, 2% of patients on pregabalin and 1% of placebo patients had a value of creatine kinase at least three times the upper limit of normal. Three pregabalin-treated subjects had events reported as rhabdomyolysis in premarketing clinical trials. The relationship between these myopathy events and pregabalin is not completely understood because the cases had documented factors that may have caused or contributed to these events. Prescribers should instruct patients to promptly report unexplained muscle pain, tenderness or weakness, particularly if these muscle symptoms are accompanied by malaise or fever. Pregabalin treatment should be discontinued if myopathy is diagnosed or suspected or if markedly elevated creatine kinase levels occur.

Laboratory Changes, Decreased Platelet Count

Pregabalin treatment was associated with a decrease in platelet count. Pregabalin-treated subjects experienced a mean maximal decrease in platelet count of 20 x 10^3/µL, compared to 11 x 10^3/µL in placebo patients. In the overall database of controlled trials, 2% of placebo patients and 3% of pregabalin patients experienced a potentially clinically significant decrease in platelets, defined as 20% below baseline value and <150 x 10^3/µL.

In randomized controlled trials, pregabalin was not associated with an increase in bleeding related adverse events.

ECG Changes, PR Interval Prolongation

Pregabalin treatment was associated with mild PR interval prolongation. In analyses of clinical trial ECG data, the mean PR interval increase was 3-6 msec at pregabalin doses ≥300 mg/day. This mean change difference was not associated with an increased risk of PR increase ≥25% from baseline, an increased percentage of subjects with on-treatment PR >200 msec, or an increased risk of adverse events of second or third degree AV block.

Information for Patients

Dizziness and Somnolence

Patients should be counseled that LYRICA (pregabalin) may cause dizziness, somnolence, blurred vision and other CNS signs and symptoms. Accordingly, they should be advised not to drive, operate complex machinery or engage in other hazardous activities until they have gained sufficient experience on pregabalin to gauge whether or not it affects their mental, visual and/or motor performance adversely.

Visual Disturbances

Patients should be counseled that LYRICA may cause visual disturbances. Patients should be informed that if changes in vision occur, they should notify their physician (see **WARNINGS AND PRECAUTIONS, Ophthalmologic Effects**).

Abrupt or Rapid Discontinuation

Patients should be advised to take LYRICA as prescribed. Abrupt or rapid discontinuation may result in insomnia, nausea, headache or diarrhea.

Edema and Weight Gain

Patients should be counseled that LYRICA may cause edema and weight gain.

Patients should be advised that concomitant treatment with LYRICA and a thiazolidinedione antidiabetic agent may lead to an additive effect on edema and weight gain. For patients with preexisting cardiac conditions, this may increase the risk of heart failure.

Muscle Pain, Tenderness or Weakness

Patients should be instructed to promptly report unexplained muscle pain, tenderness or weakness, particularly if accompanied by malaise or fever.

Concomitant Treatment with CNS Depressants, Alcohol

Patients who require concomitant treatment with central nervous system depressants such as opiates or benzodiazepines should be informed that they may experience additive CNS side effects, such as somnolence.

Patients should be told to avoid consuming alcohol while taking LYRICA, as LYRICA may potentiate the impairment of motor skills and sedation of alcohol.

Pregnant Woman

Patients should be instructed to notify their physician if they become pregnant or intend to become pregnant during therapy, and to notify their physician if they are breast-feeding or intend to breast-feed during therapy.

Animal Studies in Male Reproduction

In preclinical studies in rats, pregabalin was associated with an increased risk of male-mediated teratogenicity (see **WARNINGS AND PRECAUTIONS, Sexual Function/Reproduction**). The clinical significance of this finding is uncertain; however, men being treated with LYRICA who plan to father a child should be informed of the potential risk of male-mediated teratogenicity.

Skin

Diabetic patients should be instructed to pay particular attention to skin integrity while being treated with LYRICA. Some animals treated with pregabalin developed skin ulcerations, although no increased incidence of skin lesions associated with LYRICA was observed in clinical trials (see **PRODUCT MONOGRAPH**).

Patients should be informed of the availability of a patient information leaflet, and they should be instructed to read the leaflet prior to taking LYRICA.

Preclinical Toxicology

Carcinogenesis

A dose-dependent increase in the incidence of malignant vascular tumors (hemangiosarcomas) was observed in two strains of mice (B6C3F1 and CD-1) given pregabalin (200, 1000 or 5000 mg/kg) in the diet for two years. Plasma pregabalin exposure (AUC) in mice receiving the lowest dose that increased hemangiosarcomas was approximately equal to the human exposure at the maximum recommended dose (MRD) of 600 mg/day. A no-effect dose for induction of hemangiosarcomas in mice was not established. In an investigative study in female B6C3F1 mice, chronic treatment (24 months) with pregabalin at 1000 mg/kg caused an increased incidence of hemangiosarcoma, consistent with previous studies, but not at 50 or 200 mg/kg. Discontinuation of treatment after 12 months at 1000 mg/kg did not significantly reduce the incidence of hemangiosarcoma at 24 months. Evidence of carcinogenicity was not seen in two studies in Wistar rats following dietary administration of pregabalin for two years at doses (50, 150 or 450 mg/kg in males and 100, 300 or 900 mg/kg in females) that were associated with plasma exposures in males and females up to approximately 14 and 24 times, respectively, human exposure at the MRD. The clinical significance in humans of this finding in mice is unknown.

Mutagenesis

Pregabalin is not genotoxic based on results of a battery of in vitro and in vivo tests. Pregabalin was not mutagenic in bacteria or in mammalian cells in vitro, was not clastogenic in mammalian systems in vitro and in vivo, and did not induce unscheduled DNA synthesis in mouse or rat hepatocytes.

Dermatopathy

Skin lesions ranging from erythema to necrosis were seen in repeated-dose toxicology studies in both rats and monkeys. The etiology of these skin lesions is unknown. At the maximum recommended human dose (MRD) of 600 mg/day, there is a 2-fold safety margin for the dermatological lesions. The more severe dermatopathies involving

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necrosis were associated with pregabalin exposures (as expressed by plasma AUCs) of approximately 3 to 8 times those achieved in humans given the MRD. No increase in incidence of skin lesions was observed in clinical studies.

Ocular lesions

Ocular lesions (characterized by retinal atrophy [including loss of photoreceptor cells] and/or corneal inflammation/mineralization) were observed in two lifetime carcinogenicity studies in Wistar rats. These findings were observed at plasma pregabalin exposures (AUC) ≥2 times those achieved in humans given the maximum recommended dose of 600 mg/day. A no-effect dose for ocular lesions was not established. Similar lesions were not observed in lifetime carcinogenicity studies in two strains of mice or in monkeys treated for 1 year. The clinical significance of this finding in rats is unknown.

Monitoring and Laboratory Tests

Routine therapeutic drug monitoring or clinical laboratory testing is not required for patients treated with LYRICA (pregabalin) (see **ADVERSE REACTIONS**).

ADVERSE REACTIONS

Adverse Drug Reaction Overview

Clinical Trial Adverse Drug Reactions

In all controlled and uncontrolled trials, more than 8666 patients have received LYRICA (pregabalin), with 83% of exposure at dosages of 300 mg/day or above and 32% at dosages of 600 mg/day or higher. Approximately 4010 patients had at least 6 months of exposure, 2415 had at least 1 year of exposure, and 939 had at least 2 years of exposure to pregabalin. In controlled trials, 1831 patients with neuropathic pain received pregabalin.

Most Common Adverse Events in All Controlled Clinical Studies of Neuropathic Pain

The most commonly observed adverse events (≥5% and twice the rate of that seen in placebo) in pregabalin-treated patients were: dizziness, somnolence, peripheral edema and dry mouth. Adverse events were usually mild to moderate in intensity.

Discontinuation Due to Adverse Events

In all controlled studies, the discontinuation rate due to adverse events was 14% for patients receiving pregabalin and 7% for patients receiving placebo. The most common reasons for discontinuation due to adverse events (≥2%) in the pregabalin treatment groups were dizziness and somnolence. Other adverse events that led to withdrawal more frequently in the pregabalin group than the placebo group were ataxia (1%) and asthenia, confusion, headache and nausea (<1% each).

In controlled neuropathic pain studies, the discontinuation rate due to adverse events was 11% for pregabalin and 5% for placebo. The most common reasons for discontinuation due to adverse events (≥2%) in the pregabalin treatment groups were dizziness and somnolence. Other adverse events that led to withdrawal more frequently in the pregabalin group than the placebo group were confusion (1%) and asthenia, peripheral edema and ataxia (<1% each).

Incidence of Adverse Events in Controlled Clinical Studies of Neuropathic Pain

In summaries of adverse events, investigator's terms for individual adverse events have been grouped into a smaller number of standardized categories using the COSTART IV dictionary. The prescriber should be aware that the percentages in Table 1 through Table 6 cannot be used to predict the frequency of adverse events in the course of usual medical practice where patient characteristics and other factors may differ from those prevailing during clinical studies. Similarly, the cited frequencies cannot be directly compared with figures obtained from other clinical investigations involving different treatments, uses or investigators. An inspection of these frequencies, however, does provide the prescriber with one basis to estimate the relative contribution of drug and non-drug factors to the adverse event incidences in the population studied.

Adverse Events From Controlled Clinical Studies of Neuropathic Pain

Diabetic Peripheral Neuropathy

Table 1 lists all adverse events, regardless of causality, occurring in ≥2% of patients with neuropathic pain associated with diabetic peripheral neuropathy receiving pregabalin for at least one of the pregabalin groups, and for which the incidence was greater than in the placebo group. A majority of pregabalin-treated patients in these studies had adverse events with a maximum intensity of mild or moderate. In these studies, 979 patients received pregabalin and 459 patients received placebo for up to 13 weeks.

Table 1. Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled Studies in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy (Events in at Least 2% of Patients Receiving Pregabalin and More Frequent Than in Placebo-Treated Patients)

		Pregabalin (mg/day)			
Body System Preferred Term	Placebo (n = 459) %	75 (n = 77) %	150 (n = 212) %	300 (n = 321) %	600 (n = 369) %
Body as a whole					
Infection	6.1	3.9	7.5	8.4	4.6
Asthenia	2.4	3.9	1.9	4.4	7.3
Pain	3.9	5.2	4.2	2.5	4.9
Accidental injury	2.8	5.2	2.4	2.2	5.7
Back pain	0.4	0.0	2.4	1.2	1.9
Chest pain	1.1	3.9	1.4	1.2	1.6
Face edema	0.4	0.0	0.9	0.9	2.2
Digestive system					
Dry mouth	1.1	2.6	1.9	4.7	6.5
Constipation	1.5	0.0	2.4	3.7	6.0
Diarrhea	4.8	5.2	2.8	1.9	3.0
Flatulence	1.3	2.6	0.0	2.2	2.7
Vomiting	1.5	1.3	0.9	2.2	1.1
Hemic and lymphatic system					
Ecchymosis	0.2	2.6	0.5	0.6	0.3
Metabolic and nutritional disorders					
Peripheral edema	2.4	3.9	6.1	9.3	12.5
Weight gain	0.4	0.0	4.2	3.7	6.2
Edema	0.0	0.0	1.9	4.0	1.9
Hypoglycemia	1.1	1.3	3.3	1.6	1.1
Nervous system					
Dizziness	4.6	7.8	9.0	23.1	29.0
Somnolence	2.6	3.9	6.1	13.1	16.3
Neuropathy	3.5	9.1	1.9	2.2	5.4
Ataxia	1.3	6.5	0.9	2.2	4.3
Vertigo	1.1	1.3	1.9	2.5	3.5
Confusion	0.7	0.0	1.4	2.2	3.3
Euphoria	0.0	0.0	0.5	3.4	1.6
Thinking abnormal[a]	0.0	1.3	0.0	0.9	3.0
Abnormal gait	0.0	1.3	0.0	0.6	2.7
Reflexes decreased	1.7	3.9	0.5	1.2	1.4
Amnesia	0.2	2.6	0.9	0.0	2.2
Hypesthesia	0.7	2.6	0.0	0.0	0.8
Hyperalgesia	0.2	2.6	0.0	0.0	0.3
Respiratory system					
Dyspnea	0.7	2.6	0.0	1.9	1.9
Skin and appendages					
Pruritus	1.3	2.6	0.0	0.9	0.0
Special senses					
Blurred vision[b]	1.5	2.6	1.4	2.8	1.5
Conjunctivitis	0.2	2.6	1.4	0.6	0.3

a Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slow thinking.
b Investigator term; summary level term is amblyopia.

Discontinuation in Controlled Clinical Studies of Diabetic Peripheral Neuropathy

Approximately 9% of patients receiving pregabalin and 4% receiving placebo discontinued from controlled diabetic peripheral neuropathy studies due to adverse events. The adverse events most commonly leading to discontinuation are presented in Table 2.

Table 2. Adverse Events Most Frequently (≥2% of patients) Leading to Discontinuation in Placebo-Controlled Studies in Patients with Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

	Number (%) of Patients				
		Pregabalin (mg/day)			
COSTART Preferred Term	Placebo (n = 459)	75 (n = 77)	150 (n = 212)	300 (n = 321)	600 (n = 369)
Dizziness	2 (0.4)	0 (0.0)	3 (1.4)	6 (1.9)	21 (5.7)
Somnolence	0 (0.0)	0 (0.0)	0 (0.0)	5 (1.6)	15 (4.1)

Postherpetic Neuralgia

Table 3 lists all adverse events, regardless of causality, occurring in ≥2% of patients with neuropathic pain associated with postherpetic neuralgia receiving pregabalin for at least one of the pregabalin groups, and for which the incidence was greater than in the placebo group. A majority of pregabalin-treated patients in these studies had adverse events with a maximum intensity of mild or moderate. In these studies, 852 patients received pregabalin and 398 patients received placebo for up to 13 weeks.

Table 3. Incidence (%) of Treatment-Emergent Adverse Events in Placebo-Controlled Studies in Neuropathic Pain Associated with Postherpetic Neuralgia (Events in at Least 2% of Patients Receiving Pregabalin and More Frequent Than in Placebo-Treated Patients)

		Pregabalin (mg/day)			
Body System Preferred Term	Placebo (n = 398) %	75 (n = 84) %	150 (n = 302) %	300 (n = 312) %	600 (n = 154) %
Body as a whole					
Infection	3.5	14.3	8.3	6.4	2.6
Headache	5.3	4.8	8.9	4.5	8.4
Pain	3.8	4.8	4.3	5.4	4.5
Asthenia	4.0	3.6	5.0	2.6	5.2
Accidental injury	1.5	3.6	2.6	3.2	5.2
Flu syndrome	1.3	1.2	1.7	2.2	1.3
Face edema	0.8	0.0	1.7	1.3	3.2
Malaise	1.0	2.4	0.3	0.6	0.0
Cardiovascular system					
Vasodilatation	1.3	2.4	1.0	0.6	0.0
Digestive system					
Dry mouth	2.8	7.1	7.0	6.1	14.9
Constipation	2.3	3.6	4.6	5.4	5.2
Diarrhea	4.0	2.4	4.3	3.5	4.5
Flatulence	1.0	2.4	1.3	1.6	3.2
Vomiting	0.8	1.2	0.7	2.9	2.6
Metabolic and nutritional disorders					
Peripheral edema	3.5	0.0	7.9	15.7	16.2
Weight gain	0.3	1.2	1.7	5.4	6.5
Edema	1.3	0.0	1.0	2.2	5.8
Hyperglycemia	0.8	2.4	0.3	0.0	0.0
Nervous system					
Dizziness	9.3	10.7	17.9	31.4	37.0
Somnolence	5.3	8.3	12.3	17.9	24.7
Ataxia	0.5	1.2	2.0	5.4	9.1
Abnormal gait	0.5	0.0	2.0	3.8	7.8
Confusion	0.3	1.2	2.3	2.9	6.5
Thinking abnormal[a]	1.5	0.0	1.7	1.3	5.8
Incoordination	0.0	2.4	1.7	1.3	2.6
Amnesia	0.0	0.0	1.0	1.3	3.9
Speech disorder	0.0	0.0	0.3	1.3	3.2
Insomnia	1.8	0.0	0.7	2.2	0.0
Euphoria	0.0	2.4	0.0	1.3	1.3
Nervousness	0.5	0.0	1.0	0.3	2.6
Tremor	1.5	1.2	0.0	1.0	2.6
Hallucinations	0.0	0.0	0.3	0.3	3.2
Hyperesthesia	0.3	2.4	0.3	0.0	1.3
Respiratory system					
Bronchitis	0.8	0.0	1.3	1.0	2.6
Pharyngitis	0.8	0.0	2.6	0.6	0.6
Rhinitis	1.8	1.2	0.7	0.6	3.2
Skin and appendages					
Rash	3.0	2.4	2.0	2.9	5.2
Special senses					
Blurred vision[b]	2.5	1.2	5.0	5.1	9.1
Diplopia	0.0	0.0	1.7	1.9	3.9
Abnormal vision	0.3	0.0	1.0	1.6	5.2
Urogenital system					
Urinary tract infection	1.5	0.0	2.3	1.6	3.2

a Thinking abnormal primarily consists of events related to difficulty with concentration/attention but also includes events related to cognition and language problems and slow thinking.
b Investigator term; summary level term is amblyopia.

Discontinuation in Controlled Clinical Studies of Postherpetic Neuralgia

Approximately 14% of patients receiving pregabalin and 7% receiving placebo discontinued from controlled postherpetic neuralgia studies due to adverse events. The adverse events most commonly leading to discontinuation are presented in Table 4.

Table 4. Adverse Events Most Frequently (≥2% of patients) Leading to Discontinuation in Placebo-Controlled Studies in Patients with Neuropathic Pain Associated with Postherpetic Neuralgia

	Number (%) of Patients				
		Pregabalin (mg/day)			
COSTART Preferred Term	Placebo (n = 398)	75 (n = 84)	150 (n = 302)	300 (n = 312)	600 (n = 154)
Dizziness	3 (0.8)	0 (0.0)	11 (3.6)	12 (3.8)	12 (7.8)
Somnolence	1 (0.3)	0 (0.0)	6 (2.0)	12 (3.8)	10 (6.5)
Confusion	1 (0.3)	0 (0.0)	2 (0.7)	5 (1.6)	8 (5.2)
Peripheral edema	1 (0.3)	0 (0.0)	2 (0.7)	5 (1.6)	5 (3.2)
Ataxia	0 (0.0)	0 (0.0)	1 (0.3)	5 (1.6)	4 (2.6)
Abnormal gait	0 (0.0)	0 (0.0)	0 (0.0)	4 (1.3)	4 (2.6)
Hallucinations	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.3)	4 (2.6)
Dry mouth	1 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	4 (2.6)

Incidence of Most Common Dose-Related Treatment-Emergent Adverse Events

Most common dose-related treatment-emergent adverse events are presented in Table 5 (diabetic peripheral neuropathy) and Table 6 (postherpetic neuralgia).

Table 5. Incidence (%) of Most Common Dose-Related Treatment-Emergent Adverse Events in Placebo-Controlled Studies in Neuropathic Pain Associated with Diabetic Peripheral Neuropathy

		Pregabalin (mg/day)			
Adverse Event Preferred Term	Placebo (n = 459) %	75 (n = 77) %	150 (n = 212) %	300 (n = 321) %	600 (n = 369) %
Dizziness	4.6	7.8	9.0	23.1	29.0
Somnolence	2.6	3.9	6.1	13.1	16.3
Peripheral edema	2.4	3.9	6.1	9.3	12.5
Asthenia	2.4	3.9	1.9	4.4	7.3
Dry mouth	1.1	2.6	1.9	4.7	6.5
Weight gain	0.4	0.0	4.2	3.7	6.2
Constipation	1.5	0.0	2.4	3.7	6.0
Blurred vision[a]	1.5	2.6	1.4	2.8	5.7

a Investigator term; summary level term is amblyopia.

Table 6. Incidence (%) of Most Common Dose-Related Treatment-Emergent Adverse Events in Placebo-Controlled Studies in Neuropathic Pain Associated with Postherpetic Neuralgia

		Pregabalin (mg/day)			
Adverse Event Preferred Term	Placebo (n = 398) %	75 (n = 84) %	150 (n = 302) %	300 (n = 312) %	600 (n = 154) %
Dizziness	9.3	10.7	17.9	31.4	37.0
Somnolence	5.3	8.3	12.3	17.9	24.7
Peripheral edema	3.5	0.0	7.9	15.7	16.2
Dry mouth	2.8	7.1	7.0	6.1	14.9
Blurred vision[a]	2.5	1.2	5.0	5.1	9.1
Ataxia	0.5	1.2	2.0	5.4	9.1
Weight gain	0.3	1.2	1.7	5.4	6.5
Abnormal gait	0.5	0.0	2.0	3.8	7.8

a Investigator term; summary level term is amblyopia.

Adverse Events Following Abrupt or Rapid Discontinuation

Following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache and diarrhea. Pregabalin should be tapered gradually over a minimum of one week rather than discontinued abruptly (see **WARNINGS AND PRECAUTIONS, Abrupt or Rapid Discontinuation**).

Drug Abuse and Dependence/Liability

In a study of recreational users (n=15) of sedative/hypnotic drugs, including alcohol, a single dose of LYRICA (pregabalin) 450 mg received subjective ratings of "good drug effect", "high", and "liking" to a degree that was similar to a single dose of diazepam 30 mg. In controlled clinical studies in over 5500 patients, 4% of LYRICA-treated patients and 1% of placebo-treated patients overall reported euphoria as an adverse event. However, in clinical trials of diabetic peripheral neuropathy, euphoria was reported as an adverse event by 1.8% of LYRICA-treated patients and 0% of placebo-treated patients, and in clinical trials of postherpetic neuralgia, euphoria was reported as an adverse event by 0.9% of LYRICA-treated patients and 0% of placebo-treated patients. In clinical studies, following abrupt or rapid discontinuation of pregabalin, some patients reported symptoms including insomnia, nausea, headache or diarrhea suggestive of physical dependence (see **WARNINGS AND PRECAUTIONS, Abrupt or Rapid Discontinuation**).

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Pregabalin is not known to be active at receptor sites associated with drugs of abuse. As with any CNS active drug, physicians should carefully evaluate patients for history of drug abuse and observe them for signs of LYRICA misuse or abuse (e.g., development of tolerance, dose escalation, drug-seeking behaviour).

Other Events Observed During the Premarketing Evaluation of LYRICA

Following is a list of treatment-emergent adverse events reported during premarketing assessment of LYRICA in clinical trials (over 8600 adult subjects) except those already listed in the previous tables or elsewhere in labeling. In the tabulations that follow, a COSTART-based dictionary of terminology has been used to classify reported adverse events. The frequencies presented, therefore, represent the proportion of the over 8600 adult individuals exposed to multiple doses of LYRICA who experienced an event of the type cited on at least 1 occasion while receiving LYRICA. It is important to emphasize that although the events reported occurred during treatment with LYRICA, they were not necessarily caused by it.

Less Common Clinical Trial Adverse Drug Reactions (<2%)

Events are further categorized by body system and listed in order of decreasing frequency according to the following definitions: frequent adverse events are those occurring on 1 or more occasions in at least 1/100 patients; infrequent adverse events are those occurring in 1/100 to 1/1000 patients; rare events are those occurring in fewer than 1/1000 patients.

Body System	Adverse Events
Body as a whole	
Frequent	Flu syndrome, back pain, allergic reaction, fever, generalized edema
Infrequent	Neck pain, neoplasm, cellulitis, cyst, chills, malaise, overdose, moniliasis, hernia, viral infection, photosensitivity reaction, pelvic pain, abdomen enlarged, abscess, neck rigidity, lab test abnormal, drug level increased, carcinoma, sepsis, suicide attempt, reaction unevaluable
Rare	*Infection fungal, unexpected benefit, chills and fever,* body odor, drug level decreased, halitosis, hangover effect, injection site reaction, hormone level altered, hypothermia, infection bacterial, injection site hemorrhage, intentional overdose, mucous membrane disorder, accidental overdose, adenoma, anaphylactoid reaction, ascites, chest pain substernal, death, sarcoidosis, sudden death, immune system disorder, increased drug effect, injection site pain, Lupus Erythematosus syndrome, medication error, sarcoma, shock, tolerance decreased
Cardiovascular	
Frequent	Hypertension, vasodilatation
Infrequent	Palpitation, migraine, tachycardia, peripheral vascular disorder, electrocardiogram abnormal, cardiovascular disorder, angina pectoris, congestive heart failure, hemorrhage, myocardial infarct, hypotension, postural hypotension, ventricular extrasystoles, atrial fibrillation, coronary artery disorder, bradycardia, cerebrovascular accident, arrhythmia, cerebral ischemia, vascular disorder, sinus bradycardia, myocardial ischemia, bundle branch block, AV block first degree, arteriosclerosis, deep thrombophlebitis, phlebitis, arterial anomaly, heart failure, pulmonary embolus, retinal vascular disorder, varicose vein
Rare	Heart arrest, vascular anomaly, occlusion, supraventricular tachycardia, atrial arrhythmia, atrial flutter, cerebral infarct, coronary occlusion, thrombophlebitis, thrombosis, cardiomegaly, extrasystoles, pallor, AV block, AV block second degree, cardiomyopathy, peripheral gangrene, QT interval prolonged, *retinal artery occlusion, supraventricular extrasystoles, cerebral* hemorrhage, digitalis intoxication, ventricular arrhythmia, aortic stenosis, bigeminy, cerebrovascular disorder, left heart failure, ventricular tachycardia, AV block complete, carotid occlusion, carotid thrombosis, cor pulmonale, embolus lower extremity, endocarditis, heart block, increased capillary fragility, intracranial aneurysm, nodal tachycardia, QT interval shortened, retinal vein thrombosis, ST elevated, T inverted, vascular headache, vasculitis
Digestive system	
Frequent	Nausea, diarrhea, anorexia, gastrointestinal disorder
Infrequent	Gastroenteritis, tooth disorder, periodontal abscess, colitis, gastritis, liver function tests abnormal, increased salivation, thirst, nausea and vomiting, rectal disorder, gingivitis, dysphagia, stomatitis, mouth ulceration, cholelithiasis, rectal hemorrhage, gastrointestinal hemorrhage, glossitis, tooth caries, abnormal stools, cholecystitis, melena, oral moniliasis, esophagitis, tongue disorder, cheilitis, tongue edema
Rare	Eructation, pancreatitis, stomach ulcer, ulcerative stomatitis, esophageal stenosis, fecal incontinence, gum hemorrhage, intestinal obstruction, enteritis, peptic ulcer, enterocolitis, gum hyperplasia, hepatomegaly, liver fatty deposit, tenesmus, biliary pain, fecal impaction, jaundice, periodontitis, ulcerative colitis, aphthous stomatitis, cholestatic jaundice, gastrointestinal carcinoma, hemorrhagic gastritis, hepatitis, liver tenderness, nausea, vomiting and diarrhea, salivary gland enlargement, stomach atony, bloody diarrhea, cardiospasm, duodenal ulcer, gamma glutamyl transpeptidase increased, hematemesis, hepatoma, intestinal perforation, intestinal stenosis, intestinal ulcer, leukoplakia of mouth, necrotizing pancreatitis, pancreas disorder, pseudomembranous colitis, sialadenitis, stomach ulcer hemorrhage, tongue discoloration
Endocrine system	
Infrequent	Diabetes mellitus, hypothyroidism
Rare	Goiter, prolactin increased, thyroid disorder, gonadotropic follicle stim hormone increase, hyperthyroidism, thyroiditis, adrenal insufficiency, parathyroid disorder, thyroid carcinoma, thyroid neoplasia, virilism
Hemic and lymphatic	
Infrequent	Anemia, leukopenia, thrombocytopenia, lymphadenopathy, hypochromic anemia, leukocytosis, eosinophilia
Rare	Lymphocytosis, petechia, iron deficiency anemia, cyanosis, lymphedema, polycythemia, lymphoma like reaction, megaloblastic anemia, splenomegaly, purpura, thrombocythemia, thrombocytopenic purpura, chronic leukemia, coagulation disorder, erythrocytes abnormal, leukemoid reaction, lymphangitis, macrocytic anemia, pancytopenia, prothrombin decreased, rupture of spleen, sedimentation rate increased
Metabolic and nutritional	
Infrequent	*Hyperglycemia, SGPT increased, hypoglycemia, hypokalemia,* hypercholesteremia, SGOT increased, weight loss, hyperlipemia, amylase increased, hyperuricemia, alkaline phosphatase increased, creatinine increased, hyponatremia, gout, dehydration, BUN increased, healing abnormal
Rare	Hypercalcemia, hyperkalemia, hypocalcemia, bilirubinemia, alcohol intolerance, hypoglycemic reaction, ketosis, calcium disorder, hypochloremia, hypomagnesemia, hypoproteinemia, NPN increased, uremia, acidosis, avitaminosis, enzymatic abnormality, gamma globulins increased, hypernatremia, hypophosphatemia, lactic acidosis, obesity
Musculoskeletal system	
Frequent	Arthralgia, myalgia, arthritis, leg cramps, myasthenia
Infrequent	Tendon disorder, arthrosis, joint disorder, bone disorder, tenosynovitis, bursitis, tendinous contracture, osteoporosis, tendon rupture, bone pain
Rare	Rheumatoid arthritis, osteomyelitis, rhabdomyolysis, myopathy, muscle atrophy, myositis, pyogenic arthritis, bone neoplasm, musculoskeletal congenital anomaly, pathological fracture
Nervous system	
Frequent	Insomnia, anxiety, libido decreased, depersonalization, hypertonia, neuropathy
Infrequent	Reflexes decreased, sleep disorder, abnormal dreams, hostility, hallucinations, hyperkinesia, personality disorder, dysarthria, hyperesthesia, hypokinesia, circumoral paresthesia, libido increased, neuralgia, vestibular disorder, aphasia, movement disorder, hyperalgesia, apathy, hypotonia, convulsion, facial paralysis, psychosis
Rare	Drug dependence, neuritis, paranoid reaction, CNS depression, CNS neoplasia, manic reaction, neurosis, extrapyramidal syndrome, meningitis, hemiplegia, reflexes increased, akathisia, delirium, paralysis, withdrawal syndrome, brain edema, CNS stimulation, dyskinesia, encephalopathy, foot drop, grand mal convulsion, hypalgesia, peripheral neuritis, psychotic depression, addiction, arachnoiditis, cerebellar syndrome, cogwheel rigidity, dementia, dystonia, Guillain-Barre syndrome, intracranial hemorrhage, multiple sclerosis, myelitis, schizophrenic reaction, subarachnoid hemorrhage, torticollis
Respiratory system	
Frequent	Sinusitis, rhinitis, dyspnea, cough increased, pneumonia, lung disorder
Infrequent	Asthma, epistaxis, laryngitis, voice alteration, respiratory disorder, sputum increased
Rare	Apnea, emphysema, aspiration pneumonia, hyperventilation, lung edema, pleural disorder, atelectasis, hemoptysis, hiccup, hypoxia, laryngismus, lung fibrosis, pleural effusion, lung function decreased, pulmonary hypertension, yawn, bronchiectasis, bronchiolitis, carcinoma of lung, hypoventilation, laryngeal neoplasia, nasal septum disorder, pneumothorax
Skin and appendages	
Infrequent	Pruritus, sweating, skin disorder, acne, dry skin, alopecia, skin ulcer, herpes simplex, urticaria, nail disorder, eczema, herpes zoster, skin benign neoplasm, fungal dermatitis, maculopapular rash, vesiculobullous rash, skin carcinoma, furunculosis, skin discoloration, skin hypertrophy, psoriasis, seborrhea, hirsutism
Rare	Skin nodule, angioedema, cutaneous moniliasis, skin atrophy, exfoliative dermatitis, pustular rash, ichthyosis, skin melanoma, subcutaneous nodule, sweating decreased, hair disorder, lichenoid dermatitis, melanosis, miliaria, purpuric rash, skin necrosis, Stevens Johnson syndrome
Special sense	
Frequent	Eye disorder, conjunctivitis, otitis media
Infrequent	Retinal disorder, tinnitus, eye pain, cataract specified, dry eyes, taste perversion, ear pain, lacrimation disorder, ear disorder, deafness, eye hemorrhage, photophobia, glaucoma, vitreous disorder, corneal lesion, otitis externa, refraction disorder, blepharitis, retinal edema, taste loss, abnormality of accommodation
Rare	Hyperacusis, keratitis, mydriasis, parosmia, ptosis, retinal hemorrhage, color blindness, retinal depigmentation, retinal detachment, corneal opacity, corneal ulcer, iritis, night blindness, optic atrophy, retinal degeneration, cataract NOS, scleritis, strabismus, anisocoria, blindness, exophthalmos, keratoconjunctivitis, ophthalmoplegia, papilledema
Urogenital system	
Frequent	Anorgasmia
Infrequent	Urinary frequency, urinary incontinence, cystitis, abnormal ejaculation, urination impaired, dysuria, metrorrhagia, hematuria, vaginal moniliasis, prostatic disorder, vaginitis, dysmenorrhea, urinary urgency, kidney calculus, breast pain, menstrual disorder, amenorrhea, menorrhagia, kidney function abnormal, nephritis, urine abnormality, vaginal hemorrhage, urinary retention, urinary tract disorder, leukorrhea, breast neoplasm, menopause, oliguria, polyuria, albuminuria, pyuria
Rare	Breast carcinoma, penis disorder, papanicolau smear suspicious, fibrocystic breast, prostatic carcinoma, uterine fibroids enlarged, acute kidney failure, creatinine clearance decreased, nephrosis, nocturia, polycystic kidney, bladder carcinoma, breast enlargement, cervicitis, cervix disorder, female lactation, glycosuria, gynecomastia, hypomenorrhea, kidney pain, mastitis, pyelonephritis, kidney failure, breast abscess, epididymitis, orchitis, prostate neoplasia, prostatic specific antigen increase, salpingitis, urogenital disorder, urolithiasis, uterine disorder, vulvovaginal disorder, balanitis, bladder calculus, calcium crystalluria, cervix neoplasm, dyspareunia, endometrial carcinoma, endometrial disorder, glomerulitis, hydronephrosis, ovarian cancer, unintended pregnancy, urethral pain, urethritis, urogenital anomaly, urogenital neoplasia, uterine hemorrhage

Comparison of Gender and Race

The overall adverse event profile of pregabalin was similar between women and men. There are insufficient data to support a statement regarding the distribution of adverse experience reports by race.

Peripheral Edema

Incidence of peripheral edema in controlled neuropathic pain studies was 10.4% in the pregabalin group compared with 2.9% in the placebo group. In clinical trials, these events of peripheral edema were dose-related, mostly mild to moderate in intensity and rarely led to withdrawal. Peripheral edema was not associated with cardiovascular complications such as hypertension or congestive heart failure and there was no evidence of hemodilution or changes in any laboratory parameters indicative of underlying organ dysfunction (see **WARNINGS AND PRECAUTIONS, Peripheral Edema**).

Weight Gain

In the controlled neuropathic pain studies, patients on pregabalin had a higher incidence (5.9%) of weight gain as defined by a ≥7% increase from baseline weight as compared with the placebo group (1.6%). The mean change in the pregabalin group was an increase of 1.5 kg compared with 0.2 kg in the placebo group; few patients (0.1%) withdrew due to weight gain. This weight gain was dose-related, and not associated with clinically important changes in blood pressure or cardiovascular adverse events. There was no relationship between baseline body mass index and the incidence of ≥7% weight gain in the controlled trials.

Based on the results of a controlled study of reproductive function in healthy male volunteers, the ≥7% weight gain on pregabalin appeared to be reversible. In this study, there were no reports of peripheral edema (see **WARNINGS AND PRECAUTIONS, Weight Gain**).

Abnormal Hematologic and Clinical Chemistry Findings

In all controlled trials, 1.0% of patients on pregabalin and 0.5% of placebo patients had an increase in creatine kinase of >3x upper limit of normal. Renal dysfunction was generally not associated with the elevated creatine kinase in these patients. Mean changes in creatine kinase ranged from 9.6 to 26.3 U/L for pregabalin-treated patients and 4.8 U/L for the placebo patients (see **DOSAGE AND ADMINISTRATION**, Patients with Renal Impairment). Routine therapeutic drug monitoring or clinical laboratory testing is not required for patients treated with LYRICA (see **WARNINGS AND PRECAUTIONS**).

Post-Marketing Adverse Drug Reactions

The worldwide post-marketing experience to date with LYRICA is consistent with the clinical program. The most frequently reported adverse events from spontaneous post-marketing reports for LYRICA are shown below. There are insufficient data to support an estimate of their incidence or to establish causation.

Eye disorders: diplopia, vision blurred, visual disturbance. There have also been rare reports of accommodation disorder, eyelid edema and eye redness (see **WARNINGS AND PRECAUTIONS, Ophthalmological Effects**).

Gastrointestinal disorders: diarrhea, dry mouth, nausea, vomiting

General disorders and administration site conditions: fatigue, feeling abnormal, pain

Nervous system disorders: ataxia, coordination abnormal, dizziness, dysarthria, headache, memory impairment, paresthesia, somnolence, speech disorder, tremor (see **WARNINGS AND PRECAUTIONS, Dizziness and Somnolence**).

Psychiatric disorders: confusional state, depression, insomnia, psychotic disorder. There have been rare reports of psychotic disorders in patients receiving pregabalin.

Renal and urinary disorders: urinary retention

Respiratory, thoracic and mediastinal disorders: dyspnea

Skin and subcutaneous tissue disorders: pruritus

DRUG INTERACTIONS

Overview

Since pregabalin is predominately excreted unchanged in the urine, undergoes negligible metabolism in humans (<2% of a dose recovered in urine as metabolites), does not inhibit drug metabolism in vitro, and is not bound to plasma proteins, LYRICA (pregabalin) is unlikely to produce, or be subject to, pharmacokinetic interactions.

Pharmacokinetic

In Vitro Studies: In vitro drug metabolism studies revealed that pregabalin at concentrations which were, in general, 10-fold greater than observed in Phase 2/3 clinical trials, does not inhibit human CYP1A2, CYP2A6, CYP2C9, CYP2C19, CYP2D6, CYP2E1, and CYP3A4 enzyme systems.

In Vivo Studies: The drug interaction data described in this section were obtained from studies involving healthy adults, patients with epilepsy, and patients with chronic pain disorders.

Carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate

In vitro and in vivo studies showed that LYRICA is unlikely to be involved in significant pharmacokinetic drug interactions. Specifically, there are no clinically significant pharmacokinetic interactions between pregabalin and the following antiepileptic drugs: carbamazepine, valproic acid, lamotrigine, phenytoin, phenobarbital, and topiramate. Important pharmacokinetic interactions would also not be expected to occur between pregabalin and commonly used antiepileptic drugs.

Tiagabine: The results of a population pharmacokinetic analysis indicated that in patients with partial seizures tiagabine had no clinically significant effect on pregabalin clearance.

Gabapentin: The pharmacokinetics of pregabalin and gabapentin were investigated in 12 healthy subjects following concomitant single dose administration of 100 mg pregabalin and 300 mg gabapentin, and in 18 healthy subjects following concomitant multiple dose administration of 200 mg pregabalin q8h and 400 mg gabapentin q8h. Gabapentin pharmacokinetics following single and multiple dose administration were unaltered by pregabalin coadministration. The rate of pregabalin absorption was reduced by approximately 26% (single dose administration) and 18% (multiple dose administration) based on lower C_{max} values; however, the extent of pregabalin absorption was unaffected by gabapentin coadministration.

Oral Contraceptives: Pregabalin coadministration (200 mg TID) had no effect on the steady state pharmacokinetics of norethindrone and ethinyl estradiol (1 mg/35 µg, respectively) in healthy subjects.

Lorazepam: Multiple dose administration of pregabalin (300 mg BID) in healthy subjects had no effect on the rate and extent of lorazepam single dose pharmacokinetics and single dose administration of lorazepam (1 mg) had no clinically significant effect on the steady state pharmacokinetics of pregabalin.

Oxycodone: Multiple dose administration of pregabalin (300 mg BID) in healthy subjects had no effect on the rate and extent of oxycodone single dose pharmacokinetics. Single dose administration of oxycodone (10 mg) had no clinically significant effect on the steady state pharmacokinetics of pregabalin.

Ethanol: Multiple dose administration of pregabalin (300 mg BID) in healthy subjects had no effect on the rate and extent of ethanol single dose pharmacokinetics and single dose administration of ethanol (0.7 g/kg) had no clinically significant effect on the steady state pharmacokinetics of pregabalin.

Diuretics, Oral Hypoglycemics, and Insulin: A population pharmacokinetic analysis in patients with chronic pain showed no clinically significant effect on pregabalin clearance with the concomitant use of diuretics, oral hypoglycemics, and insulin.

https://doi.org/10.1017/S0317167100116063 Published online by Cambridge University Press

Pharmacodynamic

Multiple oral doses of pregabalin co-administered with oxycodone, lorazepam, or ethanol did not result in clinically important effects on respiration. Pregabalin appears to be additive in the impairment of cognitive and gross motor function caused by oxycodone. Pregabalin may potentiate the effects of ethanol and lorazepam.

Drug-Food Interactions

The rate of pregabalin absorption is decreased when given with food resulting in a decrease in C_{max} by approximately 25% to 30% and an increase in T_{max} to approximately 3 hours. However, administration of pregabalin with food has no clinically relevant effect on the total amount of pregabalin absorbed. Therefore, pregabalin can be taken with or without food.

Drug-Herb Interactions

LYRICA (pregabalin) has no known drug/herb interactions.

Drug-Laboratory Interactions

LYRICA (pregabalin) has no known drug/laboratory test interactions.

DOSAGE AND ADMINISTRATION

Dosing Considerations

Patients with Impaired Renal Function

Pregabalin is primarily eliminated from the systemic circulation by renal excretion as unchanged drug. In patients with a medical history of significant renal insufficiency, daily dosages should be reduced accordingly (see Dosage Adjustment Based on Renal Function, below).

In accordance with current clinical practice, if LYRICA (pregabalin) has to be discontinued, it is recommended this should be done gradually over a minimum of 1 week (see **WARNINGS AND PRECAUTIONS, Abrupt or Rapid Discontinuation**).

Adults:

Neuropathic pain associated with diabetic peripheral neuropathy

The recommended starting dose for LYRICA is 150 mg/day, given in two or three divided doses (75 mg BID or 50 mg TID), with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Efficacy of LYRICA has been demonstrated within the first week. Based on individual patient response and tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week.

For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, maximum daily dose of 600 mg (300 mg twice a day, BID) can be used. However, in clinical trials, LYRICA 600 mg/day did not provide additional *significant efficacy and patients treated with this dose experienced markedly higher* rates of adverse events and discontinued the trial more frequently.

Neuropathic pain associated with postherpetic neuralgia

The recommended starting dose for LYRICA is 150 mg/day, given in two or three divided doses (75 mg BID or 50 mg TID), with or without food in patients with a creatinine clearance rate of at least 60 mL/min. Efficacy of LYRICA has been demonstrated within the first week. Based on individual patient response and tolerability, the dose may be increased to 150 mg BID (300 mg/day) after one week.

For patients who experience significant and ongoing pain and can tolerate pregabalin 300 mg/day well, maximum daily dose of 600 mg (300 mg twice a day, BID) can be used. However, in clinical trials, LYRICA 600 mg/day did not provide additional significant efficacy and patients treated with this dose experienced markedly higher rates of adverse events and discontinued the trial more frequently.

Dosage Adjustment Based on Renal Function

LYRICA is primarily eliminated by renal excretion. Therefore, the dose should be adjusted for patients with reduced renal function. Pregabalin clearance is directly proportional to creatinine clearance. Therefore, dosing adjustment should be based on creatinine clearance (CL_{Cr}), as indicated in Table 7.

To use this dosing table, an estimate of the patient's creatinine clearance (CL_{Cr}) in mL/min is needed. CL_{Cr} in mL/min may be estimated from serum creatinine (mg/dL) determination using the Cockcroft and Gault equation:

$$CL_{Cr} = \frac{[140 - \text{age (years)}] \times \text{weight (kg)}}{72 \times \text{serum creatinine (mg/dL)}} \quad (\times 0.85 \text{ for female patients})$$

Pregabalin is effectively removed from plasma by hemodialysis. Over a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients receiving hemodialysis, pregabalin daily dose should be adjusted based on renal function. In addition to the daily dose adjustment, a supplemental dose should be given immediately following every 4-hour hemodialysis treatment (see Table 7).

Table 7. Pregabalin Dosage Adjustment Based on Renal Function

Creatinine Clearance (CL_{Cr}) (mL/min)	Total Pregabalin Daily Dose (mg/day)[a]			Dose Regimen
≥60	150	300	600	BID or TID
30-60	*75*	*150*	*300*	*BID or TID*
15-30	25-50	75	150	QD or BID
<15	25	25-50	75	QD
Supplementary dosage following hemodialysis (mg)[b]				
Patients on the 25 mg QD regimen: take one supplemental dose of 25 mg or 50 mg Patients on the 25-50 mg QD regimen: take one supplemental dose of 50 mg or 75 mg Patients on the 75 mg QD regimen: take one supplemental dose of 100 mg or 150 mg				

TID = Three divided doses; BID = Two divided doses; QD = Single daily dose.

a Total daily dose (mg/day) should be divided as indicated by dose regimen to provide mg/dose.

b Supplementary dose is a single additional dose.

Geriatrics (>65 years): Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function.

Pediatrics (<18 years of age): The safety and efficacy of pregabalin in pediatric patients (<18 years of age) have not been established and its use in this patient population is not recommended.

Administration

LYRICA (pregabalin) is given orally with or without food (see **ACTION AND CLINICAL PHARMACOLOGY**).

OVERDOSAGE

Signs, Symptoms and Laboratory Findings of Acute Overdosage in Humans

The highest known dose of pregabalin received in the clinical development program was 15,000 mg in 1 patient. The types of adverse events experienced by patients who received an overdose were not clinically different from other patients receiving recommended doses of pregabalin.

Treatment or Management of Overdose

There is no specific antidote for overdose with pregabalin. If indicated, elimination of unabsorbed drug may be attempted by emesis or gastric lavage; usual precautions should be observed to maintain the airway. General supportive care of the patient is indicated including monitoring of vital signs and observation of the clinical status of the patient. A Certified Poison Control Center should be contacted for up-to-date information on the management of overdose with pregabalin.

Hemodialysis

Standard hemodialysis procedures result in significant clearance of pregabalin (approximately 50% in 4 hours) and should be considered in cases of overdose. Although hemodialysis has not been performed in the few known cases of overdose, it may be indicated by the patient's clinical state or in patients with significant renal impairment.

ACTION AND CLINICAL PHARMACOLOGY

Mechanism of Action

Pharmacodynamics

LYRICA (pregabalin) binds with high affinity to the alpha$_2$-delta protein (a calcium channel subunit) of brain tissues and has analgesic, antiepileptic and anxiolytic activity. Pregabalin is known chemically as (S)-3-(aminomethyl)-5-methylhexanoic acid.

Although the mechanism of action of pregabalin is unknown, results with genetically modified mice and with compounds structurally-related to pregabalin indicate that selective binding to the alpha$_2$-delta protein is required for analgesic, antiepileptic and anxiolytic action in animal models. In vitro, pregabalin reduces the release of several neurotransmitters, suggesting a modulatory action on calcium channel function.

Pregabalin does not mimic GABA at $GABA_A$ or $GABA_B$ receptors, nor does it augment $GABA_A$ responses like benzodiazepines or barbiturates. In contrast to vascular calcium channel blockers, pregabalin does not alter systemic blood pressure or cardiac function. Various in vitro and in vivo results differentiate pregabalin from GABA uptake inhibitors or GABA transaminase inhibitors. In addition, pregabalin does not block sodium channels, it is not active at opiate receptors, it does not alter cyclooxygenase enzyme activity, it is not a serotonin agonist, it is not a dopamine antagonist, and it is not an inhibitor of dopamine, serotonin or noradrenaline reuptake.

Pregabalin treatment reduces pain-related behavior in neuropathic animal models of diabetes, peripheral nerve damage or chemotherapeutic insult and in a model of musculoskeletal-associated pain. Pregabalin given intrathecally prevents pain-related behaviors and reduces pain-related behavior caused by spinally administered agents, suggesting that it acts directly on tissues of the spinal cord or brain.

Pharmacokinetics

All pharmacological actions following pregabalin administration are due to the activity of the parent compound; pregabalin is not appreciably metabolized in humans. Mean steady-state plasma pregabalin concentration-time profiles following 75, 300 and 600 mg/day given in equally divided doses every 8 hours (TID) and 600 mg/day given in equally divided doses every 12 hours (BID) are shown in Table 8. Pregabalin pharmacokinetics are linear over the recommended daily dose range. Inter-subject pharmacokinetic variability for pregabalin is low (<20%).

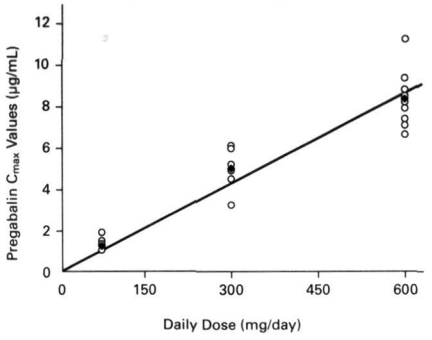
Table 8. Pregabalin Mean (CV%[a]) Steady-State Pharmacokinetic Parameter Values in Healthy Volunteers

Dose (mg)	Regimen	Daily Dose (mg/day)	n	C_{maxss} (µg/mL)	t_{max} (hr)	C_{minss} (µg/mL)	$AUC_{(0-t)}$ (µg•hr/mL)	$t_{1/2}$ (hr)	$C_{L/F}$ (mL/min)
25	TID[b]	75	8	1.39	0.9	0.45	6.7	5.9	64.1
				-19.5	-34.2	-25	-18.3	-17.3	-16.1
100	TID	300	6	5.03	0.8	1.94	25.2	6.3	68.9
				-21.3	-31	-33.6	-23	-19.6	-20.9
200	TID	600	11	8.52	0.9	3.28	41.7	6.3	81
				-14.8	-22.2	-29.2	-12.8	-13.6	-11.7
300	*BID*[c]	*600*	*8*	*9.07*	*1.4*	*2.6*	*59*	*6.7*	*85.1*
				-10.5	-57.1	-15.5	-6.4	-16.2	-6.4

C_{maxss}: Steady-state peak plasma concentration.
t_{max}: Time of peak plasma concentration at steady state.
C_{minss}: Steady-state trough plasma concentration
$AUC_{(0-t)}$: Area under the plasma concentration-time curve during one dosing interval at steady state
$t_{1/2}$: Elimination half-life
$C_{L/F}$: Oral clearance
a: Percent coefficient of variation
b: Total daily dose given in equally divided doses every 8 hours
c: Total daily dose given in equally divided doses every 12 hours

Absorption: Pregabalin is rapidly absorbed when administered in the fasted state, with peak plasma concentrations occurring within 1.5 hours following both single- and multiple-dose administration. Pregabalin oral bioavailability is ≥90% and is independent of dose. C_{max} (Figure 1) and AUC values increase proportionally following single- and multiple-dose administration. Following repeated administration, steady state is achieved within 24 to 48 hours. Multiple dose pharmacokinetics are predictable from single-dose data.

Figure 1. Individual and Mean Steady-State Pregabalin C_{max} Values Following 75, 300 and 600 mg/day Given in Equally Divided Doses TID (q8h) to Healthy Volunteers[a]



a: Solid line is the regression line going through the origin; individual (O) and mean (◆) values.

Distribution: In preclinical studies, pregabalin has been shown to readily cross the blood brain barrier in mice, rats and monkeys. Pregabalin is a substrate for system L transporter which is responsible for the transport of large amino acids across the blood-brain barrier. Pregabalin has been shown to cross the placenta in rats and is present in the milk of lactating rats. In humans, the apparent volume of distribution of pregabalin following oral administration is approximately 0.5 L/kg. Pregabalin is not bound to plasma proteins. At clinically efficacious doses of 150 and 600 mg/day, the average steady-state plasma pregabalin concentrations were approximately 1.5 and 6.0 µg/mL, respectively.

Metabolism: Pregabalin undergoes negligible metabolism in humans. Following a dose of radiolabeled pregabalin, approximately 98% of the radioactivity recovered in the urine was unchanged pregabalin. The N-methylated derivative of pregabalin, *the major metabolite of pregabalin found in urine, accounted for 0.9% of the dose.* In preclinical studies, pregabalin (S-enantiomer) did not undergo racemization to the R-enantiomer in mice, rats, rabbits or monkeys.

Excretion: Pregabalin is eliminated from the systemic circulation primarily by renal excretion as unchanged drug. Pregabalin mean $t_{1/2}$ is 6.3 hours. Pregabalin elimination is proportional to creatinine clearance. Pregabalin clearance is reduced in patients with impaired renal function (see **DOSAGE AND ADMINISTRATION**).

Special Populations and Conditions

Pregabalin undergoes negligible metabolism, is not bound to plasma proteins and is eliminated predominately as unchanged drug by renal excretion. Clinically important differences in pregabalin pharmacokinetics due to race and gender have not been observed and are not anticipated.

Pediatrics: Pharmacokinetics of pregabalin have not been studied in paediatric patients.

Geriatrics: Pregabalin oral clearance tended to decrease with increasing age. This decrease in pregabalin oral clearance is consistent with age-related decreases in creatinine clearance. Reduction of pregabalin dose may be required in patients who have age-related compromised renal function (see **WARNINGS AND PRECAUTIONS** and **DOSAGE AND ADMINISTRATION**).

Gender: A population pharmacokinetic analysis of the Phase 2/3 clinical program showed that the relationship between daily dose and pregabalin drug exposure is similar between genders when adjusted for gender-related differences in creatinine clearance.

Race: A population pharmacokinetic analysis of the Phase 2/3 clinical program showed that the relationship between daily dose and pregabalin drug exposure is similar among Caucasians, Blacks and Hispanics.

Renal Insufficiency: Because renal elimination is the major elimination pathway, dosage reduction in patients with renal dysfunction is necessary. Pregabalin is effectively removed from plasma by hemodialysis. Following a 4-hour hemodialysis treatment, plasma pregabalin concentrations are reduced by approximately 50%. For patients on hemodialysis, dosing must be modified (see **DOSAGE AND ADMINISTRATION**).

STORAGE AND STABILITY

Store at 15°C-30°C.

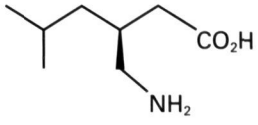
DOSAGE FORMS, COMPOSITION AND PACKAGING

Each capsule of LYRICA (pregabalin) contains 25, 50, 75, 150 or 300 mg pregabalin, lactose monohydrate, maize starch and talc. The capsule shells contain gelatin and titanium dioxide. In addition, the orange capsule shells contain red iron oxide and the white capsule shells contain sodium lauryl sulfate and colloidal silicon dioxide. Colloidal silicon dioxide is a manufacturing aid, which may not be present. The markings on the capsules are in black ink, which contains shellac, black iron oxide, propylene glycol, potassium hydroxide and water.

Capsules are packaged in HDPE bottles containing 60 capsules, and PVC/aluminum blisters.

PHARMACEUTICAL INFORMATION

Drug Substance

Proper name:	pregabalin
Chemical name:	(S)-3-(aminomethyl)-5-methylhexanoic acid
Molecular formula:	$C_8H_{17}NO_2$
Molecular mass:	159.23
Structural formula:	
Physicochemical properties:	Pregabalin is a white crystalline solid. It is soluble in water and in both basic and acidic aqueous solutions.

Product Monograph available upon request.

Last revised: June 3, 2005.

References:

1. LYRICA Product Monograph, June 2005. **2.** Data on file, Pfizer Canada Inc., study 1008-196. **3.** Freynhagen R, et al. Efficacy of pregabalin in neuropathic pain evaluated in a 12-week, randomised, double-blind, multicentre, placebo-controlled trial of flexible- and fixed-dose regimens. Pain 2005;115:254-263.

Pfizer

Life is our life's work

See pages A-8, A-9, A-14, A-15

Ebixa®
memantine

Memantine Hydrochloride Tablets 10 mg
THERAPEUTIC CLASSIFICATION:
N-methyl-D-aspartate (NMDA)
receptor antagonist

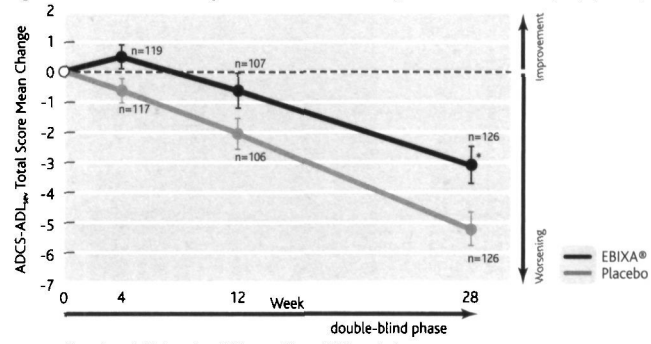
EBIXA®, indicated for the symptomatic treatment of patients with moderate to severe dementia of the Alzheimer's type, has been issued marketing authorization with conditions, to reflect the promising nature of the clinical evidence and the need for a confirmatory study to verify the clinical benefit. Patients should be advised of the nature of the authorization assessment.

ACTION AND CLINICAL PHARMACOLOGY: Persistent activation of the central nervous system N-methyl-D-aspartate (NMDA) receptors by the excitatory amino acid glutamate has been hypothesized to contribute to the symptomatology of Alzheimer's disease. Memantine is postulated to exert its therapeutic effect through its action as a low to moderate affinity uncompetitive (open channel) NMDA receptor antagonist, which binds preferentially to the NMDA receptor-operated cation channels. It blocks the effects of pathologically elevated sustained levels of glutamate that may lead to neuronal dysfunction. There is no clinical evidence that memantine prevents or slows neurodegeneration or alters the course of the underlying dementing process in patients with Alzheimer's disease. Memantine exhibits low to negligible affinity for other receptors (GABA, benzodiazepine, dopamine, adrenergic, noradrenergic, histamine and glycine) or voltage-dependent Ca^{2+}, Na^{+} or K^{+} channels. In addition, it does not directly affect the acetylcholine receptor or cholinergic transmission, which have been implicated in the cholinomimetic side effects (e.g., increased gastric acid secretion, nausea and vomiting) seen with acetylcholinesterase inhibitors. Memantine showed antagonist effects at the $5HT_3$ receptor with a potency similar to that for the NMDA receptor. In vitro studies have shown that memantine does not affect the reversible inhibition of acetylcholinesterase by donepezil or galantamine.

PHARMACOKINETICS: ABSORPTION: Orally administered memantine is completely absorbed. Oral bioavailability is almost 100%. Time to maximum plasma concentration (t_{max}) following single oral doses of 10 to 40 mg memantine ranged between 3 to 8 hours. It has a terminal elimination half-life of about 60-80 hours, with the majority of the dose excreted unchanged in urine. There is no indication that food influences the absorption of memantine. Studies in volunteers have demonstrated linear pharmacokinetics in the dose range of 10 to 40 mg. Daily doses of 20 mg lead to steady-state plasma concentrations of memantine ranging from 70 to 150 ng/ml (0.5-1 μM) with large inter-individual variations. **DISTRIBUTION:** The apparent volume of distribution of memantine is approximately 9-11 L/kg and the plasma protein binding is approximately 45%. Memantine rapidly crosses the blood-brain barrier with a CSF/serum ratio of about 0.5. **METABOLISM AND ELIMINATION:** In a study using orally administered ^{14}C-memantine, a mean of 84% of the dose was recovered within 20 days, more than 99% being excreted renally. Memantine undergoes little metabolism being in majority excreted unchanged in urine (75-90%). The remaining dose is converted primarily to three polar metabolites: the N-gludantan conjugate, 6-hydroxy memantine and 1-nitroso-deaminated memantine. These metabolites possess minimal NMDA receptor antagonist activity. The hepatic microsome CYP450 enzyme system does not play a significant role in the metabolism of memantine. In volunteers with normal kidney function, total clearance (Cl_{tot}) amounts to 170 ml/min/1.73 m^2 and part of total renal clearance is achieved by tubular secretion. Renal handling also involves tubular reabsorption, probably mediated by cation transport proteins. The renal elimination rate of memantine under alkaline urine conditions may be reduced by a factor of 7 to 9 resulting in increased plasma levels of memantine (see WARNINGS, Genitourinary Conditions). Alkalisation of urine may result from drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or from the massive ingestion of alkalising gastric buffers. **SPECIAL POPULATIONS: ELDERLY PATIENTS:** The pharmacokinetics of memantine in young and elderly subjects is similar. No adjustment of dosage on the basis of age is recommended. **REDUCED HEPATIC FUNCTION:** The pharmacokinetics of memantine in patients with hepatic impairment has not been investigated. As memantine is metabolized to a minor extent into metabolites with no NMDA-antagonistic activity, changes in the pharmacokinetics are not expected to result in clinically relevant effects in patients with mild to moderate liver impairment. **REDUCED RENAL FUNCTION:** In elderly volunteers with normal and reduced renal function (creatinine clearance of 50 to ≤80 ml/min/1.73 m^2), a significant correlation was observed between creatinine clearance and total renal clearance of memantine. Following a single 20 mg oral dose of memantine, systemic exposure in geriatric subjects with mild and moderate renal impairment was 14% and 39% greater, respectively, compared to geriatric subjects with normal renal function (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

NOC/c – CLINICAL TRIALS: The potential efficacy of EBIXA® (memantine hydrochloride) as a treatment for the symptomatic management of moderate to severe Alzheimer's disease was demonstrated by the results of 2 randomized, double-blind, placebo-controlled 6-month clinical studies. Both studies were conducted in patients with Alzheimer's disease. The mean age of patients participating in the EBIXA® trials was 76 with a range of 50 to 93 years. Approximately 66% of patients were women. Female patients participating in the clinical trials were required to be at least 50 years of age and at least 2 years postmenopausal or surgically sterile. The racial distribution was approximately 91% Caucasian. Study Outcome Measures: In each study, the effectiveness of EBIXA® was determined from instruments evaluating activities of daily living through caregiver-related evaluation, a measure of cognition, and a clinician's global assessment of change. The ability of EBIXA® to improve day-to-day function was assessed in both studies (Study 1 and Study 2) using the modified Alzheimer's Disease Cooperative Study – Activities of Daily Living Inventory (ADCS-ADL_{sev}). The ADCS-ADL_{sev} consists of a comprehensive battery of ADL questions used to measure the functional capabilities of patients. Each ADL item is rated from the highest level of independent performance to complete loss. The inventory is performed by interviewing a caregiver familiar with the behaviour of the patient. The modified ADCS-ADL_{sev} consists of a subset of 19 items including ratings of the patients' ability to eat, dress, bathe, telephone, travel, shop, and perform other household chores, and has been validated for the assessment of patients with moderate to severe dementia. The modified ADCS-ADL_{sev} scoring range is from 0 to 54, with lower scores indicating greater functional impairment. The ability of EBIXA® to improve cognitive performance was assessed in both studies (Study 1 and Study 2) with the Severe Impairment Battery (SIB), a multi-item instrument that has been validated for the evaluation of cognitive function in patients with moderate to severe dementia. Unlike the Alzheimer's Disease Assessment Scale - cognitive subscale (ADAS-cog) the sensitivity of the SIB is not limited by floor effects in patients with advanced dementia. The SIB examines selected aspects of cognitive performance including elements of attention, orientation, language, memory, visuospatial ability, construction, praxis, and social interaction. The SIB scoring range is from 0 to 100, with lower scores indicating greater cognitive impairment. The SIB has been shown to be a valid and reliable instrument sensitive to longitudinal changes in patients with moderate to severe dementia. The ability of EBIXA® to produce an overall clinical effect was assessed in both studies (Study 1 and Study 2) using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC-Plus. The CIBIC-Plus used in both trials was a structured instrument based on a comprehensive evaluation at baseline and subsequent time-points of four domains: general (overall clinical status), functional (including activities of daily living), cognitive, and behavioural. It represents the assessment of a skilled clinician using validated scales based on his/her observation at an interview with the patient, in combination with information supplied by a caregiver familiar with the behaviour of the patient over the interval rated. The CIBIC-Plus is scored as a seven point categorical rating, ranging from a score of 1, indicating "markedly improved" to a score of 4, indicating "unchanged" to a score of 7, indicating "markedly worse." The CIBIC-Plus has not been systematically compared directly to assessments not using information from caregivers (CIBIC) or other global methods. **Study 1 (Twenty-Eight-Week Study):** In a study of 28 weeks duration, 252 patients with moderate to severe Alzheimer's disease (diagnosed by DSM-IV and NINCDS-ADRDA criteria, with Mini-Mental State Examination scores ≥3 and ≤14 and Global Deterioration Scale Stages 5-6) were randomized to EBIXA® or placebo. For patients randomized to EBIXA®, treatment was initiated at 5 mg/day and increased weekly by 5 mg/day to a dose of 20 mg/day (10 mg twice a day). The percentages of randomized patients who completed the study were: placebo 67% and EBIXA® 77%. Results are presented for analyses based on all patients (ITT, Intent-to treat population) and carrying their last study observation forward (LOCF analysis). Primary efficacy endpoints were the ADCS-ADL_{sev} and CIBIC-Plus. **Effects on the ADCS-ADL_{sev}:** Figure 1 illustrates the time course for the change from baseline in the ADCS-ADL_{sev} score for the two treatment groups over the 28 weeks of the study. At endpoint, the mean difference in the ADCS-ADL_{sev} change scores for the EBIXA® -treated patients compared to the patients on placebo was 2.1 units (p=0.022). EBIXA® treatment was statistically significantly superior to placebo.

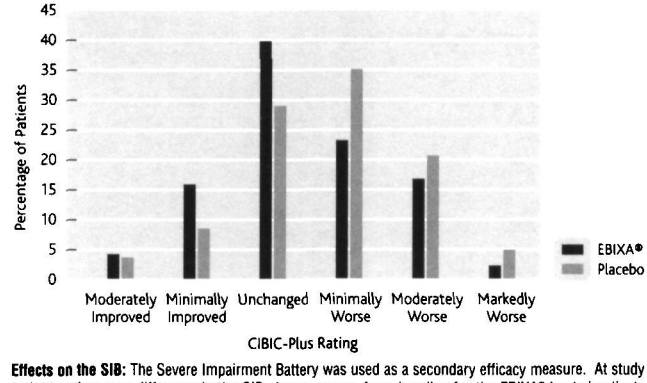
Figure 1: Time course of the change from baseline in ADCS-ADL_{sev} score at week 28-LOCF (ITT population)



*p-value <0.05 based on Wilcoxon-Mann-Whitney test.
**LOCF

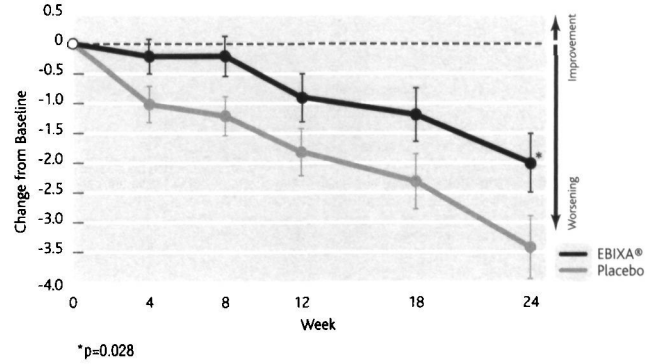
Effects on the CIBIC-Plus: Figure 2 is a histogram of the percentage distribution of CIBIC-Plus scores attained by patients assigned to each of the treatment groups. The EBIXA®-placebo difference for these groups of patients in the mean rating was 0.25 units (p=0.06). EBIXA® treatment was numerically superior but not statistically significantly superior to placebo.

Figure 2: Distribution of CIBIC-Plus ratings at week 28-LOCF (ITT population)



Effects on the SIB: The Severe Impairment Battery was used as a secondary efficacy measure. At study endpoint, the mean difference in the SIB change scores from baseline for the EBIXA®-treated patients compared to the patients on placebo was 5.9 units (p<0.001). EBIXA® treatment was statistically significantly superior to placebo. **Study 2 (Twenty-Four-Week Study):** In a study of 24 weeks duration, 404 patients with moderate to severe Alzheimer's disease (diagnosed by NINCDS-ADRDA criteria, with Mini-Mental State Examination scores ≥5 and ≤14) who had been treated with donepezil for at least 6 months and who had been on a stable dose of donepezil for 3 months prior to randomization were then randomized to EBIXA® or placebo, while still receiving donepezil. For patients randomized to EBIXA®, treatment was initiated at 5 mg/day and increased weekly by 5 mg/day to a dose of 20 mg/day (10 mg twice a day). The percentages of randomized patients who completed the study were: placebo/donepezil 75% and EBIXA®/donepezil 85%. The primary endpoints were the ADCS-ADL_{sev} and SIB. **Effects on the ADCS-ADL_{sev}:** Figure 3 illustrates the time course for the change from baseline in the ADCS-ADL_{sev} score for the two treatment groups over the 24 weeks of the study. The mean difference in the ADCS-ADL_{sev} change scores for the EBIXA®/donepezil treated patients compared to the patients on placebo/donepezil was 1.4 units (p=0.028). EBIXA®/donepezil treatment was statistically significantly superior to placebo/donepezil.

Figure 3: Time course of the change from baseline in ADCS-ADL_{sev} score at 24 weeks-LOCF (ITT Population)



*p=0.028

Effects on the SIB: Figure 4 illustrates the time course for the change from baseline in SIB score for the two treatment groups over the 24 weeks of the study. The mean difference in the SIB change scores for the EBIXA®/donepezil treated patients compared to the patients on placebo/donepezil was 3.4 units (p<0.001). EBIXA® /donepezil treatment was statistically significantly superior to placebo/donepezil.

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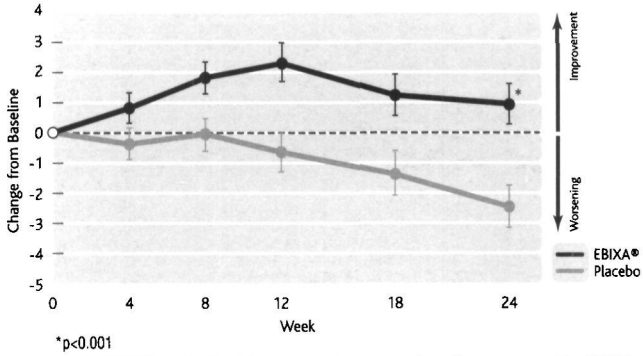
Figure 4: Time course of the change from baseline in SIB score at 24 weeks-LOCF (ITT Population)



Effects on the CIBIC-Plus: The CIBIC-Plus was used as a secondary efficacy measure. The EBIXA® - placebo difference of CIBIC-Plus mean rating was 0.25 units (p=0.027). EBIXA® /donepezil treatment was statistically significantly superior to placebo/donepezil.

NOC/c INDICATION AND CLINICAL USE: EBIXA® (memantine hydrochloride) may be useful as monotherapy or as adjunctive therapy with cholinesterase inhibitors[1] for the symptomatic treatment of patients with moderate to severe dementia of the Alzheimer's type. EBIXA® tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease. In a 28-week placebo controlled monotherapy trial, patients with moderate to severe Alzheimer's disease showed stabilization or less worsening of functional and cognitive symptoms and of global assessment when treated with EBIXA® compared to placebo. In a 24 week "add-on" placebo controlled trial in which patients were treated with either EBIXA® or placebo as add-on to ongoing donepezil therapy, stabilization or less worsening of functional and cognitive symptoms and of global assessment was observed in patients with moderate to severe Alzheimer's disease when treated with EBIXA® compared to placebo. EBIXA® has not been studied in controlled clinical trials for the symptomatic treatment of moderate to severe Alzheimer's disease for more than 6 months.

[1] Cholinesterase inhibitors refers to only those which are approved in Canada for the symptomatic treatment of Alzheimers disease.

CONTRAINDICATIONS: EBIXA® (memantine hydrochloride) is contraindicated in patients with known hypersensitivity to memantine hydrochloride or to any excipients used in the formulation.

WARNINGS: NEUROLOGICAL CONDITIONS: Seizures: EBIXA® (memantine hydrochloride) has not been systematically evaluated in patients with a seizure disorder. These patients were excluded from clinical studies during the premarketing testing of EBIXA®. In clinical trials, seizures occurred in 0.3% of patients treated with EBIXA® and 0.4% of patients treated with placebo. Seizure activity may be a manifestation of Alzheimer's disease. The risk/benefit of memantine treatment for patients with a history of seizure disorder must therefore be carefully evaluated. **GENITOURINARY CONDITIONS:** Conditions that raise urine pH may reduce the urinary elimination of memantine by a factor of 7 to 9, resulting in increased plasma levels of memantine (see ACTIONS AND CLINICAL PHARMACOLOGY). These conditions include drastic changes in diet, e.g. from a carnivore to a vegetarian diet, or a massive ingestion of alkalising gastric buffers (see Drugs Which Make Urine Alkaline, PRECAUTIONS). Also, urine pH may be elevated by states of renal tubulary acidosis (RTA) or severe infections of the urinary tract with *Proteus bacteria.* **CARDIOVASCULAR CONDITIONS:** In most clinical trials, patients with recent myocardial infarction, uncompensated congestive heart failure (NYHA III-IV), and uncontrolled hypertension were excluded. However, patients such as those with controlled hypertension (DBP <105 mm/Hg), right bundle branch blockage and pacemaker were included. Although cardiovascular adverse events occurred at low frequencies in the two placebo-controlled clinical trials involving patients with moderate to severe Alzheimer's disease, there were increased frequencies of hypertension, chest pain, bradycardia and cardiac failure adverse events in patients who were treated with EBIXA® compared to placebo in these trials. Consequently, caution should be observed when memantine is initiated in patients with cardiovascular conditions.

PRECAUTIONS: OPTHALMIC CONDITIONS: In an open label study where EBIXA® was administered to 10 elderly patients at a dose of 20 mg/day for approximately 48 months, memantine concentrations in lacrimal fluid were about 3 fold higher than in plasma and did not show ophthalmologic effects. In another 6-month placebo-controlled trial, no major treatment differences were reported for ocular effects but worsening of the corneal condition was reported for slightly more patients treated with EBIXA® than placebo (5.4% memantine vs. 3.3% placebo). Repeat-dose toxicology studies demonstrated corneal and lens histopathological changes in rodents treated with EBIXA®. Therefore, periodic monitoring of the patient's ophthalmic condition is recommended. **CONCOMITANT USE WITH OTHER DRUGS:** *Use with compounds chemically related to N-methyl-D-aspartate (NMDA) antagonists:* As these compounds act at the same receptor system as memantine, adverse drug reactions (mainly CNS-related) may be more frequent or pronounced. Pharmacotoxic psychosis has been reported in the literature in two Parkinson's disease patients who were treated concomitantly with memantine, amantadine, L-dopa and terguride (see PRECAUTIONS, Drug Interactions, Other agents). The combined use of EBIXA® with other compounds chemically related to NMDA antagonists such as amantadine, ketamine or dextromethorphan has not been systematically evaluated and is therefore not recommended. **DRUGS THAT MAKE URINE ALKALINE:** The clearance of memantine was reduced by about 80% under alkaline urine conditions at pH 8. Therefore, alterations of urine pH towards the alkaline condition may lead to an accumulation of the drug with a possible increase in adverse effects. Urine pH is altered by diet, drugs (e.g. carbonic anhydrase inhibitors, sodium bicarbonate) and clinical state of the patient (e.g. renal tubular acidosis or severe infections of the urinary tract). Hence, memantine should be used with caution under these conditions. (see ACTION AND CLINICAL PHARMACOLOGY and WARNINGS). **SPECIAL POPULATIONS: HEPATIC IMPAIRMENT:** The pharmacokinetics or pharmacodynamic effects of EBIXA® have not been studied in patients with hepatic impairment. As EBIXA® undergoes minimal hepatic metabolism and is excreted primarily in its unchanged form by the kidneys, the pharmacokinetics of memantine would be expected to be only modestly affected. No adjustment in dosage is therefore recommended in hepatically impaired patients. **RENAL IMPAIRMENT:** There are limited data available from clinical trials for patients with mild to moderate renal impairment. In patients with normal to mildly impaired renal function (creatinine clearance >60 ml/min/1.73 m²) no dose reduction is needed. In patients with moderate renal impairment (creatinine clearance 40-60 ml/min/1.73 m²) daily dose should be reduced to 10 mg/day. (see PHARMACOKINETICS). There are no data available in patients with severe renal impairment (creatinine clearance less than 9 ml/min/1.73 m²), and the use of EBIXA® in these patients is not recommended. (see ACTION AND CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION). **USE IN PATIENTS ≥85 YEARS OLD:** In placebo-controlled clinical studies, the number of patients aged 85 years or older who received memantine at the therapeutic dose of 20 mg/day was 40. There is limited safety information for EBIXA® in this patient population. **USE IN PATIENTS WITH SERIOUS CO-MORBID CONDITIONS:** There is limited information on the safety of memantine treatment in patients with moderate to severe Alzheimer's disease with serious co-morbidities, as these patients were excluded from clinical trials. The use of EBIXA® in Alzheimer's disease patients with chronic illnesses common among the geriatric population should be considered only after a proper risk/benefit assessment. Dose escalation in this patient population should proceed with caution. **PREGNANCY:** Oral treatment of female rats with memantine once daily during organogenesis produced mild maternal toxicity at doses of 6-18 mg/kg/day (3-9 times the Maximum Recommended Human Dose [MRHD] on a mg/m² basis); however, memantine was not teratogenic at doses up to 18 mg/kg/day (9 times the MRHD on a mg/m² basis), the highest dose tested. In a rat reproduction and fertility study, reduced growth and a developmental delay were observed at 18 mg/kg/day (9 times the MRHD on a mg/m² basis). Memantine doses of 0, 3, 10 and 30 mg/kg/day were orally administered to pregnant rabbits during the period of organogenesis. At 30 mg/kg/day (30 times the MRHD on a mg/m² basis) maternal toxicity and a slight increase in post-implantation loss were observed. No teratogenic effects were observed in rabbits administered memantine 30 mg/kg/day (30 times the MRHD on a mg/m² basis). The maternal and fetal no observed effect level (NOEL) was 10 mg/kg/day (10 times the MRHD on a mg/m² basis). In a peri and postnatal study, memantine was orally administered in rats at up to 18 mg/kg/day (9 times the MRHD on a mg/m² basis). At 18 mg/kg/day pups showed reduced mean body weights but there was no effect on their development or behaviour. Animal studies showed no indication of an adverse effect of memantine on labor and delivery. There are no adequate and well-controlled studies of memantine in pregnant women to establish the safe use of EBIXA® for this population. Therefore, EBIXA® should not be used in women of childbearing potential, unless, in the opinion of the physician, the expected benefits to the patient markedly outweigh the possible hazards to the foetus. **NURSING MOTHERS:** It is not known whether memantine is excreted in human breast milk. Therefore EBIXA® should not be used in nursing mothers. **PEDIATRIC USE:** The safety and effectiveness of EBIXA® in any illness occurring in pediatric patients has not been established. Therefore, EBIXA® is not recommended for use in children. **DRUG INTERACTIONS:** *Effects of EBIXA® on substrates of microsomal enzymes:* In vitro studies conducted with marker substrates of CYP450 enzymes (CYP1A2, -2A6, -2C9, -2D6, -2E1, -3A4) revealed minimal inhibition of these enzymes by memantine. No pharmacokinetic interactions with drugs metabolized by these enzymes are expected. *Effects of inhibitors and/or substrates of microsomal enzymes on EBIXA®:* Memantine is predominantly renally eliminated, and drugs that are substrates and/or inhibitors of the CYP450 system are not expected to alter the metabolism of memantine. *Acetylcholinesterase (AChE) inhibitors: In vitro* studies have shown that memantine does not affect the reversible inhibition of acetylcholinesterase by donepezil or galantamine. In healthy adult volunteers, under steady-state conditions of the AChE inhibitor donepezil HCl, coadministration of a single dose of EBIXA® did not affect the pharmacokinetics of either compound and did not affect donepezil-mediated AChE inhibition. In a 24-week study of patients with moderate to severe Alzheimer's disease the adverse event profiles were similar for patients treated with a combination of memantine and donepezil or placebo and donepezil. The mechanism of action and pharmacokinetics of other AChE inhibitors (e.g. galantamine and rivastigmine) differ from donepezil and the safety of co-administration of these drugs with EBIXA® has not been evaluated in clinical studies. *Drugs eliminated via renal mechanisms:* Co-administration of drugs that use the same renal cationic transport system as memantine, such as cimetidine, ranitidine, quinidine, hydrochlorothiazide (HCTZ), triamterene (TA), and nicotine could potentially alter the plasma levels of both agents. Coadministration of EBIXA® and hydrochlorothiazide/triamterene (HCTZ/TA) did not affect the bioavailability of either memantine or triamterene, and the bioavailability of HCTZ decreased by 20%. The pharmacokinetics of memantine is similar in smokers and non-smokers, suggesting that nicotine may not affect the disposition of memantine. *Drugs highly bound to plasma proteins:* Because the plasma protein binding of memantine is low (45%), an interaction with drugs that are highly bound to plasma proteins, such as warfarin and digoxin, is unlikely. Other agents: Since the effects of L-dopa, dopaminergic agonists, and anticholinergics may be enhanced by concomitant treatment with EBIXA®, dosage adjustment of these other agents may be necessary. **CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY:** There was no evidence of carcinogenicity in a 113-week oral study in mice for either sex at doses up to 40 mg/kg/day (10 times the maximum recommended human dose [MRHD] on a mg/m² basis). There was also no evidence of carcinogenicity in rats orally dosed at up to 40 mg/kg/day for 71 weeks followed by 20 mg/kg/day (19 and 10 times the MRHD on a mg/m² basis, respectively) through 128 weeks. Memantine did not show any genotoxic potential in assays for gene mutation (bacterial and mammalian cells in vitro) or in clastogenicity assays (human lymphocytes in vitro and mouse bone marrow in vivo). No impairment of fertility or reproductive performance was seen in rats administered up to 18 mg/kg/day (9 times the MRHD on a mg/m² basis) orally from 14 days prior to mating through gestation and lactation in females, or for 60 days prior to mating in males. **ADVERSE EVENTS:** A total of 738 patients were treated with memantine in double-blind, placebo-controlled dementia studies. Of these patients, 592 (80%) completed the studies. Patients were treated with memantine for a mean of 150.3 days. Approximately 60% of patients received memantine for at least 24 weeks. **Adverse Events Leading to Discontinuation of Treatment:** In placebo-controlled trials in which dementia patients received doses of EBIXA® up to 20 mg/day, 10.8 % (80/738) of the EBIXA®-treated patients discontinued treatment due to an adverse event. The discontinuation rate in the placebo-treated patients was 11.2% (81/721). The most frequent adverse event leading to discontinuation was agitation with an observed frequency among patients who discontinued treatment of 1.2% in patients receiving memantine vs. 2.1% in patients administered placebo. None of the other adverse events leading to discontinuation met the criteria for most common adverse events, defined as those occurring at a frequency of at least 2% and at twice the incidence seen in placebo patients. **Adverse Events Reported in Placebo-Controlled Dementia Trials:** Table 1 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled dementia trials and for which the rate of occurrence was greater for patients treated with EBIXA® than for those treated with placebo. The prescriber should be aware that these figures cannot be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those that prevailed in the clinical trials. Similarly, the cited frequencies cannot be compared with figures obtained from other clinical investigations involving different treatments, uses, and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse event incidence rate in the population studied.

Table 1: Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving EBIXA® and at a Higher Frequency than Placebo-treated Patients

Body System	%	
Adverse Event	Placebo (N=721)	EBIXA® (N=738)
Body as a Whole		
Fatigue	0.7	2.3
Pain	1.0	2.4
Cardiovascular System		
Hypertension	2.4	3.3
Central and Peripheral Nervous System		
Dizziness	4.6	6.9
Headache	3.6	5.6
Gastrointestinal System		
Constipation	3.5	6.1
Nausea	2.4	2.8
Vomiting	2.1	3.0
Musculoskeletal System		
Back pain	2.5	2.7
Psychiatric Disorders		
Anorexia	1.2	2.2
Anxiety	0.8	2.6
Confusion	5.5	5.7
Hallucinations	1.2	2.6
Somnolence	2.2	2.8
Respiratory System		
Dyspnea	1.2	2.3

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Other adverse events occurring with an incidence of at least 2% in EBIXA® -treated patients but at an equal or lower rate than placebo were agitation, arthralgia, bronchitis, cataract, coughing, depression, diarrhea, fall, gait abnormal, inflicted injury, influenza-like symptoms, insomnia, urinary incontinence and urinary tract infection. **Vital Sign Changes:** EBIXA® and placebo groups were compared with respect to (1) mean change from baseline in vital signs (pulse, systolic blood pressure, and diastolic blood pressure) and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses did not reveal any clinically important changes in vital signs associated with EBIXA® treatment. **Laboratory Changes:** EBIXA® and placebo groups were compared with respect to (1) mean change from baseline in various serum chemistry, hematology, and urinalysis variables and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in laboratory test parameters associated with EBIXA® treatment. **ECG Changes:** EBIXA® and placebo groups were compared with respect to (1) mean change from baseline in various ECG parameters and (2) the incidence of patients meeting criteria for potentially clinically significant changes from baseline in these variables. These analyses revealed no clinically important changes in ECG parameters associated with EBIXA® treatment. **Adverse Events Observed in Placebo-Controlled Trial in Patients Previously Treated with Donepezil:** In an additional double-blind, placebo-controlled study, 202 patients who had been treated with donepezil for at least 6 months and who had been on stable doses of donepezil for 3 months prior to randomization were treated with memantine for a period of 24 weeks while still receiving donepezil. Of these patients, 172 (85%) completed the study. In this clinical trial, a total of 14.9% (30/202) of the memantine/donepezil patients discontinued the study compared to 25.4% (51/201) of the placebo/donepezil patients. The most frequent reason for discontinuation was adverse events and included 12% of placebo/donepezil patients and 7% of memantine/donepezil patients. Overall, the safety profile of the memantine/donepezil treated patients was similar to the one observed for the placebo-controlled dementia trials. The adverse events leading to discontinuation of the treatment, and for which the incidence was greater in the memantine/donepezil than in the placebo/donepezil group were: asthenia (memantine 1.0%; placebo 0%) dehydration (memantine 1.5%; placebo 0%) and confusion (memantine 2.0 %; placebo 1.5%). Table 2 lists treatment emergent signs and symptoms that were reported in at least 2% of patients in placebo-controlled dementia trials and for which the rate of occurrence was greater for patients treated with EBIXA®/donepezil than for those treated with placebo/donepezil.

Table 2: Adverse Events Reported in Controlled Clinical Trials in at Least 2% of Patients Receiving EBIXA®/donepezil and at a Higher Frequency than Placebo/donepezil-treated Patients

Body System	%	
Adverse Event	**Placebo/donepezil (N=201)**	**EBIXA®/donepezil (N=202)**
Body as a Whole		
Chest pain	0.0	2.5
Fall	7.0	7.4
Fever	0.5	2.0
Oedema peripheral	4.0	5.0
Pain	0.5	3.0
Cardiovascular System		
Hypertension	1.5	4.5
Central and Peripheral Nervous System		
Gait abnormal	1.0	3.0
Headache	2.5	6.4
Gastrointestinal System		
Constipation	1.5	3.0
Vomiting	3.0	3.5
Metabolic and Nutritional Disorders		
Weight increase	0.0	2.5
Musculoskeletal System		
Arthralgia	1.5	2.5
Psychiatric Disorders		
Confusion	2.0	7.9
Depression	3.0	4.0
Red Blood Cell Disorder		
Anemia	0.5	2.0
Reproductive Disorders, Male		
Prostatic disorder	0.0	4.1
Respiratory System		
Coughing	1.0	3.0
Influenza-like symptoms	6.5	7.4
Skin and Appendages Disorders		
Rash	1.5	2.5
Urinary System Disorders		
Urinary tract infection	5.0	5.9
Urinary incontinence	3.0	5.4
Micturition frequency	0.5	2.0

Treatment emergent signs and symptoms that were reported in at least 2% of EBIXA®/donepezil treated patients (but less than 9%) were abdominal pain, agitation, anorexy, anxiety, asthenia, back pain, bronchitis, dehydration, diarrhea, dizziness, fatigue, fecal incontinence, hallucinations, inflicted injury, insomnia, personality disorder, somnolence, syncope, tremor, upper respiratory tract infection. **Other Adverse Events Observed During Clinical Trials:** EBIXA® has been administered to approximately 1150 patients with dementia, of whom more than 1000 received the maximum recommended dose of 20 mg/day. Approximately 739 patients received EBIXA® for at least 6 months of treatment and 387 patients were treated for approximately a year or more. All adverse events occurring in at least two patients are included, except for those already listed in Tables 1 and 2, WHO terms too general to be informative, or events unlikely to be caused by the drug. Also included are the adverse events observed in the placebo-controlled trial in patients who had been previously treated with donepezil prior to EBIXA® treatment. Events are classified by body system and listed using the following definitions: *frequent* – those occurring on one or more occasions in at least 1/100 patients; *infrequent* – those occurring in less than 1/100 patients but at least in 1/1000 patients. These adverse events are not necessarily related to EBIXA® treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. **Autonomic Nervous System:** *Infrequent:* sweating increased, mouth dry. **Body as a Whole:** *Frequent:* asthenia, oedema, leg pain, malaise, sepsis, syncope. *Infrequent:* abscess, allergic reaction, allergy, chest pain precordial, choking, condition aggravated, ESR increased, flushing, hernia NOS, hot flushes, hypothermia, infection, infection fungal, infection viral, moniliasis, oedema peripheral, pallor, rigors, sudden death. **Cardiovascular System:** *Frequent:* angina pectoris, bradycardia, cardiac failure, cardiac failure left, heart murmur, oedema dependent. *Infrequent:* aneurysm, arrhythmia, cardiac arrest, embolism pulmonary, fibrillation atrial, heart block, heart disorder, hypertension aggravated, hypotension, hypotension postural, myocardial infarction, palpitation, phlebitis, pulmonary oedema, tachychardia, thrombophlebitis, thrombophlebitis deep, vascular disorder. **Central and Peripheral Nervous System:** *Frequent:* aphasia, ataxia, cerebrovascular disorder, hypokinesia, transient ischemic attack, vertigo. *Infrequent:* absences, cerebral hemorrhage, coma, convulsions, coordination abnormal, extrapyramidal disorder, hemiparesis, hemiplegia, hyperkinesia, hypertonia, hypoesthesia, muscle contractions involuntary, neuralgia, neuropathy, paralysis, paresthesia, ptosis, speech disorder, stupor, tremor. **Gastrointestinal System:** *Frequent:* abdominal pain, dyspepsia, fecal incontinence, hemorrhoids, tooth disorder. *Infrequent:* diverticulitis, dysphagia, esophageal ulceration, esophagitis, flatulence, gastroenteritis, gastroesophageal reflux, gastrointestinal disorder NOS, GI hemorrhage, gingivitis, hemorrhage rectum, melena, mucositis NOS, oesophagitis, saliva altered, saliva increased, stomatitis ulcerative, tooth ache, tooth caries. **Hemic and Lymphatic Disorders:** *Frequent:* purpura. *Infrequent:* epistaxis, hematoma, leukocytosis, leukopenia, polycythemia. **Metabolic and Nutritional Disorders:** *Frequent:* hyperglycemia, hypernatremia, hypokalemia, phosphatase alkaline increased, weight decrease. *Infrequent:* bilirubinemia, BUN increased, dehydration, diabetes mellitus, diabetes mellitus aggravated, gamma-GT increased, gout, hepatic enzymes increased, hepatic function abnormal, hypercholesterolemia, hyperkalemia, hyperuricemia, hyponatremia, NPN increased, polydipsia, AST increased, ALT increased, thirst. **Musculoskeletal System:** *Frequent:* arthritis, arthrosis, muscle weakness, myalgia. *Infrequent:* arthritis aggravated, arthritis rheumatoid, bursitis, skeletal pain. **Neoplasms:** *Infrequent:* basal cell carcinoma, breast neoplasm benign (female), breast neoplasm malignant (female), carcinoma, neoplasm NOS, skin neoplasm malignant. **Psychiatric Disorders:** *Frequent:* aggressive reaction, apathy, cognitive disorder, delusion, nervousness. *Infrequent:* amnesia, appetite increased, concentration impaired, crying abnormal, delirium, depersonalization, emotional lability, libido increased, neurosis, paranoid reaction, paroniria, personality disorder, psychosis, sleep disorder, suicide attempt, thinking abnormal. **Reproductive Disorders, Female:** *Infrequent:* vaginal hemorrhage, moniliasis; **Male:** *Frequent:* moniliasis. **Respiratory System:** *Frequent:* pharyngitis, pneumonia, upper respiratory tract infection, rhinitis. *Infrequent:* apnea, asthma, bronchospasm, hemoptysis, respiratory disorder, sinusitis. **Skin and Appendages:** *Frequent:* bullous eruption, herpes zoster, skin disorder, skin ulceration. *Infrequent:* alopecia, cellulitis, dermatitis, eczema, pruritus, rash erythematous, seborrhea, skin dry, skin reaction localized, urticaria. **Special Senses:** *Frequent:* cataract, conjunctivitis, eye abnormality, macula lutea degeneration, vision abnormal. *Infrequent:* blepharitis, blurred vision, conjunctival hemorrhage, corneal opacity, decreased visual acuity, diplopia, ear ache, ear disorder NOS, eye infection, eye pain, glaucoma, hearing decreased, lacrimation abnormal, myopia, xerophthalmia, retinal detachment, retinal disorder, retinal hemorrhage, tinnitus. **Urinary System:** *Frequent:* cystitis, dysuria. *Infrequent:* hematuria, micturition disorder, polyuria, pyuria, renal function abnormal, urinary retention. **Adverse Events From Other Sources:** Memantine has been commercially available in Europe since 1982, and has been evaluated in clinical trials including patients with neuropathic pain, Parkinson's disease, organic brain syndrome, and spasticity. Although no causal relationship to memantine treatment has been found, the following adverse events have been reported to be temporally associated with memantine treatment in more than one patient and are not described elsewhere in labeling: acne, bone fracture, carpal tunnel syndrome, claudication, hyperlipidemia, impotence, otitis media, thrombocytopenia.

SYMPTOMS AND TREATMENT OF OVERDOSAGE: SYMPTOMS: In a documented case of an overdosage with up to 400 mg memantine, the patient experienced restlessness, psychosis, visual hallucinations, proconvulsiveness, somnolence, stupor and loss of consciousness. The patient recovered without permanent sequelae. **TREATMENT OF OVERDOSAGE:** Because strategies for the management of overdose are continually evolving, it is advisable to contact a poison control center to determine the latest recommendations for the management of an overdose of any drug. Establish and maintain an airway to ensure adequate ventilation and oxygenation. Gastric lavage and use of activated charcoal should be considered. Cardiac and vital sign monitoring are recommended, along with general symptomatic and supportive measures. There are no specific antidotes for EBIXA®. Elimination of memantine can be enhanced by acidification of urine.

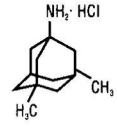
DOSAGE AND ADMINISTRATION: EBIXA® (memantine hydrochloride) should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease. Therapy should only be started if a caregiver is available who will regularly monitor drug intake by the patient. Diagnosis should be made according to current guidelines. *Adults:* The recommended maintenance dose for memantine is 20 mg/day. In order to reduce the risk of side effects the maintenance dose is achieved by upward titration as follows: the usual starting dose is 5 mg/day. The dose should then be increased in 5 mg increments to 10 mg/day (5 mg twice a day), 15 mg/day (10 mg and 5 mg as separate doses), and 20 mg/day (10 mg twice a day), depending on the patient's response and tolerability. The minimum recommended interval between dose increases is one week. The recommended dose titration is summarized in the following table.

	10 mg Tablets	
	AM	**PM**
Week 1	1/2 tablet	None
Week 2	1/2 tablet	1/2 tablet
Week 3	1 tablet	1/2 tablet
Week 4 and beyond	1 tablet	1 tablet

The tablets can be taken with or without food.

DOSES IN SPECIAL POPULATIONS: *Elderly:* On the basis of the clinical studies the recommended dose for patients over the age of 65 years is 20 mg/day (10 mg twice a day) as described above (see PHARAMCOKINETICS). *Renal impairment:* In patients with normal to mildly impaired renal function (creatinine clearance >60 ml/min/1.73 m^2) no dose reduction is needed. In patients with moderate renal impairment (creatinine clearance 40-60 ml/min/1.73 m^2) daily dose should be reduced to 10 mg/day. In patients with severe renal impairment the use of EBIXA® has not been systematically evaluated and is therefore not recommended in these patients (See PHARMACOKINETICS and PRECAUTIONS). *Hepatic impairment:* There are no data on the use of memantine in patients with hepatic impairment (see PHARMACOKINETICS and PRECAUTIONS). No adjustment in dosage is recommended in hepatically impaired patients.

PHARMACEUTICAL INFORMATION:
DRUG SUBSTANCE:
Common Name: Memantine hydrochloride.
Code Name: MEM3; D145; MRZ 2/145
Chemical Name: 1-amino-3,5-dimethyladamantane hydrochloride.
Structural Formula:



Molecular Formula: $C_{12}H_{22}ClN$
Molecular Weight: 215.77 (hydrochloride) 179.31 (base)
Description: White, crystalline, practically odourless powder
pH: 5.5 – 6.0
pKa: 10.27
Solubility: water, hydrochloridic acid, methanol, n-hexane (soluble), methylene chloride, chloroform (freely soluble), ethylacetate (practically insoluble)
Partition Coefficient: Log P (n-octanol/water): 3.28
Composition: EBIXA® tablets contain 10 mg of memantine hydrochloride and the following non-medicinal ingredients: lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica, talc, magnesium stearate, methacrylic acid-ethyl acrylate copolymer, sodium lauryl sulphate, polysorbate 80, triacetin, simethicone emulsion.
Stability and Storage Recommendations: EBIXA® tablets should be stored in a dry place at room temperature between 15° and 30°C.
AVAILABILITY OF DOSAGE FORMS: EBIXA® (memantine hydrochloride) is available as white to off-white tablets.
10 mg tablets: White to off-white, centrally tapered oblong, biconvex, film-coated tablet with a single break line on both sides. Blister packages of 30 tablets.

Product Monograph available to Healthcare professionals upon request.

Lundbeck Canada Inc.
413 St-Jacques Street West, Suite FB-230
Montreal (Quebec), Canada H2Y 1N9

Lundbeck

EBX-011-05 E

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See pages A-6, A-7

ALTACE® ramipril

PHARMACOLOGIC CLASSIFICATION:
Angiotensin Converting Enzyme Inhibitor

ACTION AND CLINICAL PHARMACOLOGY
ALTACE (ramipril) is an angiotensin converting enzyme (ACE) inhibitor.

Following oral administration, ALTACE is rapidly hydrolyzed to ramiprilat, its principal active metabolite.

INDICATIONS AND CLINICAL USE: *Essential Hypertension.* ALTACE (ramipril) is indicated in the treatment of essential hypertension. It may be used alone or in association with thiazide diuretics. ALTACE should normally be used in patients in whom treatment with a diuretic or a beta-blocker was found ineffective or has been associated with unacceptable adverse effects. ALTACE can also be tried as an initial agent in those patients in whom use of diuretics and/or beta-blockers are contraindicated or in patients with medical conditions in which these drugs frequently cause serious adverse effects. The safety and efficacy of ALTACE in renovascular hypertension have not been established and therefore, its use in this condition is not recommended. The safety and efficacy of concurrent use of ALTACE with antihypertensive agents other than thiazide diuretics have not been established.

Treatment Following Acute Myocardial Infarction
ALTACE is indicated following acute myocardial infarction in clinically stable patients with signs of left ventricular dysfunction to improve survival and reduce hospitalizations for heart failure. Sufficient experience in the treatment of patients with severe (NYHA class IV) heart failure immediately after myocardial infarction is not yet available. (See WARNINGS – Hypotension.)

MANAGEMENT OF PATIENTS AT INCREASED RISK OF CARDIOVASCULAR EVENTS: ALTACE may be used to reduce the risk of myocardial infarction, stroke or cardiovascular death in patients over 55 years of age who are at high risk of cardiovascular events because of a history of coronary artery disease, stroke, peripheral artery disease, or diabetes that is accompanied by at least one other cardiovascular risk factor such as hypertension, elevated total cholesterol levels, low high density lipoprotein levels, cigarette smoking, or documented microalbuminuria. The incidence of the primary outcome (composite of myocardial infarction, stroke and death from cardiovascular causes) was reduced from 17.8% in the placebo-treated group to 14.0% in the ramipril-treated group.

GENERAL: In using ALTACE consideration should be given to the risk of angioedema (see WARNINGS). **When used in pregnancy during the second and third trimesters, ACE inhibitors can cause injury or even death of the developing fetus. When pregnancy is detected ALTACE should be discontinued as soon as possible (see WARNINGS – Use in Pregnancy, and INFORMATION FOR THE PATIENT).**

CONTRAINDICATIONS: ALTACE (ramipril) is contraindicated in patients who are hypersensitive to this drug, or to any ingredient in the formulation, or in those patients who have a history of angioedema.

WARNINGS: *Angioedema:* Angioedema has been reported in patients with ACE inhibitors, including ALTACE (ramipril). Angioedema associated with laryngeal involvement may be fatal. If laryngeal stridor or angioedema of the face, tongue, or glottis occurs, ALTACE should be discontinued immediately, the patient treated appropriately in accordance with accepted medical care, and carefully observed until the swelling disappears. In instances where swelling is confined to the face and lips, the condition generally resolves without treatment, although antihistamines may be useful in relieving symptoms. Where there is involvement of tongue, glottis, or larynx, likely to cause airway obstruction, appropriate therapy (including, but not limited to 0.3 to 0.5 mL of subcutaneous epinephrine solution 1:1000) should be administered promptly (see ADVERSE REACTIONS).

The incidence of angioedema during ACE inhibitor therapy has been reported to be higher in black than in non-black patients. Patients with a history of angioedema unrelated to ACE inhibitor therapy may be at increased risk of angioedema while receiving an ACE inhibitor (see CONTRAINDICATIONS).

Hypotension: Symptomatic hypotension has occurred after administration of ALTACE, usually after the first or second dose or when the dose was increased. It is more likely to occur in patients who are volume depleted by diuretic therapy, dietary salt restriction, dialysis, diarrhea, or vomiting. In patients with ischemic heart disease or cerebrovascular disease, an excessive fall in blood pressure could result in a myocardial infarction or cerebrovascular accident (see ADVERSE REACTIONS). Because of the potential fall in blood pressure in these patients, therapy with ALTACE should be started under close medical supervision. Such patients should be followed closely for the first weeks of treatment and whenever the dose of ALTACE is increased. In patients with severe congestive heart failure, with or without associated renal insufficiency, ACE inhibitor therapy may cause excessive hypotension and has been associated with oliguria, and/or progressive azotemia, and rarely, with acute renal failure and/or death.

If hypotension occurs, the patient should be placed in a supine position and, if necessary, receive an intravenous infusion of 0.9% sodium chloride. A transient hypotensive response may not be a contraindication to further doses which usually can be given without difficulty once the blood pressure has increased after volume expansion in hypertensive patients. However, lower doses of ALTACE and/or reduced concomitant diuretic therapy should be considered. *In patients receiving treatment following acute myocardial infarction, consideration should be given to discontinuation of ALTACE (see ADVERSE REACTIONS – Treatment Following Acute Myocardial Infarction, DOSAGE AND ADMINISTRATION – Treatment Following Acute Myocardial Infarction).*

Neutropenia/Agranulocytosis: Agranulocytosis and bone marrow depression have been caused by ACE inhibitors. Several cases of agranulocytosis, neutropenia or leukopenia have been reported in which a causal relationship to ALTACE cannot be excluded. Current experience with the drug shows the incidence to be rare. Periodic monitoring of white blood cell counts should be considered, especially in patients with collagen vascular disease and/or renal disease. Use in Pregnancy: ACE inhibitors can cause fetal and neonatal morbidity and mortality when administered to pregnant women. Several dozen cases have been reported in the world literature. When pregnancy is detected, ALTACE should be discontinued as soon as possible.

PRECAUTIONS: Renal Impairment: *As a consequence of inhibiting the renin-angiotensin-aldosterone system, changes in renal function have been seen in susceptible individuals. In patients whose renal function may depend on the activity of the renin-angiotensin-aldosterone system, such as patients with bilateral renal artery stenosis, unilateral renal artery stenosis to a solitary kidney, or severe congestive heart failure, treatment with agents that inhibit this system has been associated with oliguria, progressive azotemia, and rarely, acute renal failure and/or death. In susceptible patients, concomitant diuretic use may further increase risk. Use of ALTACE should include appropriate assessment of renal function. ALTACE should be used with caution in patients with renal insufficiency as they may require reduced or less frequent doses (see DOSAGE AND ADMINISTRATION). Close monitoring of renal function during therapy should be performed as deemed appropriate in patients with renal insufficiency.*

Anaphylactoid Reactions during Membrane Exposure: Anaphylactoid reactions have been reported in patients dialyzed with high-flux membranes (e.g. polyacrylonitrile [PAN]) and treated concomitantly with an ACE inhibitor. Dialysis should be stopped immediately if symptoms such as nausea, abdominal cramps, burning, angioedema, shortness of breath and severe hypotension occur. Symptoms are not relieved by antihistamines. In these patients consideration should be given to using a different type of dialysis membrane or a different class of antihypertensive agents.

Anaphylactoid Reactions during Desensitization: There have been isolated reports of patients experiencing sustained life threatening anaphylactoid reactions while receiving ACE inhibitors during desensitization treatment with hymenoptera (bees, wasps) venom. In the same patients, these reactions have been avoided when ACE inhibitors were temporarily withheld for at least 24 hours, but they have reappeared upon inadvertent rechallenge.

Hyperkalemia and Potassium-Sparing Diuretics: Elevated serum potassium (greater than 5.7 mEq/L) was observed in approximately 1% of hypertensive patients in clinical trials treated with ALTACE. In most cases these were isolated values which resolved despite continued therapy. Hyperkalemia was not a cause of discontinuation of therapy in any hypertensive patient. Risk factors for the development of hyperkalemia may include renal insufficiency, diabetes mellitus, and the concomitant use of agents to treat hypokalemia or other drugs associated with increases in serum potassium (see PRECAUTIONS – Drug Interactions).

Surgery/Anesthesia: In patients undergoing surgery or anesthesia with agents producing hypotension, ALTACE may block angiotensin II formation secondary to compensatory renin release. If hypotension occurs and is considered to be due to this mechanism, it may be corrected by volume repletion.

Aortic Stenosis: There is concern, on theoretical grounds, that patients with aortic stenosis might be at particular risk of decreased coronary perfusion when treated with vasodilators because they do not develop as much afterload reduction.

Patients with Impaired Liver Function: Hepatitis (hepatocellular and/or cholestatic), elevations of liver enzymes and/or serum bilirubin have occurred during therapy with ACE inhibitors in patients with or without pre-existing liver abnormalities. In most cases the changes were reversed on discontinuation of the drug.

Elevations of liver enzymes and/or serum bilirubin have been reported with ALTACE (see ADVERSE REACTIONS). Should the patient receiving ALTACE experience any unexplained symptoms particularly during the first weeks or months of treatment, it is recommended that a full set of liver function tests and any other necessary investigations be carried out. Discontinuation of ALTACE should be considered when appropriate. There are no adequate studies in patients with cirrhosis and/or liver dysfunction. ALTACE should be used with particular caution in patients with pre-existing liver abnormalities. In such patients baseline liver function tests should be obtained before administration of the drug and close monitoring of response and metabolic effects should apply.

Nursing Mothers: Ingestion of a single 10 mg oral dose of ALTACE resulted in undetectable amounts of ramipril and its metabolites in breast milk. However, because multiple doses may produce low milk concentrations that are not predictable from single doses, ALTACE should not be administered to nursing mothers.

Pediatric Use: The safety and effectiveness of ALTACE in children have not been established; therefore use in this age group is not recommended.

Use in Elderly: Although clinical experience has not identified differences in response between the elderly (>65 years) and younger patients, greater sensitivity of some older individuals cannot be ruled out.

Patient Alertness: ALTACE may lower the state of patient alertness and/or reactivity, particularly at the start of treatment (see ADVERSE REACTIONS).

Cough: A dry, persistent cough, which usually disappears only after withdrawal or lowering of the dose of ALTACE, has been reported. Such possibility should be considered as part of the differential diagnosis of cough.

Drug Interactions: Concomitant Diuretic Therapy: Hypotension may result but can be minimized by discontinuing diuretic or increasing salt intake prior to ramipril treatment and/or reducing initial dose. Agents increasing serum potassium: Use potassium sparing diuretics with caution and monitor frequently. Agents causing renin release: *ALTACE antihypertensive effect increased.* Lithium: *Lithium levels may* be increased. Administer lithium with caution and monitor levels frequently. Antacids: The bioavailability of ALTACE and the pharmacokinetics of ramiprilat were not affected. Digoxin: No change in ramipril, ramiprilat or digoxin serum levels. Warfarin: The co-administration of ALTACE with warfarin did not alter the anticoagulant effects. Acenocoumarol: No significant changes. Non-steroidal anti-inflammatory agents (NSAID): The antihypertensive effects of ACE inhibitors may be reduced with concomitant administration of NSAIDs (*e.g. indomethacin).*

ADVERSE REACTIONS: *Essential Hypertension.* Serious adverse events occurring in North American placebo-controlled clinical trials with ramipril monotherapy in hypertension (*n*=972) were: hypotension (0.1%); myocardial infarction (0.3%); cerebrovascular accident (0.1%); edema (0.2%); syncope (0.1%). Among all North American ramipril patients (*n*=1,244), angioedema occurred in patients treated with ramipril and a diuretic (0.1%). The most frequent adverse events occurring in these trials with ALTACE monotherapy in hypertensive patients (*n*=651) were: headache (15.1%); dizziness (3.7%); asthenia (3.7%); chest pain (2.0%); nausea (1.8%); peripheral edema (1.8%); somnolence (1.7%); impotence (1.5%); rash (1.4%); arthritis (1.1%); dyspnea (1.1%). Discontinuation of therapy due to clinical adverse events was required in 5 patients (0.8%). In placebo-controlled trials, an excess of upper respiratory infection and flu syndrome was seen in the ramipril group. As these studies were carried out before the relationship of cough to ACE inhibitors was recognized, some of these events may represent ramipril-induced cough. In a later 1-year study, increased cough was seen in almost 12% of ALTACE patients, with about 4% of these patients requiring discontinuation of treatment. Approximately 1% of patients treated with ALTACE monotherapy in North American controlled clinical trials (*n*=972) have required discontinuation because of cough.

Treatment Following Acute Myocardial Infarction
Adverse events (except laboratory abnormalities) in a controlled clinical trial of post-AMI patients with clinical signs of heart failure considered possibly/probably related to ALTACE and occurring in more than 1% of stabilized patients (n=1,004) were: hypotension (10.7%); increased cough (7.6%); dizziness/vertigo (5.6%); nausea/vomiting (3.8%); angina pectoris (2.9%); postural hypotension (2.2%); syncope (2.1%); heart failure (2.0); severe/resistant heart failure (2.0%); myocardial infarction (1.7%); vomiting (1.6%); headache (1.2%); abnormal kidney function (1.2%); abnormal chest pain (1.1%); diarrhea (1.1%). Isolated cases of death have been reported with the use of ramipril that appear to be related to hypotension (including first dose effects), but many of these are difficult to differentiate from progression of underlying disease (see WARNINGS – Hypotension). Discontinuation of therapy due to adverse reactions was required in 368/1,004 post-AMI patients taking ramipril (36.7%), compared to 401/982 patients receiving placebo (40.8%).

Clinical Laboratory Test Findings: increased creatinine; increases in blood urea nitrogen (*BUN*); decreases in hemoglobin or hematocrit; hyponatraemia; elevations of liver enzymes, serum bilirubin, uric acid, blood glucose; proteinuria and significant increases in serum potassium.

DOSAGE AND ADMINISTRATION

Essential Hypertension: Dosage of ALTACE (ramipril) must be individualized. Initiation of therapy requires consideration of recent antihypertensive drug treatment, the extent of blood pressure elevation and salt restriction. The dosage of other antihypertensive agents being used with ALTACE may need to be adjusted.

Monotherapy: The recommended initial dosage of ALTACE in patients not on diuretics is 2.5 mg once daily. Dosage should be adjusted according to blood pressure response, generally, at intervals of at least two weeks. The usual dose range is 2.5 to 10 mg once daily. A daily dose of 20 mg should not be exceeded.

In some patients treated once daily, the antihypertensive effect may diminish towards the end of the dosing interval. This can be evaluated by measuring blood pressure just prior to dosing to determine whether satisfactory control is being maintained for 24 hours. If it is not, either twice daily administration with the same total daily dose, or an increase in dose should be considered. If blood pressure is not controlled with ALTACE alone, a diuretic may be added. After the addition of a diuretic, it may be possible to reduce the dose of ALTACE.

Concomitant Diuretic Therapy: Symptomatic hypotension occasionally may occur following the initial dose of ALTACE and is more likely in patients who are currently being treated with a diuretic. The diuretic should, if possible, be discontinued for two to three days before beginning therapy with ALTACE to reduce the likelihood of hypotension (see WARNINGS). If the diuretic cannot be discontinued, an initial dose of 1.25 mg of ALTACE should be used with careful medical supervision for several hours and until blood pressure has stabilized. The dosage of ALTACE should subsequently be titrated (as described above) to the optimal response.

Use in Renal Impairment: For patients with a creatinine clearance below 40 mL/min/1.73 m² (serum creatinine above 2.5 mg/dL), the recommended initial dose is 1.25 mg of ALTACE once daily. Dosage may be titrated upward until blood pressure is controlled or to a maximum total daily dose of 5 mg. In patients with severe renal impairment (creatinine clearance below 10 mL/min/1.73 m²) the maximum total daily dose of 2.5 mg of ALTACE should not be exceeded.

Treatment Following Acute Myocardial Infarction:
Initiation of therapy requires consideration of concomitant medication and baseline blood pressure and should be instituted under close medical supervision, usually in a hospital, three to ten days following an acute myocardial infarction in haemodynamically stable patients with clinical signs of heart failure. The recommended initial dosage of ALTACE is 2.5 mg given twice a day (b.i.d.), one in the morning and one in the evening. If tolerated, and depending on the patient's response, dosage may be increased by doubling at intervals of one to three days. The maximum daily dose of ALTACE should not exceed 5 mg twice daily (b.i.d). After the initial dose of ALTACE, the patient should be observed under medical supervision for at least two hours and until blood pressure has stabilized for at least an additional hour. If a patient becomes hypotensive at this dosage, it is recommended that the dosage be lowered to 1.25 mg b.i.d. following effective management of the hypotension. (see WARNINGS – Hypotension).

Patients who have been fluid or salt depleted, or treated with diuretics are at an increased risk of hypotension (see WARNINGS – Hypotension). An excessive fall in blood pressure may occur particularly in the following: after the initial dose of ALTACE; after every first increase of dose of ALTACE; after the first dose of a concomitant diuretic and/or when increasing the dose of the concomitant diuretic. If appropriate, the dose of any concomitant diuretic should be reduced which may diminish the likelihood of hypotension (see PRECAUTIONS – Drug Interactions). Consideration should be given to reducing the initial dose to 1.25 mg of ALTACE in these patients.

Use in Renal Impairment: In patients with impaired renal function (creatinine clearance of 20-50 mL/min/1.73 m² body surface area), the initial recommended dosage is generally 1.25 mg of ALTACE once daily. This dosage may be increased with caution up to 1.25 mg of ALTACE twice daily, depending upon clinical response and tolerability.

Insufficient data is available concerning the use of ramipril following acute myocardial infarction in patients with heart failure and severe renal failure. (see ACTION AND CLINICAL PHARMACOLOGY – Pharmacokinetics and Metabolism, PRECAUTIONS – Renal Impairment).

Use in Hepatic Impairment: Insufficient data is available concerning the use of ramipril following acute myocardial infarction in patients with heart failure and hepatic dysfunction. Dose reduction and careful monitoring of these patients is required (see ACTIONS AND CLINICAL PHARMACOLOGY – Pharmacokinetics and Metabolism, PRECAUTIONS – Patients with Impaired Liver Function).

Management of Patients at Increased Risk of Cardiovascular Events: Recommended initial dose: 2.5 mg of ALTACE once daily. Depending on the tolerability, the dose is gradually increased. It is recommended to double the dose after one week of treatment and – after another three weeks – to increase it to 10 mg. Usual maintenance dose: 10 mg of ALTACE daily (see ACTION AND CLINICAL PHARMACOLOGY, WARNINGS and PRECAUTIONS). Dosage recommendations for special risk groups such as patients with renal or hepatic impairment, or at an increased risk of hypotension (fluid or salt depletion, treated with diuretics) are to be followed as previously described (see WARNINGS and PRECAUTIONS).

DOSAGE FORM

a) Composition
ALTACE (ramipril) capsules 1.25 mg, 2.5 mg, 5.0 mg, and 10.0 mg contain the medicinal ingredient ramipril in quantities of 1.25 mg, 2.5 mg, 5.0 mg, and 10.0 mg respectively. The qualitative formulation for all potencies of ALTACE is: ramipril, pre-gelatinized starch NF (as filler, gliding agent and disintegration agent) and empty gelatin capsules. Empty gelatin capsules for all potencies of ALTACE are composed of gelatin NF and coloring agents specific to each potency (see below).

POTENCY	CAP	BODY
1.25 mg	Yellow iron oxide Titanium dioxide	Titanium dioxide
2.5 mg	Yellow iron oxide FD & C red no. 3 Titanium dioxide	Titanium dioxide
5.0 mg	FD & C blue no. 2 FD & C red no. 3 Titanium dioxide	Titanium dioxide
10.0 mg	FD & C blue no. 2 FD & C red no. 3 Black iron oxide Titanium dioxide	Titanium dioxide

b) Stability and storage recommendations
Store ALTACE (ramipril) in original container at room temperature, below 25°C and not beyond the date indicated on the container.

AVAILABILITY: No. 4 hard gelatin capsules:

- 1.25 mg (white/yellow);
- 2.5 mg (white/orange);
- 5.0 mg (white/red);
- 10.0 mg (white/blue).

ALTACE capsules 1.25 mg, 2.5 mg, 5.0 mg and 10.0 mg are packaged in cartons of 30 (2 x 15 blister-packed) capsules. Bottles of 100 capsules and 500 capsules also available.

Product monograph available upon request.

References:
1. ALTACE Product Monograph. 2. The Heart Outcomes Prevention Evaluation Study Investigators (HOPE) Trial. Effects of an angiotensin-converting-enzyme inhibitor, ramipril, on cardiovascular events in high-risk patients. *N Engl J Med* 2000;342(3):145-53.

See page A-11

BRIEF PRESCRIBING INFORMATION
CONSULT FULL PRODUCT MONOGRAPH FOR COMPLETE PRESCRIBING INFORMATION

Reminyl®

galantamine hydrobromide tablets
4 mg, 8 mg, 12 mg galantamine base

Reminyl® ER

galantamine hydrobromide extended release capsules
8 mg, 16 mg, 24 mg galantamine base
Cholinesterase Inhibitor

INDICATIONS AND CLINICAL USE REMINYL (galantamine hydrobromide) and REMINYL ER are indicated for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer's type. REMINYL and REMINYL ER have not been studied in controlled clinical trials for longer than 6 months. *REMINYL and REMINYL ER should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease.* **Geriatrics (≥ 85 years of age):** There is limited safety information for REMINYL and REMINYL ER in this patient population (see **WARNINGS AND PRECAUTIONS, Pediatrics:** No data are available in children. Therefore, the use of REMINYL and REMINYL ER are not recommended in children under 18 years of age.

CONTRAINDICATIONS REMINYL and REMINYL ER are contraindicated in patients with known hypersensitivity to galantamine hydrobromide, other tertiary alkaloid derivatives or to any excipients used in the formulation.

WARNINGS AND PRECAUTIONS Carcinogenesis and Mutagenesis See ***Product Monograph Part II:*** **TOXICOLOGY- Carcinogenicity, Mutagenicity** for discussion on animal data. **Cardiovascular** Because of their pharmacological action, cholinesterase inhibitors have vagotonic effects on the sinoatrial and atrioventricular nodes, leading to bradycardia and heart block. These actions may be particularly important to patients with "sick sinus syndrome" or other supraventricular cardiac conduction disorders, or to patients taking other drugs concomitantly which significantly slow heart rate. In clinical trials, patients with serious cardiovascular disease were excluded. Caution should be exercised in treating patients with active coronary artery disease or congestive heart failure. It is recommended that REMINYL and REMINYL ER not be used in patients with cardiac conduction abnormalities (except for right bundle branch block) including "sick sinus syndrome" and those with unexplained syncopal episodes. In randomized controlled trials, bradycardia was reported at 2-3% for galantamine doses up to 24 mg/day compared with <1% for placebo, but was rarely severe and rarely led to treatment discontinuation. No increased incidence of heart block was observed at the recommended doses. Patients treated with galantamine up to 24 mg/day at the recommended dosing schedule showed a dose-related increase in risk of syncope (placebo, 0.7% [2/286]; 4 mg b.i.d., 0.4% [3/692]; 8 mg b.i.d., 1.3% [7/552]; 12 mg b.i.d., 2.2% [6/273]). A 6-week cardiovascular safety clinical trial (GAL-USA-16; n=139) was performed to investigate the effect of galantamine at doses up to 32 mg/day. This dosing regimen was: 8 mg/day in Week 1, 16 mg/day in Week 2, 24 mg/day in Weeks 3 and 4, and 32 mg/day in Weeks 5 and 6. Heart block/pauses greater than two seconds were more common in galantamine-treated patients than in placebo-treated patients. It should be noted that a forced 1-week dose escalation was used in this study, which is not recommended. Whether these cardiac effects are attenuated by slower titration rates is not known. Particular caution is warranted during titration where the majority of pauses occurred in the above study. **Metabolism** Cholinesterase inhibitors as well as Alzheimer's disease can be associated with significant weight loss. In controlled clinical trials, the use of REMINYL was associated with weight loss. Weight decrease occurred early during treatment and was related to dose. Weight loss of ≥7% occurred more frequently in patients treated with REMINYL and in female patients than in patients receiving placebo. Where weight loss may be of clinical concern, body weight should be monitored. **Gastrointestinal** Through their primary action, cholinesterase inhibitors may be expected to increase gastric acid secretion due to increased cholinergic activity. Therefore, patients should be monitored closely for symptoms of active or occult gastrointestinal bleeding, especially those with an increased risk for developing ulcers, e.g. those with a history of ulcer disease or patients using concurrent nonsteroidal anti-inflammatory drugs (NSAIDs). In controlled clinical studies with galantamine, patients with symptomatic peptic ulceration were excluded. Clinical studies of galantamine have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding (see **ADVERSE REACTIONS**). Galantamine, as a predictable consequence of its pharmacological properties, has been shown to produce nausea, vomiting and diarrhea, anorexia and weight loss. These effects appeared more frequently at higher doses (see **ADVERSE REACTIONS**), with nausea and vomiting being more prevalent in women and patients with lower body weight and correspondingly higher plasma drug concentrations. Females are more sensitive to the cholinergic adverse effects associated with cholinesterase inhibitors and in general are more likely to experience nausea and vomiting than are males. In most cases, these effects were of mild to moderate intensity and transient and have resolved during continued REMINYL treatment or upon treatment discontinuation. **Genitourinary** Although not observed in clinical trials of galantamine, cholinomimetics may cause bladder outflow obstruction. **Neurologic** Seizures: In placebo-controlled trials with galantamine, cases of seizure were reported; there was no increase in incidence compared with placebo. Although cholinomimetics are believed to have some potential to cause seizures, seizure activity may also be a manifestation of Alzheimer's disease. The risk/benefit of REMINYL and REMINYL ER treatment for patients with a history of seizure disorder must therefore be carefully evaluated. REMINYL and REMINYL ER have not been studied in patients with moderately severe or severe Alzheimer's disease, non-Alzheimer dementias or individuals with Parkinsonian features. The efficacy and safety of REMINYL and REMINYL ER in these patient populations are unknown. **Peri-Operative Considerations** Anesthesia: Galantamine, as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia. **Respiratory** Like other cholinomimetic drugs, REMINYL and REMINYL ER should be prescribed with care for patients with a history of asthma or obstructive pulmonary disease. **Special Populations Hepatic Impairment:** There is limited information on the pharmacokinetics of galantamine in hepatically impaired patients. It is therefore recommended that dose escalation with REMINYL or REMINYL ER in Alzheimer's disease patients with hepatic impairment be undertaken with caution and under conditions of close monitoring for adverse effects (see **DOSAGE AND ADMINISTRATION, Special Populations**). Since no data are available on the use of REMINYL or REMINYL ER in patients with a creatinine clearance of less than 9 mL/min, REMINYL and REMINYL ER are not recommended for this population. **Geriatrics (≥85 years of age):** In controlled clinical studies, the number of patients aged 85 years or over who received REMINYL at therapeutic doses of 16 or 24 mg/day was 123. Of these patients, 70 received the maximum recommended dose of 24 mg/day. There is limited safety information for REMINYL in this patient population. Since cholinomimetics as well as Alzheimer's disease can be associated with significant weight loss, caution is advised regarding the use of REMINYL and REMINYL ER in elderly patients with low body weight, especially in those ≥85 years old. Use in Elderly Patients with Serious Comorbid Disease There is limited information on the safety of galantamine treatment in patients with mild to moderate Alzheimer's disease and serious/significant comorbidity. The use of REMINYL and REMINYL ER in Alzheimer's disease patients with chronic illnesses common among the geriatric population, should be considered only after careful risk/benefit assessment and include close monitoring for adverse events. Dose escalation in this patient population should proceed with caution. **Patients with Mild Cognitive Impairment (MCI):** Mortality in Investigational Trials in MCI Two randomized, double-blind, placebo-controlled efficacy and safety studies of 2 years' duration were completed in non-demented subjects with MCI. Individuals with MCI demonstrate isolated memory impairment greater than expected for their age and education, but do not meet current diagnostic criteria for Alzheimer's Disease. In these trials, REMINYL was not shown to be effective in patients with MCI. In the double-blind portion of these two trials, a total of 13 deaths in subjects on REMINYL (n=1026) were recorded and 1 death in subjects on placebo (n=1022); the reason for this difference is currently unknown. This difference in mortality has not been observed in REMINYL studies in Alzheimer's Disease. Approximately half of the REMINYL deaths appeared to have resulted from various vascular causes (myocardial infarction, stroke, and sudden death); other deaths appeared to have resulted from infection, suicide and cancer. There is no evidence of an increased risk of mortality when REMINYL is used in patients with mild to moderate Alzheimer's Disease. **Pregnant Women:** In a teratology study in which rats were dosed from Day 14 (females) or Day 60 (males) prior to mating through the period of organogenesis, a slightly increased incidence of skeletal variations was observed at doses of 8 mg/kg/day (3 times the MRHD on a mg/m² basis) and 16 mg/kg/day. In a study in which pregnant rats were dosed from the beginning of organogenesis through day 21 post-partum, pup weights were decreased at 8 and 16 mg/kg/day, but no adverse effects on other postnatal developmental parameters were seen. The doses causing the above effects in rats produced slight maternal toxicity. No major malformations were caused in rats given up to 16 mg/kg/day. No drug related teratogenic effects were observed in rabbits given up to 40 mg/kg/day (32 times the MRHD on a mg/m² basis) during the period of organogenesis. The safety of REMINYL and REMINYL ER in pregnant women has not been established. REMINYL and REMINYL ER should not be used in women of childbearing potential unless, in the opinion of the physician, the potential benefit to the patient justifies the potential risk to the fetus. **Nursing Women:** It is not known whether galantamine is excreted in human breast milk and therefore REMINYL and REMINYL ER should not be used in nursing mothers. **Pediatrics:** The safety and effectiveness of REMINYL and REMINYL ER in any illness occurring in pediatric patients have not been established.

ADVERSE REACTIONS Clinical Trial Adverse Drug Reactions Because clinical trials are conducted under very specific conditions, the adverse drug reaction rates observed in the clinical trials may not reflect the rates observed in practice and should not be compared to the rates in the clinical trials of another drug. Adverse drug reaction information from clinical trials is useful for identifying drug-related adverse events and for approximating rates. A total of 2287 patients with mild to moderate Alzheimer's disease were treated with REMINYL in Phase III controlled clinical studies using either a 1-week or 4-week dose-escalation period, and 761 patients received REMINYL 24 mg/day, the maximum recommended maintenance dose. The number of patients who completed the studies was 1686 (72%). The mean duration of treatment for all REMINYL groups was 130 days (range 1-214 days). Adverse Events Leading to Discontinuation Overall, 19% (441/2287) of patients treated with REMINYL discontinued from Phase III controlled clinical trials due to adverse events compared to 8% (98/1159) in the placebo group. For patients treated with REMINYL, the rate of discontinuation due to adverse events was 14% for males and 22% for females. In the 4-week dose-escalation fixed-dose study (GAL-USA-10), 8% (55/692) of patients treated with REMINYL withdrew due to adverse events compared to 7% (20/286) in the placebo group. During the dose-escalation phase of this study the incidence of discontinuations due to adverse events was 4% for placebo, 5% for REMINYL 16 mg/day and 6% for REMINYL 24 mg/day. During the maintenance phase, 4% of patients who received placebo, 3% of patients who received REMINYL 16 mg/day and 4% of patients who received REMINYL 24 mg/day withdrew from this study due to adverse events. Table 1.1 shows the most frequent adverse events leading to discontinuation for study GAL-USA-10, in which the recommended 4-week dose-escalation schedule was used.

Table 1.1: Most frequent adverse events leading to discontinuation in a placebo-controlled, double-blind trial with a 4-week dose-escalation schedule (GAL-USA-10)

Adverse Events	Recommended 4-week dose escalation		
	Placebo n=286 %	16 mg/day n=279 %	24 mg/day n=273 %
Nausea	<1	2	4
Vomiting	0	1	3
Anorexia	<1	1	<1
Dizziness	<1	2	1
Syncope	0	0	1

Most Frequent Adverse Clinical Events Seen in Association with the Use of REMINYL The most frequent adverse events, defined as those occurring at a frequency of at least 5% and at least twice the rate of placebo in study GAL-USA-10, in which the recommended 4-week dose-escalation schedule was used are shown in Table 1.2. These events were primarily gastrointestinal and tended to occur at a lower rate with 16 mg/day, the initial recommended maintenance dose. Administration of REMINYL with food, the use of anti-emetic medication and ensuring adequate fluid intake may reduce the impact of these events.

Table 1.2: Most frequent adverse events in a randomized placebo-controlled clinical trial with a 4-week dose increment during dose-escalation and maintenance phases (GAL-USA-10)

Adverse Events	Week 1-12[1]			Week 13-21		
	Placebo n=286 %	16 mg/day n=279 %	24 mg/day n=273 %	Placebo n=259 %	16 mg/day n=243 %	24 mg/day n=241 %
Nausea	5	11	13	<1	4	6
Vomiting	<1	5	6	<1	2	6
Diarrhea	5	9	4	2	5	2
Anorexia	2	5	5	1	2	5

[1] Dose escalation occurred with 4 weeks per dose increment.

The majority of these adverse events occurred during the dose-escalation period. Nausea and vomiting, the most frequent adverse events, occurred more frequently at higher doses, lasted 5-7 days in most cases, and the majority of patients had one episode. The incidence of weight loss in this study was, during dose escalation (Weeks 1-12): placebo, 1%; 16 mg/day, 3%; 24 mg/day, 2%; and during the maintenance phase (Weeks 13-21): placebo, <1%; 16 mg/day, 3%; 24 mg/day, 3%. Dose-escalation should be cautious and maintenance dosing should remain flexible and be adjusted according to individual needs. Adverse Events Reported in Controlled Trials The reported adverse events in REMINYL trials reflect experience gained under closely monitored conditions in a highly selected patient population. In actual practice or in other clinical trials, these frequency estimates may not apply, as the conditions of use, reporting behaviour and the types of patients treated may differ. Table 1.3 lists the most common adverse events (adverse events occurring with an incidence of 2% with REMINYL treatment and in which the incidence was greater than with placebo treatment) for four placebo-controlled trials for patients treated with 16 or 24 mg/day of REMINYL. The combined values presented in Table 1.3 were derived from trials using a 1-week or the recommended 4-week dose-escalation period.

Table 1.3: Adverse events reported in at least 2% of patients with Alzheimer's disease administered REMINYL and at a frequency greater than with placebo (combined 1- and 4-week dose-escalation data)

Body System/ Adverse Events	Placebo (n=801) %	REMINYL[1] (n=1040) %
Body as a whole - general disorders		
Fatigue	3	5
Syncope	1	2
Central & peripheral nervous system disorders		
Dizziness	6	9
Headache	5	8
Tremor	2	3
Gastrointestinal system disorders		
Nausea	9	24
Vomiting	4	13
Diarrhea	7	9
Abdominal pain	4	5
Dyspepsia	2	5
Heart rate and rhythm disorders		
Bradycardia	1	2
Metabolic and nutritional disorders		
Weight decrease	2	7
Psychiatric disorders		
Anorexia	3	9
Depression	5	7
Insomnia	4	5
Somnolence	3	4
Red blood cell disorders		
Anemia	2	3
Respiratory system disorders		
Rhinitis	3	4
Urinary system disorders		
Urinary tract infection	7	8
Hematuria	2	3

[1] Adverse events in patients treated with 16 or 24 mg/day of REMINYL in three placebo-controlled trials with a 1-week dose-escalation period and a 26-week fixed-dose REMINYL treatment, and one placebo-controlled trial with the recommended 4-week dose-escalation period and a 21-week fixed-dose REMINYL treatment are included.

No clinically relevant abnormalities in laboratory values were observed. In a cardiovascular safety clinical trial (GAL-USA-16), pauses greater than two seconds were more common in galantamine-treated patients than in placebo-treated patients during the dose-escalation period (see **WARNINGS AND PRECAUTIONS**). Most Frequent Adverse Clinical Events Seen in Association with the Use of REMINYL ER Adverse reactions in clinical trials of once-daily treatment with REMINYL ER extended release capsules were similar to those seen with REMINYL immediate release tablets (see Table 1.4).

Table 1.4: Adverse events reported in at least 2% of patients with Alzheimer's disease administered REMINYL or REMINYL ER and at a frequency greater than placebo

System Organ Class / Preferred Term	Placebo (n=320) %	REMINYL (n=326) %	REMINYL ER (n=319) %
Body as a whole – general disorders			
Injury [6]		4	8
Edema peripheral	3	2	4
Fatigue	1	4	4
Syncope	1	1	2
Fever [1]		2	1
Leg pain	1	2	<1
Central & peripheral nervous system disorders			
Dizziness	4	7	10
Headache	6	6	8
Tremor	0	1	2
Gastrointestinal system disorders			
Nausea	5	14	17
Vomiting	2	9	7
Abdominal pain	2	3	2
Dyspepsia	2	3	2
Heart rate and rhythm disorders			
Bradycardia	2	2	3
Metabolic and nutritional disorders			
Weight decrease	1	5	4
Hyperglycemia	1	2	2
Musculoskeletal system disorders			
Arthralgia	2	2	3
Skeletal pain [1]		3	2
Arthritis	1	1	2
Myalgia	1	1	2
Psychiatric disorders			
Anorexia	3	7	6
Depression	3	5	6
Anxiety	3	1	4
Somnolence	2	2	3
Depression aggravated	1	2	2
Aggressive reaction	1	2	2
Nervousness	1	2	1
Respiratory system disorders			
Rhinitis	3	4	4
Pneumonia	1	2	2
Secondary terms			
Abrasion nos[4]	1	1	2
Skin and appendages disorders			
Rash	1	<1	3
Urinary system disorders			
Hematuria	1	1	2
Micturition frequency	1	2	1
Vision disorders			
Cataract	1	1	2

[4] not otherwise specified

Other Adverse Events Observed During Clinical Trials REMINYL has been administered to 3055 patients with Alzheimer's disease during clinical trials worldwide. A total of 2357 patients received galantamine in placebo-controlled trials and 761 patients with Alzheimer's disease received galantamine 24 mg/day, the maximum recommended maintenance dose. About 1000 patients received galantamine for at least one year and approximately 200 patients received galantamine for two years. To establish the rate of adverse events, data from all patients for any dose of REMINYL in 8 placebo-controlled trials and 6 open-label extension trials were pooled. The methodology to gather and codify these adverse events was standardized across trials, using WHO terminology. All events occurring in approximately 0.1% of patients are included, except for those already listed elsewhere in labelling, WHO terms too general to be informative, or relatively minor events. Events are classified by body system and listed using the following definitions: *frequent adverse events* - those occurring in at least 1/100 patients; *infrequent adverse events* - those occurring in 1/100 to 1/1000 patients; *rare* - those occurring in 1/1000 to 1/10000 patients; *very rare* - those occurring in fewer than 1/10000 patients. These adverse events are not necessarily related to REMINYL treatment and in most cases were observed at a similar frequency in placebo-treated patients in the controlled studies. Body as a Whole - General Disorders: *Frequent:* chest pain, asthenia, fever, malaise. Cardiovascular System Disorders: *Frequent:* hypertension; *Infrequent:* postural hypotension, hypotension, dependent edema, cardiac failure, myocardial ischemia or infarction. Central & Peripheral Nervous System Disorders: *Infrequent:* vertigo, hypertonia, convulsions, involuntary muscle contractions, paresthesia, ataxia, hypokinesia, hyperkinesia, aphonia, aphasia, leg cramps, tinnitus, transient ischemic attack or cerebrovascular accident. Gastrointestinal System Disorders: *Frequent:* flatulence; *Infrequent:* gastritis, melena, dysphagia, rectal hemorrhage, dry mouth, saliva increased, diverticulitis, gastroenteritis, hiccup; *Rare:* esophageal perforation. Heart Rate & Rhythm Disorders: *Infrequent:* AV block, palpitation, atrial arrhythmias including atrial fibrillation and supraventricular tachycardia, QT prolonged, bundle branch block, T-wave inversion, ventricular tachycardia; *Rare:* severe bradycardia. Metabolic & Nutritional Disorders: *Infrequent:* hyperglycemia, alkaline phosphatase increased, NPN increased. Platelet, Bleeding & Clotting Disorders: *Infrequent:* purpura, epistaxis, thrombocytopenia. Psychiatric Disorders: *Infrequent:* apathy, paranoia, paranoid reaction, libido increased, delirium; *Rare:* suicidal ideation, suicide attempt. Urinary System Disorders: *Frequent:* incontinence; *Infrequent:* hematuria, micturition frequency, cystitis, urinary retention, nocturia, renal calculi. **Post-Market Adverse Drug Reactions** Other adverse events from post-approval controlled and uncontrolled clinical trials and post-marketing experience observed in patients treated with REMINYL include: Body as a Whole - General Disorders: dehydration (including rare, severe cases leading to renal insufficiency and renal failure). Central & Peripheral Nervous System Disorders: behavioural disturbances including agitation, aggression and hallucinations. Gastrointestinal: upper and lower GI bleeding. Metabolic & Nutritional Disorders: hypokalemia. Some of these adverse events may be attributable to cholinomimetic properties of REMINYL or in some cases may represent manifestations or exacerbations of the underlying disease processes common in the elderly population.

DRUG INTERACTIONS Overview Multiple metabolic pathways and renal excretion are involved in the elimination of galantamine so no single pathway appears predominant. Based on *in vitro* studies, CYP2D6 and CYP3A4 were the major enzymes involved in the metabolism of galantamine. CYP2D6 was involved in the formation of O-desmethyl-galantamine, whereas CYP3A4 mediated the formation of galantamine-N-oxide. Use with Anticholinergics Because of their mechanism of action, cholinesterase inhibitors have the potential to interfere with the activity of anticholinergic medications. Use with Cholinomimetics and Other Cholinesterase Inhibitors A synergistic effect may be expected when cholinesterase inhibitors are given concurrently with succinylcholine, similar neuromuscular blocking agents or cholinergic agonists such as bethanechol. Use with other Psychoactive Drugs Few patients in the clinical trials received neuroleptics, antidepressants or anticonvulsants, there is thus limited information concerning the interaction of REMINYL and REMINYL ER with these drugs. **Drug-Drug Interactions** Effect of Other Drugs on the Metabolism of Galantamine Pharmacokinetic studies to assess the potential of galantamine for interaction with cimetidine, ranitidine, ketoconazole, erythromycin, paroxetine, warfarin and digoxin were limited to short-term, mostly single-dose studies in young healthy volunteers. Similar studies in elderly patients were not done. *In vitro* CYP3A4 and CYP2D6 are the major enzymes involved in the metabolism of galantamine. CYP3A4 mediates the formation of galantamine-N-oxide, whereas CYP2D6 is involved in the formation of O-desmethyl-galantamine. Because galantamine is also glucuronidated and excreted unchanged in urine, no single pathway appears predominant. *In vivo Cimetidine and Ranitidine:* Galantamine was administered as a single dose of 4 mg on Day 2 of a 3-day treatment with either cimetidine (800 mg daily; n=6 males and 6 females) or ranitidine (300 mg daily; n=6 males and 6 females). Cimetidine increased the bioavailability of galantamine by approximately 16%. Ranitidine had no effect on the pharmacokinetics of galantamine. *Ketoconazole:* Ketoconazole, a strong inhibitor of CYP3A4 and an inhibitor of CYP2D6, at a dose of 200 mg b.i.d. for 4 days, increased the AUC of galantamine by 30% when subjects were treated with galantamine 4 mg b.i.d. for 8 days (n=8 males and 8 females). *Erythromycin:* Erythromycin, a moderate inhibitor of CYP3A4 at a dose of 500 mg q.i.d. for 4 days increased the AUC of galantamine by 10% when subjects received galantamine 4 mg b.i.d. for 6 days (n=8 males and 8 females). *Paroxetine:* Paroxetine, a strong inhibitor of CYP2D6, increased the AUC of 4 mg b.i.d., 8 mg b.i.d. and 12 mg b.i.d. galantamine by 40%, 45% and 48%, respectively, in 16 healthy volunteers (8 males and 8 females) who received galantamine together with 20 mg/day paroxetine. Effect of Galantamine on the Metabolism of Other Drugs *In vitro* Galantamine did not inhibit the metabolic pathways catalyzed by CYP1A2, CYP2A6, CYP3A4, CYP4A, CYP2C, CYP2D6 or CYP2E1. This indicates that the inhibitory potential of galantamine towards the major forms of cytochrome P450 is very low. *In vivo Warfarin:* Galantamine at 12 mg b.i.d. had no effect on the pharmacokinetics of R- and S-warfarin (25 mg single dose) or on the prothrombin time (n=16 males). The protein binding of warfarin was unaffected by galantamine. *Digoxin:* Galantamine at 12 mg b.i.d. had no effect on the steady-state pharmacokinetics of digoxin (0.375 mg once daily) when they were co-administered. In this study, however, one healthy subject was hospitalized for 2nd and 3rd degree heart block and bradycardia (n=8 males and 8 females). *Nicotinic Receptor Modulation* Single *in vitro* applications of galantamine dose-dependently modulate the effect on nicotinic receptors, having a positive allosteric (sensitizing) effect at concentrations below 0.28 µg/mL (1 µM) and an inhibitory effect at higher concentrations. Chronic *in vitro* or *in vivo* studies on nicotinic receptor modulation have not been conducted. It is unknown whether galantamine has an effect on the pharmacodynamic action of other drugs that act on cholinergic nicotinic receptors. **Drug-Food Interactions** Interactions with food have not been established. **Drug-Herb Interactions** Interactions with herbal products have not been established. **Drug-Laboratory Interactions** Interactions with laboratory tests have not been established.

DOSAGE AND ADMINISTRATION REMINYL (galantamine hydrobromide) and REMINYL ER are not indicated for use in patients with mild cognitive impairment (see WARNINGS AND PRECAUTIONS, Special Populations, Patients with Mild Cognitive Impairment (MCI): Mortality in Investigational Trials in MCI. *REMINYL and REMINYL ER should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's disease.* REMINYL tablets should be administered twice a day, preferably with morning and evening meals. REMINYL ER extended release capsules should be administered once daily in the morning, preferably with food. Patients and caregivers should be advised to ensure adequate fluid intake during treatment. **Dosing Considerations** • Concomitant Treatment In patients treated with potent CYP2D6 or CYP3A4 inhibitors, dose reductions can be considered. • Special Populations: Dosage adjustments may be required for elderly patients (>85 years old) with low body weight (especially females), and patients with hepatic and/or renal impairment. • Missed Dose: The missed dose should be taken at the next scheduled dose. Doses should not be doubled. If therapy has been interrupted for several days or longer, the patient should be restarted at the lowest dose and the dose escalated to the current dose. **Recommended Dose and Dosage Adjustment** The dosage of REMINYL shown to be effective in controlled clinical trials is 16-32 mg/day given as twice daily dosing. As the dose of 32 mg/day is less well tolerated than lower doses and does not provide increased effectiveness, the recommended dose range is 16-24 mg/day. The dose of 24 mg/day did not provide a statistically significant greater clinical benefit than 16 mg/day. It is possible, however, that a daily dose of 24 mg of REMINYL might provide additional benefit for some patients. The recommended starting dose is 8 mg/day. The dose should be increased to the initial maintenance dose of 16 mg/day after 4 weeks. If this initial maintenance dose is well tolerated, a further increase to 24 mg/day may be considered only after a minimum of 4 weeks at 16 mg/day. The abrupt withdrawal of REMINYL or REMINYL ER in those patients who had been receiving doses in the effective range was not associated with an increased frequency of adverse events in comparison with those continuing to receive the same doses of that drug. The beneficial effects of REMINYL and REMINYL ER are lost, however, when the drug is discontinued. Special Populations Dose escalation for elderly patients (>85 years old) with low body weight (especially females) or serious comorbid diseases should be undertaken with particular caution. *Hepatic Impairment* Galantamine plasma levels may be increased in patients with moderate to severe hepatic impairment. In patients with moderately impaired hepatic function (Child-Pugh score of 7-9), based on pharmacokinetic modelling, dosing with REMINYL tablets should begin with 4 mg once daily in the morning, preferably with food, for at least 1 week. Then the dosage should be increased to 4 mg twice a day for at least 4 weeks. For REMINYL ER extended release capsules, based on pharmacokinetic modelling, dosing should begin with 8 mg every other day in the morning, preferably with food, for at least 1 week. Then the dosage should be increased to 8 mg once daily for at least 4 weeks. In these patients, daily doses should not exceed a total of 16 mg/day. Since no data are available on the use of REMINYL or REMINYL ER in patients with severe hepatic impairment (Child-Pugh score of 10-15), REMINYL and REMINYL ER are not recommended for this population (see **WARNINGS AND PRECAUTIONS**). *Renal Impairment* For patients with renal impairment (creatinine clearance of 9 to 60 mL/min), dose escalation should proceed cautiously and the maintenance dose should generally not exceed 16 mg/day. Since no data are available on the use of REMINYL or REMINYL ER in patients with a creatinine clearance less than 9 mL/min, REMINYL and REMINYL ER are not recommended for this population (see **WARNINGS AND PRECAUTIONS**). In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision.

OVERDOSAGE Symptoms Overdosage with cholinesterase inhibitors can result in cholinergic crisis characterized by severe nausea, vomiting, salivation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. In a postmarketing report, one patient who had been taking 4 mg of galantamine daily inadvertently ingested eight 4 mg tablets (32 mg total) on the tenth day of treatment. Subsequently, she developed bradycardia, QT prolongation, ventricular tachycardia and torsades de pointes accompanied by a brief loss of consciousness for which she required hospital treatment. ECG obtained just prior to initiation of galantamine treatment was normal. Two additional cases of accidental ingestion of 32 mg (nausea, vomiting, and dry mouth; nausea, vomiting, and substernal chest pain) and one of 40 mg (vomiting), resulted in brief hospitalizations for observation with full recovery. One patient, who was prescribed 24 mg/day and had a history of hallucinations over the previous two years, mistakenly received 24 mg twice daily for 34 days and developed hallucinations requiring hospitalization. Another patient, who was prescribed 16 mg/day, inadvertently ingested 160 mg and experienced sweating, vomiting, bradycardia, and near-syncope one hour later, which necessitated hospital treatment. His symptoms resolved within 24 hours. **Treatment** Galantamine has a plasma half-life of approximately 7-8 hours. It is recommended that, in case of asymptomatic overdose, no further dose of REMINYL or REMINYL ER should be administered and the patient should be monitored. As in any case of overdose, general supportive measures should be utilized. Signs and symptoms of significant overdosing of galantamine are predicted to be similar to those of overdosing of other cholinomimetics. These effects generally involve the central nervous system, the parasympathetic nervous system, and the neuromuscular junction. In addition to muscle weakness or fasciculations, some or all of the following signs of cholinergic crisis may develop: severe nausea, vomiting, gastrointestinal cramping, salivation, lacrimation, urination, defecation, sweating, bradycardia, hypotension, respiratory depression, collapse and convulsions. Increasing muscle weakness is a possibility and may result in death if respiratory muscles are involved. Tertiary anticholinergics such as atropine may be used as an antidote for galantamine overdosage. Intravenous atropine sulphate titrated to effect is recommended at an initial dose of 0.5 to 1.0 mg i.v. with subsequent doses based upon clinical response. Atypical responses in blood pressure and heart rate have been reported with other cholinomimetics when co-administered with quaternary anticholinergics. It is not known whether galantamine and/or its metabolites can be removed by dialysis (hemodialysis, peritoneal dialysis, or hemofiltration). Dose-related signs of toxicity in animals included hypoactivity, tremors, clonic convulsions, salivation, lacrimation, chromodacryorrhea, mucoid feces, and dyspnea.

DOSAGE FORMS REMINYL (galantamine hydrobromide), expressed as galantamine base, is available as film-coated tablets in the following strengths: 4 mg galantamine as off-white, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G4" on the other side; 8 mg galantamine as pink, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G8" on the other side; 12 mg galantamine as orange-brown, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G12" on the other side. REMINYL ER (galantamine hydrobromide) extended release capsules contain white to off-white pellets. The following strengths are available: 8 mg galantamine as white opaque capsules imprinted with "G 8"; 16 mg galantamine as pink opaque capsules imprinted with "G 16"; 24 mg galantamine as caramel opaque capsules imprinted with "G 24".

Product Monograph available upon request.

JANSSEN-ORTHO

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See OBC

Pr REQUIP® ropinirole

Ropinirole (as ropinirole hydrochloride)

TABLETS: 0.25 mg, 1.0 mg, 2.0 mg, 5.0 mg

THERAPEUTIC CLASSIFICATION: AntiParkinsonian Agent / Dopamine Agonist

INDICATIONS AND CLINICAL USE: REQUIP® (ropinirole hydrochloride) is indicated in the treatment of the signs and symptoms of idiopathic Parkinson's disease. REQUIP® can be used both as early therapy, without concomitant levodopa and as an adjunct to levodopa. Three year and five year active-comparator controlled clinical trials have been conducted.

CONTRAINDICATIONS: REQUIP® (ropinirole hydrochloride) is contraindicated in patients with a known hypersensitivity to ropinirole hydrochloride or the excipients of the drug product.

WARNINGS: Sudden Onset of Sleep – Patients receiving treatment with REQUIP® (ropinirole hydrochloride), and other dopaminergic agents have reported suddenly falling asleep while engaged in activities of daily living, including operating a motor vehicle, which has sometimes resulted in accidents. Although some of the patients reported somnolence while on REQUIP®, others perceived that they had no warning signs, such as excessive drowsiness, and believed that they were alert immediately prior to the event. Physicians should alert patients of the reported cases of sudden onset of sleep, bearing in mind that these events are NOT limited to initiation of therapy. Patients should also be advised that sudden onset of sleep has occurred without warning signs. If drowsiness or sudden onset of sleep should occur, patients should immediately contact their physician. Until further information is available on the management of this unpredictable and serious adverse event, patients should be warned not to drive or engage in other activities where impaired alertness could put themselves and others at risk of serious injury or death (e.g., operating machines). Episodes of falling asleep while engaged in activities of daily living have also been reported in patients taking other dopaminergic agents, therefore, symptoms may not be alleviated by substituting these products. Presently, the precise cause of this event is unknown. It is known that many Parkinson's disease patients experience alterations in sleep architecture, which results in excessive daytime sleepiness or spontaneous dozing, and that dopaminergic agents can also induce sleepiness. There is insufficient information to determine whether this event is associated with REQUIP®, all dopaminergic agents or Parkinson's disease itself. **Orthostatic Symptoms** – Dopamine agonists appear to impair the systemic regulation of blood pressure with resulting orthostatic symptoms of dizziness or lightheadedness, with or without documented hypotension. These symptoms appear to occur especially during dose escalation. Therefore, patients treated with dopamine agonists should be carefully monitored for signs and symptoms of orthostatic hypotension, especially during dose escalation (see DOSAGE and ADMINISTRATION) and should be informed of this risk. **Hallucinations** – ***Early Therapy:*** In placebo- controlled trials, REQUIP® (ropinirole hydrochloride) caused hallucination in 5.1% of patients during early therapy (1.4% in the placebo group). Hallucination was of sufficient severity that it led to discontinuation in 1.3% of patients. The incidence of hallucination was dose-dependent. In a 5-year study comparing REQUIP® with levodopa in early Parkinson's patients, the overall incidence of hallucinations was 17.3% (31/179) for patients treated with REQUIP® and 5.6% (5/89) for levodopa patients. Hallucinations led to discontinuation of the study treatment in 5.0% of REQUIP® and 2.2% of levodopa patients. In a 3-year study comparing REQUIP® with another dopamine agonist, the overall incidence of hallucinations was 9.5% (16/168) for patients treated with REQUIP® and 9.0% (15/167) for patients receiving active comparator. Hallucinations led to discontinuation of the study treatment in 2.4% of REQUIP® patients and 3.0% of comparator patients. Concomitant Selegiline: In a 5-year study, REQUIP® patients receiving concomitant selegiline reported a higher incidence of hallucinations (23.5%) than did those without (12.2%); this subpopulation effect was not seen in the L-dopa arm (hallucinations with concomitant selegiline = 2.0% vs hallucinations without selegiline = 8.0%). ***Adjunct Therapy***: Hallucinations were experienced by 10.1% of patients receiving REQUIP® and levodopa, compared to 4.2% receiving placebo and levodopa. Hallucinations were of sufficient severity that it led to discontinuation in 1.9% of patients. The incidence of hallucinations was dose dependent.

PRECAUTIONS: Cardiovascular – Since REQUIP® (ropinirole hydrochloride) has not been studied in patients with a history or evidence of significant cardiovascular disease including myocardial infarction, unstable angina, cardiac decompensation, cardiac arrhythmias, vaso-occlusive disease (including cerebral) or cardiomyopathy, it should be used with caution in such patients. There is limited experience with REQUIP® in patients treated with antihypertensive and antiarrhythmic agents. Consequently, in such patients, the dose of REQUIP® should be titrated with caution. **Orthostatic Symptoms** - Orthostatic symptoms of dizziness or lightheadedness as well as somnolence may occur during REQUIP® therapy. **Neuroleptic Malignant Syndrome** – A symptom complex resembling the neuroleptic malignant syndrome (characterized by elevated temperature, muscular rigidity, altered consciousness, and autonomic instability), with no other obvious etiology, has been reported in association with rapid dose reduction, withdrawal of, or changes in anti-Parkinsonian therapy. A single spontaneous report of a symptom complex resembling the neuroleptic malignant syndrome has been observed in a 66 year old diabetic male patient with Parkinson's disease, who developed fever, muscle stiffness, and drowsiness 8 days after beginning REQUIP® treatment. The patient also experienced acute bronchitis, which did not respond to antibiotic treatment. REQUIP® was discontinued three days before the patient died. The reporting physician considered these events to be possibly related to REQUIP® treatment. (see DOSAGE AND ADMINISTRATION). A single spontaneous report of severe muscle pain has been reported in a 66 year old male patient around his thigh. The reporting physician considered the event to be probably related to REQUIP® treatment. **Retinal Pathology in Rats** – In a two year carcinogenicity study in albino Sprague-Dawley rats, retinal atrophy was observed at incidences of 0%, 1.4%, 1.4% and 10% of male rats and 0%, 4.4%, 2.9% and 12.9% of female rats dosed at 0, 1.5, 15 and 50 mg/kg/day respectively. The incidence was significantly higher in both male and female animals dosed at 50 mg/kg/day. The 50 mg/kg/day dose represents a 2.8 fold greater exposure (AUC) and a 13.1 fold greater exposure (C_{max}) to ropinirole in rats than the exposure would be in humans at the maximum recommended dose of 24 mg/day. The relevance of this finding to humans is not known. **Pregnancy** – The use of REQUIP® during pregnancy is not recommended. REQUIP® given to pregnant rats during organogenesis (gestation days 8 through 15) resulted in decreased fetal body weight at 60 mg/kg/day (approximately 3–4 times the AUC at the maximal human dose of 8 mg t.i.d.), increased fetal death at 90 mg/kg/day (approximately 5 times the AUC at the maximal human dose of 8 mg t.i.d.) and digital malformations at 150 mg/kg/day (approximately 8–9 times the AUC at the maximal human dose of 8 mg t.i.d.). These effects occurred at maternally toxic doses. There was no indication of an effect on development of the conceptus at a maternally toxic dose of 20 mg/kg/day in the rabbit. In a perinatal-postnatal study in rats, 10 mg/kg/day of REQUIP® (approximately 0.5 – 0.6 times the AUC at the maximal human dose of 8 mg t.i.d.) impaired growth and development of nursing offspring and altered neurological development of female offspring. **Nursing Mothers** – Since REQUIP® suppresses lactation, it should not be administered to mothers who wish to breast-feed infants. Studies in rats have shown that REQUIP® and/or its metabolites cross the placenta and are excreted in breast milk. Consequently, the human fetus and/or neonate may be exposed to dopamine agonist activity. **Use in Women Receiving Estrogen Replacement Therapy**– In female patients on long-term treatment with conjugated estrogens, oral clearance was reduced and elimination half-life prolonged compared to patients not receiving estrogens. In patients, already receiving estrogen replacement therapy, REQUIP® may be titrated in the recommended manner according to clinical response. However, if estrogen replacement therapy is stopped or introduced during treatment with REQUIP®, adjustment of the REQUIP® dosage may be required. **Pediatric Use** – Safety and effectiveness in the pediatric population have not been established. **Renal and Hepatic Impairment** – No dosage adjustment is needed in patients with mild to moderate renal impairment (creatinine clearance of 30 to 50 mL/min). Because the use of REQUIP® in patients with severe renal impairment or hepatic impairment has not been studied, administration of REQUIP® to such patients is not recommended. **Drug Interactions** – ***Psychotropic Drugs:*** Neuroleptics and other centrally active dopamine antagonists may diminish the effectiveness of REQUIP®. Therefore, concomitant use of these products is not recommended. Based on population pharmacokinetic assessment, no interaction was seen between REQUIP® and tricyclic antidepressants or benzodiazepines. ***Anti-Parkinson Drugs:*** Based on population pharmacokinetic assessment, there were no interactions between REQUIP® and drugs commonly used to treat Parkinson's disease, i.e., selegiline, amantadine, and anticholinergics. ***Levodopa:*** The potential pharmacokinetic interaction of levodopa/ carbidopa (100 mg/10 mg b.i.d.) and REQUIP® (2 mg t.i.d.) was assessed in levodopa naive (de novo) male and female patients with Parkinson's disease (n=30, mean age 64 years). The rate and extent of availability of REQUIP® at steady state were essentially the same with or without levodopa. Similarly, the rate and extent of availability of levodopa, as well as its elimination half-life, were essentially the same in the presence and absence of REQUIP®. ***Inhibitors of CYP1A2: Ciprofloxacin:*** The effect of ciprofloxacin (500 mg b.i.d.) on the pharmacokinetics of REQUIP® (2 mg t.i.d.) was studied in male and female patients with Parkinson's disease (n=12, mean age 55 years). The extent of systemic availability of REQUIP® was significantly increased when coadministered with ciprofloxacin (AUC increased by 1.84 fold). Thus, in patients already receiving CYP1A2 inhibitors such as ciprofloxacin, REQUIP® therapy may be instituted in the recommended manner and the dose titrated according to clinical response. However, if therapy with a drug known to be an inhibitor of CYP1A2 is stopped or introduced during treatment with REQUIP®, adjustment of the REQUIP® dosage will be required. ***Substrates of CYP1A2: Theophylline:*** The effect of oral theophylline (300 mg b.i.d.) on the pharmacokinetics of REQUIP® (2 mg t.i.d.) was studied in male and female patients with Parkinson's disease (n=12, mean age 59 years). There was no marked change in the rate or extent of availability of REQUIP® when coadministered with theophylline. Similarly, coadministration of REQUIP® with intravenous theophylline (5 mg/kg) did not result in any marked change in the pharmacokinetics of theophylline. It is therefore unlikely that substrates of CYP1A2 would significantly alter the pharmacokinetics of REQUIP®, and vice-versa. ***Digoxin:*** The effect of REQUIP® (2 mg t.i.d.) on the pharmacokinetics of digoxin (0.125–0.25 mg o.d.) was studied in male and female patients with Parkinson's disease (n=10, mean age 72 years). Coadministration at steady state with REQUIP® resulted in a 10% decrease in digoxin AUC although mean trough digoxin plasma concentrations were unaltered. However, the effect of higher recommended doses of REQUIP® on the pharmacokinetics of digoxin is not known. ***Alcohol:*** No information is available on the potential for interaction between REQUIP® and alcohol. As with other centrally active medications, patients should be cautioned against taking REQUIP® with alcohol. **Psycho-Motor Performance** – (see WARNINGS - Sudden Onset of Sleep).

ADVERSE REACTIONS: Adverse Reactions Associated with Discontinuation of Treatment – Of 1599 patients who received REQUIP® (ropinirole hydrochloride) during the premarketing clinical trials, 17.1% in early-therapy studies and 17.3% in adjunct-therapy studies discontinued treatment due to adverse reactions. The events resulting in discontinuation of REQUIP® in 1% or more of patients were as follows: ***Early therapy:*** nausea (6.4%), dizziness (3.8%), aggravated Parkinson's disease (1.3%), hallucination (1.3%), headache (1.3%), somnolence (1.3%) and vomiting (1.3%). ***Adjunct therapy:*** dizziness (2.9%), dyskinesia (2.4%), confusion (2.4%), vomiting (2.4%), hallucination (1.9%), nausea (1.9%), anxiety (1.9%), and increased sweating (1.4%). Patients over 75 years of age (n=130) showed slightly higher incidences of withdrawal due to hallucination, confusion and dizziness than patients less than 75 years of age. **Most Frequent Adverse Events** – Adverse events occurring with an incidence of greater than, or equal to, 10% were as follows: ***Early therapy:*** nausea, dizziness, somnolence, headache, peripheral edema, vomiting, syncope, fatigue and viral infection. ***Adjunct therapy:*** dyskinesia, nausea, dizziness, somnolence and headache. Dopamine agonists, with an ergoline chemical structure have been associated with adverse experiences such as retroperitoneal fibrosis, erythromelalgia and pulmonary reactions. REQUIP® has a novel, non-ergoline chemical structure and no reports of such events have been observed in clinical trials. **Incidence of Adverse Events in Placebo Controlled Trials** – The incidence of postural hypotension, an event commonly associated with initiation of dopamine agonist therapy, was not notably different from placebo in clinical trials. However, decreases in systolic blood pressure to < 90 mmHg have been observed in 13% (<65 years), 16% (65 – 75 years) and 7.6% (>75 years) of patients treated with REQUIP®. **Table 2** lists adverse events that occurred at an incidence of 1% or more among REQUIP®-treated patients who participated in placebo-controlled trials for up to one year. Patients were dosed in a range of 0.75 mg to 24 mg/day. Reported adverse events were classified using a standard World Health Organization (WHO)-based dictionary terminology. The prescriber should be aware that these figures can not be used to predict the incidence of adverse events in the course of usual medical practice where patient characteristics and other factors differ from those which prevailed in the clinical trials. Similarly, the cited frequencies can not be compared with figures obtained from other clinical investigations involving different treatments, uses and investigators. The cited figures, however, do provide the prescribing physician with some basis for estimating the relative contribution of drug and non-drug factors to the adverse events incidence rate in the population studied.

TABLE 2
Adverse events with incidence ≥1% from all placebo-controlled early and adjunct therapy studies

	Early Therapy		Adjunct Therapy	
	REQUIP® N = 157 % occurrence	Placebo N = 147 % occurrence	REQUIP® N = 235 % occurrence	Placebo N = 120 % occurrence
Autonomic Nervous System				
Sweating Increased	6.4	4.1	7.2	1.7
Mouth Dry	5.1	3.4	5.3	0.8
Flushing	3.2	0.7	1.4	0.8
Body as a Whole General				
Peripheral Edema	13.4	4.1	3.9	2.5
Fatigue	10.8	4.1	–	–
Injury	–	–	10.6	9.2
Pain	7.6	4.1	5.3	3.3
Asthenia	6.4	1.4	–	–
Drug Level Increased	4.5	2.7	6.7	3.3
Chest Pain	3.8	2.0	–	–
Malaise	3.2	0.7	1.4	0.8
Therapeutic Response Decreased	1.9	0.7	–	–
Cellulitis	1.3	0.0	–	–
Influenza-like Symptoms	–	–	1.0	0.0
Fever	–	–	1.4	0.0
Cardiovascular General				
Syncope	11.5	1.4	2.9	1.7
Hypotension Postural	6.4	4.8	–	–
Hypertension	4.5	3.4	3.4	3.3
Hypotension	1.9	0.0	2.4	0.8
Cardiac Failure	–	–	1.0	0.0
Central and Peripheral Nervous System				
Dizziness	40.1	21.8	26.0	15.8
Dyskinesia	–	–	33.7	12.5
Headache	17.2	17.0	16.8	11.7
Ataxia (Falls)	–	–	9.6	6.7
Tremor	–	–	6.3	2.5
Paresthesia	–	–	5.3	2.5
Hyperesthesia	3.8	2.0	–	–
Dystonia	–	–	4.3	4.2
Hypokinesia	–	–	5.3	4.2
Paresis	–	–	2.9	0.0
Speech Disorder	–	–	1.0	0.0
Vertigo	1.9	0.0	–	–
Carpal Tunnel Syndrome	1.3	0.7	–	–
Gastrointestinal System				
Nausea	59.9	21.8	29.8	18.3
Vomiting	12.1	6.8	7.2	4.2
Dyspepsia	9.6	4.8	–	–
Constipation	8.3	7.5	5.8	3.3
Abdominal Pain	6.4	2.7	8.7	7.5
Diarrhea	–	–	4.8	2.5
Anorexia	3.8	1.4	–	–
Flatulence	2.5	1.4	1.9	0.8
Tooth Disorder	1.9	0.7	1.0	0.8
Saliva Increased	–	–	2.4	0.8
Colitis	1.3	0.0	–	–
Dysphagia	1.3	0.0	2.4	0.8
Periodontitis	1.3	0.0	1.4	0.8
Eructation	–	–	1.4	0.0
Fecal Incontinence	–	–	1.0	0.0
Hemorrhoids	–	–	1.0	0.0
Gastroesophageal Reflux	–	–	1.0	0.0
Gastrointestinal Disorder (NOS)	–	–	1.0	0.0
Tooth Ache	–	–	1.0	0.0
Hearing and Vestibular				
Tinnitus	1.3	0.0	–	–
Heart Rate and Rhythm				
Palpitation	3.2	2.0	2.9	2.5

	Early Therapy		Adjunct Therapy	
	REQUIP® N = 157 % occurrence	Placebo N = 147 % occurrence	REQUIP® N = 206 % occurrence	Placebo N = 120 % occurrence
Heart Rate and Rhythm				
Extrasystoles	1.9	0.7	–	–
Tachycardia	1.9	0.0	1.0	0.0
Fibrillation Atrial	1.9	0.0	–	–
Tachycardia Supraventricular	1.3	0.0	–	–
Bradycardia	–	–	1.0	0.0
Liver and Billary System				
Gamma - GT Increased	1.3	0.7	1.0	0.0
Hepatic Enzymes Increased	1.3	0.0	–	–
Metabolic and Nutritional				
Alkaline Phosphate Increased	2.5	1.4	1.0	0.0
Weight Decrease	–	–	2.4	0.8
Hypoglycemia	1.3	0.0	–	–
Musculoskeletal System				
Arthralgia	–	–	6.7	5.0
Arthritis	–	–	2.9	0.8
Arthritis Aggravated	1.3	0.0	1.4	0.0
Myocardial, Endocardial, Pericardial Valve				
Myocardial Ischemia	1.3	0.7	–	–
Psychiatric				
Somnolence	40.1	6.1	20.2	8.3
Anxiety	–	–	6.3	3.3
Confusion	5.1	1.4	8.7	1.7
Hallucination	5.1	1.4	10.1	4.2
Nervousness	–	–	4.8	2.5
Yawning	3.2	0.0	–	–
Amnesia	2.5	1.4	4.8	0.8
Dreaming Abnormal	–	–	2.9	1.7
Depersonalization	–	–	1.4	0.0
Paranoid Reaction	–	–	1.4	0.0
Agitation	1.3	0.7	1.0	0.0
Concentration Impaired	1.9	0.0	1.0	0.0
Illusion	1.3	0.0	–	–
Thinking Abnormal	–	–	1.4	0.8
Apathy	–	–	1.0	0.0
Increased Libido	–	–	1.0	0.0
Personality Disorder	–	–	1.0	0.0
Red Blood Cell				
Anemia	–	–	2.4	0.0
Reproductive Male				
Impotence	2.5	1.4	–	–
Prostatic Disorder	–	–	1.0	0.0
Penis Disorder	–	–	1.3	0.0
Resistance Mechanism				
Upper Respiratory Tract Infection	–	–	8.7	8.3
Infection Viral	10.8	3.4	7.2	6.7
Respiratory System				
Pharyngitis	6.4	4.1	–	–
Rhinitis	3.8	2.7	–	–
Sinusitis	3.8	2.7	–	–
Dyspnea	3.2	0.0	2.9	1.7
Bronchitis	2.5	1.4	–	–
Respiratory Disorder	1.9	1.4	1.9	0.0
Pneumonia	1.3	0.7	1.0	0.8
Coughing	–	–	1.4	0.8
Skin/Appendages				
Pruritis	–	–	1.0	0.0
Urinary System				
Urinary Tract Infection	5.1	4.1	6.3	2.5
Cystitis	1.3	0.7	–	–
Micturition Frequency	–	–	1.4	0.0
Pyuria	–	–	1.9	0.8
Urinary Incontinence	–	–	1.9	0.8
Urinary Retention	1.3	0.7	–	–
Dysuria	–	–	1.0	0.0
Vascular Extracardiac				
Peripheral Ischemia	2.5	0.0	–	–
Vision				
Vision Abnormal	5.7	3.4	–	–
Eye Abnormality	3.2	1.4	–	–
Diplopia	–	–	1.9	0.8
Xerophthalmia	1.9	0.0	1.4	0.8
Cataract	–	–	1.4	0.8
Lacrimation Abnormal	–	–	1.4	0.0
White Cell and Reticuloendothelial System				
Eosinophilia	–	–	1.4	0.0

a: Incidence of adverse event <1%.

Post-Marketing Experience - Patients treated with REQUIP® have rarely reported suddenly falling asleep while engaged in activities of daily living, including operation of motor vehicles which has sometimes resulted in accidents (see WARNINGS).

DOSAGE AND ADMINISTRATION: REQUIP® (ropinirole hydrochloride) should be taken three times daily. While administration of REQUIP® with meals may improve gastrointestinal tolerance, REQUIP® may be taken with or without food. The recommended starting dosage is 0.25 mg three times daily. Based on individual patient response, dosage should then be titrated by weekly increments of 0.25 mg per dose as described in the table below. After week 4, daily dosage may be increased by 0.5 to 1.0 mg per dose on a weekly basis until an optimal therapeutic response is established. Smaller dose increments are recommended for patients who may be at risk for orthostatic symptoms.

	Week			
	1	2	3	4
Unit Dose (mg)	0.25	0.5	0.75	1.0
Total Daily Dose (mg)	0.75	1.5	2.25	3.0

In clinical trials, initial benefits were observed with 3 mg/day and higher doses. Doses greater than 24 mg/day have not been included in clinical trials. In a 5-year, double-blind study of early therapy in Parkinson's disease patients, the average daily dose of REQUIP® (based on the observed data set) was 10.1 mg at 6 months (median dose = 9.0 mg), 14.4 mg at 3 years (median dose = 15.0 mg), and 16.6 mg at 5 years (median dose = 18.0 mg), regardless of levodopa supplementation. When REQUIP® is administered as adjunct therapy to levodopa, the dose of levodopa may be decreased gradually as tolerated once a therapeutic effect with REQUIP® has been observed. REQUIP® should be discontinued gradually over a 7-day period. The frequency of administration should be reduced from three times daily to twice daily for 4 days. For the remaining 3 days, the frequency should be reduced to once daily prior to complete withdrawal of REQUIP®. **Renal and Hepatic Impairment:** In patients with mild to moderate renal impairment, REQUIP® may be titrated in the recommended manner according to clinical response. Patients with severe renal impairment or on hemodialysis have not been studied and administration of REQUIP® to such patients is not recommended. Patients with hepatic impairment have not been studied and administration of REQUIP® to such patients is not recommended. **Estrogen Replacement Therapy:** In patients already receiving estrogen replacement therapy, REQUIP® may be titrated in the recommended manner according to clinical response. However, if estrogen replacement therapy is stopped or started during treatment with REQUIP®, adjustment of the REQUIP® dosage may be required. **AVAILABILITY OF DOSAGE FORM:** REQUIP® is supplied as a pentagonal film-coated Tiltab® tablet with beveled edges containing ropinirole (as ropinirole hydrochloride) as follows: 0.25 mg – white imprinted with SB and 4890; 1.0 mg – green imprinted with SB and 4892; 2.0 mg – pale pink imprinted with SB and 4893; 5.0 mg – blue tablets imprinted with SB and 4894. REQUIP® is available in bottles in the pack size of 100 tablets. Full Product Monograph available to practitioners upon request.

GlaxoSmithKline Inc.
7333 Mississauga Road North
Mississauga, Ontario
L5N 6L4

Date of preparation: June 18, 2001
Date of revisions: March 31, 2004

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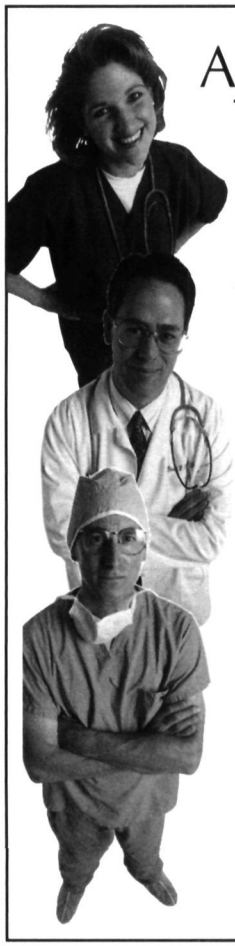

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IMITREX DF™ (sumatriptan succinate) is a selective 5-HT_1 receptor agonist indicated for the acute treatment of migraine attacks with or without aura.[3] IMITREX DF™ is not indicated for prophylactic therapy of migraine, or for the management of hemiplegic, basilar, or ophthalmoplegic migraine. Safety and efficacy have not been established for cluster headache.[3]

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*Dissolution testing was performed using USP II apparatus in 0.01M HCL (aq) at 30 rpm.[1]
Δ 2-hour post-dose time point was the primary endpoint.[1]
≈Prospective, double-blind, placebo-controlled, parallel-group, single attack study in migraine patients randomized to receive either placebo or the new formulation of sumatriptan 50 mg or 100 mg tablets (n = 432). Patients were instructed to treat during the mild pain phase and within 1 hour of onset of pain. Results presented are for the intent-to-treat population (IMITREX DF 100 mg, n = 142; placebo, n = 153; p<0.001 vs placebo).[2]
**ZERO PAIN™ refers to complete relief of pain or "0" (zero) on a 4-point scale where 0 = no pain, 1 = mild pain, 2 = moderate pain and 3 = severe pain.[2]
ß Randomized, open-label, 4-way crossover study (n=32) showed the new formulation of sumatriptan tablets to be bioequivalent to the conventional tablets as demonstrated by the finding that the 90% confidence intervals for sumatriptan $AUC_{0-\infty}$, AUC_{0-t} and C_{max} fell within the predetermined bounds defining bioequivalence (0.80 to 1.25) for both 50 mg and 100 mg doses.[1]

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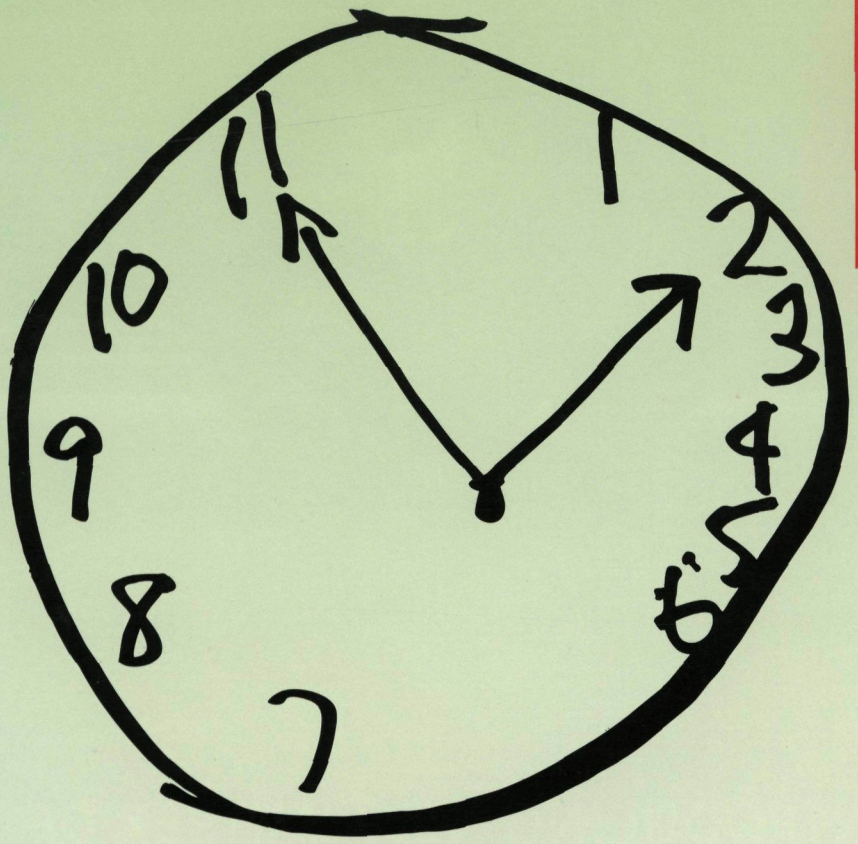

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There is no evidence that galantamine alters the course of the underlying dementing process.

REFERENCE: 1. REMINYL* (galantamine hydrobromide tablets), REMINYL* ER (galantamine hydrobromide extended-release capsules) Product Monograph, JANSSEN-ORTHO Inc., April 8, 2005.

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