BRIEF PRESCRIBING INFORMATION
CONSULT FULL PRODUCT MONOGRAPH FOR COMPLETE PRESCRIBING INFORMATION

Pr Topamax®

topiramate
25, 100 and 200 mg Tablets and
15 and 25 mg Sprinkle Capsules
Antiepileptic

INDICATIONS AND CLINICAL USE

TOPAMAX (topiramate) is indicated as adjunctive therapy for the management of patients (adults and children two years and older) with epilepsy who are not satisfactorily controlled with conventional therapy. There is limited information on the use of topiramate in monotherapy at this time.

CONTRAINDICATIONS

TOPAMAX (topiramate) is contraindicated in patients with a history of hypersensitivity to any components of this product.

WARNINGS

Antiepileptic drugs, including TOPAMAX (topiramate), should be withdrawn gradually to minimize the potential of increased seizure frequency. In adult clinical trials, dosages were decreased by 100 mg/day at weekly intervals.

Central Nervous System Effects Adverse events most often associated with the use of TOPAMAX were central nervous system-related. In adults, the most significant of these can be classified into two general categories: i) psychomotor slowing: difficulty with concentration and speech or language problems, in particular, word-finding difficulties and ii) somnolence or fatigue.

Additional nonspecific CNS effects occasionally observed with topiramate as add-on therapy include dizziness or imbalance, confusion, memory problems, and exacerbation of mood disturbances (e.g. irritability and depression).

These events were generally mild to moderate, and generally occurred early in therapy. While the incidence of psychomotor slowing does not appear to be dose related, both language problems and difficulty with concentration or attention increased in frequency with increasing dosage in the six double-blind trials, suggesting that these events are dose related. (See **ADVERSE REACTIONS**.)

Acute Myopia and Secondary Angle Closure Glaucoma A syndrome consisting of acute myopia associated with secondary angle closure glaucoma has been reported in patients receiving TOPAMAX. Symptoms include acute onset of decreased visual acuity and/or ocular pain. Ophthalmologic findings can include myopia, anterior chamber shallowing, ocular hyperemia (redness) and increased intraocular pressure. Mydriasis may or may not be present. This syndrome may be associated with supraciliary effusion resulting in anterior displacement of the lens and iris, with secondary angle closure glaucoma. Symptoms typically occur within a few days to 1 month of initiating TOPAMAX therapy. In contrast to primary narrow angle glaucoma, which is rare under 40 years of age, secondary angle closure glaucoma associated with topiramate has been reported in pediatric patients as well as adults. The primary treatment to reverse symptoms is discontinuation of TOPAMAX as rapidly as possible, according to the judgement of the treating physician. Other measures, in conjunction with discontinuation of TOPAMAX may be helpful (see **PRECAUTIONS** and **Post-Marketing Adverse Reactions**).

In all cases of acute visual blurring and/or painful/red eye(s), immediate consultation with an ophthalmologist is recommended.

Elevated intraocular pressure of any etiology, if left untreated, can lead to serious sequelae including permanent vision loss.

PRECAUTIONS

Effects Related to Carbonic Anhydrase Inhibition Kidney Stones A total of 32/1,715 (1.5%) of patients exposed to TOPAMAX (topiramate) during its development reported the occurrence of kidney stones, an incidence about 10 times that expected in a similar, untreated population (M/F ratio: 27/1,092 male; 5/623 female). In the general population, risk factors for kidney stone formation include gender (male), ages between 20-50 years, prior stone formation, family history of nephrolithiasis, and hypercalciuria. Based on logistic regression analysis of the clinical trial data, no correlation between mean topiramate dosage, duration of topiramate therapy, or age and the occurrence of kidney stones was established; of the risk factors evaluated, only gender (male) showed a correlation with the occurrence of kidney stones. In the pediatric patients studied, there were no kidney stones observed.

Carbonic anhydrase inhibitors, e.g. acetazolamide, promote stone formation by reducing urinary citrate excretion and by increasing urinary pH. Concomitant use of TOPAMAX, a weak carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors may create a physiological environment that increases the risk of kidney stone formation, and should therefore be avoided.

Patients, especially those with a predisposition to nephrolithiasis, may have an increased risk of renal stone formation. Increased fluid intake increases the urinary output, lowering the concentration of substances involved in stone formation. Therefore, adequate hydration is recommended to reduce this risk. None of the risk factors for nephrolithiasis can reliably predict stone formation during TOPAMAX treatment.

Paresthesia Paresthesia, an effect associated with the use of other carbonic anhydrase inhibitors, appears to be a common effect of TOPAMAX therapy. These events were usually intermittent and mild, and not necessarily related to the dosage of topiramate.

Nutritional Supplementation A dietary supplement or increased food intake may be considered if the patient is losing weight while on this medication.

Weight Loss in Pediatrics Topiramate administration is associated with weight loss in some children that generally occurs early in therapy. Of those pediatric subjects treated in clinical trials for at least a year who experienced weight loss, 96% showed a resumption of weight gain within the period tested. In 2-4 year olds, the mean change in weight from baseline at 12 months (n=25) was +0.7 kg (range -1.1 to 3.2); at 24 months (n=14), the mean change was +2.2 (range -1.1 to 6.1). In 5-10 year olds, the mean change in weight from baseline at 12 months (n=88) was +0.7 kg (range -6.7 to 11.8); at 24 months (n=67), the mean change was +3.3 (range -8.6 to 20.0). Weight decreases, usually associated with anorexia or appetite changes, were reported as adverse events for 9% of topiramate-treated pediatric patients. The long term effects of reduced weight gain in pediatric patients is not known.

Adjustment of Dose in Renal Failure The major route of elimination of unchanged topiramate and its metabolites is via the kidney. Renal elimination is dependent on renal function and is independent of age. Patients with impaired renal function (Cl_{CR} < 70 mL/min/1.73m²) or with end-stage renal disease receiving hemodialysis treatments may take 10 to 15 days to reach steady-state plasma concentrations as compared to 4 to 8 days in patients with normal renal function. As with all patients, the titration schedule should be guided by clinical outcome (i.e. seizure control, avoidance of side effects) with the knowledge that patients with known renal impairment may require a longer time to reach steady-state at each dose. (See **DOSAGE AND ADMINISTRATION.**)

Decreased Hepatic Function In hepatically impaired patients, topiramate should be administered with caution as the clearance of topiramate was decreased compared with normal subjects.

Information for Patients Adequate Hydration Patients, especially those with predisposing factors, should be instructed to maintain an adequate fluid intake in order to minimize the risk of renal stone formation.

Effects on Ability to Drive and Use Machines Patients should be warned about the potential for somnolence, dizziness, confusion, and difficulty concentrating and advised not to drive or operate machinery until they have gained sufficient experience on topiramate to gauge whether it adversely affects their mental and/or motor performance.

Acute Myopia and Secondary Angle Closure Glaucoma Patients taking TOPAMAX should be told to immediately contact their doctor and/or go to the Emergency Room if they/their child experience(s) sudden worsening of vision, blurred vision or painful/red eye(s).

Drug Interactions Antiepileptic Drugs

Effects of TOPAMAX on Other Antiepileptic Drugs Potential interactions between topiramate and standard AEDs were measured in controlled clinical pharmacokinetic studies in patients with epilepsy. The addition of TOPAMAX to other antiepileptic drugs (phenytoin, carbamazepine, valproic acid, phenobarbital, primidone) has no effect on their steady-state plasma concentrations, except in the occasional patient, where the addition of TOPAMAX to phenytoin may result in an increase of plasma concentrations of phenytoin.

The effect of topiramate on steady-state pharmacokinetics of phenytoin may be related to the frequency of phenytoin dosing. A slight increase in steady-state phenytoin plasma concentrations was observed, primarily in patients receiving phenytoin in two divided doses. The slight increase may be due to the saturable nature of phenytoin pharmacokinetics and inhibition of phenytoin metabolism ($CYP2C_{mephi}$).

The addition of TOPAMAX therapy to phenytoin should be guided by clinical outcome. In general, as evidenced in clinical trials, patients do not require dose adjustments. However, any patient on phenytoin showing clinical signs or symptoms of toxicity should have phenytoin levels monitored.

Effects of Other Antiepileptic Drugs on TOPAMAX Phenytoin and carbamazepine decrease the plasma concentration of TOPAMAX. The addition or withdrawal of phenytoin and/or carbamazepine during adjunctive therapy with TOPAMAX may require adjustment of the dose of TOPAMAX. This should be done by titrating to clinical effect. The addition or withdrawal of valproic acid does not produce clinically significant changes in plasma concentrations of TOPAMAX, and therefore, does not warrant dosage adjustment of TOPAMAX.

The effect of these interactions on plasma concentrations are summarized in Table 1:

Table 1
Drug Interactions with TOPAMAX Therapy

AED Co-administered	AED Concentration	TOPAMAX Concentration
Phenytoin	↔**	↓59%
Carbamazepine (CBZ)	↔	↓40%
CBZ epoxide*	↔	NS
Valproic acid	↓11%	↓14%
Phenobarbital	↔	NS
Primidone	↔	NS

* Is not administered but is an active metabolite of carbamazepine
↔ No effect on plasma concentration (< 15% change)
** Plasma concentrations increased 25% in some patients, generally those on a b.i.d. dosing regimen of phenytoin
↓ Plasma concentrations decrease in individual patients
NS Not studied
AED Antiepileptic drug

Other Drug Interactions: *Digoxin* In a single-dose study, serum digoxin AUC decreased 12% due to concomitant TOPAMAX administration. Multiple-dose studies have not been performed. When TOPAMAX is added or withdrawn in patients on digoxin therapy, careful attention should be given to the routine monitoring of serum digoxin.

CNS Depressants: Concomitant administration of TOPAMAX topiramate and alcohol or other CNS depressant drugs has not been evaluated in clinical studies. It is recommended that TOPAMAX topiramate not be used concomitantly with alcohol or other CNS depressant drugs.

Oral Contraceptives: In a pharmacokinetic interaction study with oral contraceptives using a combination product containing norethindrone plus ethinyl estradiol, TOPAMAX topiramate did not significantly affect the oral clearance of norethindrone. The serum levels of the estrogenic component decreased by 18%, 21%, and 30% at daily doses of 200, 400 and 800 mg, respectively. Consequently, the efficacy of low-dose (e.g. 20 µg) oral contraceptives may be reduced in this situation. Patients taking oral contraceptives should receive a preparation containing not less than 50 µg of estrogen. Patients taking oral contraceptives should be asked to report any change in their bleeding patterns.

Others: Concomitant use of TOPAMAX topiramate, a weak carbonic anhydrase inhibitor, with other carbonic anhydrase inhibitors, e.g. acetazolamide, may create a physiological environment that increases the risk of renal stone formation, and should therefore be avoided if possible.

Laboratory Tests There are no known interactions of TOPAMAX topiramate with commonly used laboratory tests.

Use in Pregnancy and Lactation Like other antiepileptic drugs, topiramate was teratogenic in mice, rats, and rabbits. In rats, topiramate crosses the placental barrier.

There are no studies using TOPAMAX topiramate in pregnant women. However, TOPAMAX therapy should be used during pregnancy only if the potential benefit outweighs the potential risk to the fetus.

Topiramate is excreted in the milk of lactating rats. It is not known if topiramate is excreted in human milk. Since many drugs are excreted in human milk, and because the potential for serious adverse reactions in nursing infants to TOPAMAX topiramate exists, the prescriber should decide whether to discontinue nursing or discontinue the drug, taking into account the risk / benefit ratio of the importance of the drug to the mother and the risks to the infant.

In post-marketing experience, cases of hypospadias have been reported in male infants exposed in-utero to topiramate, with or without other anticonvulsants, however, a causal relationship with topiramate has not been established.

The effect of TOPAMAX topiramate on labour and delivery in humans is unknown.

Pediatric Use Safety and effectiveness in children under 2 years of age have not been established.

Geriatric Use There is limited information in patients over 65 years of age. The possibility of age-associated renal function abnormalities should be considered when using TOPAMAX topiramate.

Race and Gender Effects Although direct comparison studies of pharmacokinetics have not been conducted, analysis of plasma concentration data from clinical efficacy trials have shown that race and gender appear to have no effect on the plasma clearance of topiramate. In addition, based on pooled analyses, race and gender appear to have no effect on the efficacy of topiramate.

ADVERSE REACTIONS

Adults The most commonly observed adverse events associated with the adjunctive use of TOPAMAX topiramate at dosages of 200 to 400 mg/day in controlled trials in adults that were seen at greater frequency in topiramate-treated patients and did not appear to be dose related within this dosage range were: somnolence, dizziness, ataxia, speech disorders and related speech problems, psychomotor slowing, nystagmus, and paresthesia (see Table 2).

The most common dose-related adverse events at dosages of 200 to 1,000 mg/day were: nervousness, difficulty with concentration or attention, confusion, depression, anorexia, language problems, and mood problems (see Table 3).

Table 2
Incidence of Treatment-Emergent Adverse Events in Placebo-Controlled, Add-On Trials in ADULTS [12]
(Events that occurred in ≥ 2% of topiramate-treated patients and occurred more frequently in topiramate-treated than placebo-treated patients)

	TOPAMAX Dosage (mg/day)		
Body System/ Adverse Event	Placebo (n=216)	200-400 (n=113)	600-1,000 (n=414)
Body as a Whole			
Asthenia	1.4	8.0	3.1
Back Pain	4.2	6.2	2.9
Chest Pain	2.8	4.4	2.4
Influenza-Like Symptoms	3.2	3.5	3.6
Leg Pain	2.3	3.5	3.6
Hot Flushes	1.9	2.7	0.7
Nervous System			
Dizziness	15.3	28.3	32.1
Ataxia	6.9	21.2	14.5
Speech Disorders/Related Speech Problems	2.3	16.8	11.4
Nystagmus	9.3	15.0	11.1
Paresthesia	4.6	15.0	19.1
Tremor	6.0	10.6	8.9
Language Problems	0.5	6.2	10.4
Coordination Abnormal	1.9	5.3	3.6
Hypoaesthesia	0.9	2.7	1.2
Abnormal Gait	1.4	1.8	2.2
Gastrointestinal System			
Nausea	7.4	11.5	12.1
Dyspepsia	6.5	8.0	6.3
Abdominal Pain	3.7	5.3	7.0
Constipation	2.3	5.3	3.4
Dry Mouth	0.9	2.7	3.9
Metabolic and Nutritional			
Weight Decrease	2.8	7.1	12.8
Neuropsychiatric			
Somnolence	9.7	30.1	27.8
Psychomotor Slowing	2.3	16.8	20.8
Nervousness	7.4	15.9	19.3
Difficulty with Memory	3.2	12.4	14.5
Confusion	4.2	9.7	13.8
Depression	5.6	8.0	13.0
Difficulty with Concentration/Attention	1.4	8.0	14.5
Anorexia	3.7	5.3	12.3
Agitation	1.4	4.4	3.4
Mood Problems	1.9	3.5	9.2
Aggressive Reaction	0.5	2.7	2.9
Apathy	0	1.8	3.1
Depersonalization	0.9	1.8	2.2
Emotional Lability	0.9	1.8	2.7
Reproductive, Female	(n=59)	(n=24)	(n=128)
Breast Pain, Female	1.7	8.3	0
Dysmenorrhea	6.8	8.3	3.1
Menstrual Disorder	0	4.2	0.8
Reproductive, Male	(n=157)	(n=89)	(n=286)
Prostatic Disorder	0.6	2.2	0
Respiratory System			
Pharyngitis	2.3	7.1	3.1
Rhinitis	6.9	7.1	6.3
Sinusitis	4.2	4.4	5.6
Dyspnea	0.9	1.8	2.4
Skin and Appendages			
Pruritus	1.4	1.8	3.1
Vision			
Diplopia	5.6	14.2	10.4
Vision Abnormal	2.8	14.2	10.1
White Cell and RES			
Leukopenia	0.5	2.7	1.2

* Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX topiramate or placebo.
† Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

Table 3

Incidence (%) of Dose-Related Adverse Events From Placebo-Controlled, Add-On Trials in ADULTS

Adverse Event	Placebo (n=216)	TOPAMAX Dosage (mg/day) 200 (n=45)	400 (n=68)	600 – 1,000 (n=414)
Fatigue	13.4	11.1	11.8	29.7
Nervousness	7.4	13.3	17.6	19.3
Difficulty with Concentration/Attention	1.4	6.7	8.8	14.5
Confusion	4.2	8.9	10.3	13.8
Depression	5.6	8.9	7.4	13.0
Anorexia	3.7	4.4	5.9	12.3
Language problems	0.5	2.2	8.8	10.1
Anxiety	6.0	2.2	2.9	10.4
Mood problems	1.9	0.0	5.9	9.2

In six double-blind clinical trials, 10.6% of subjects (n=113) assigned to a topiramate dosage of 200 to 400 mg/day in addition to their standard AED therapy discontinued due to adverse events, compared to 5.8% of subjects (n=69) receiving placebo. The percentage of subjects discontinuing due to adverse events appeared to increase at dosages above 400 mg/day. Overall, approximately 17% of all subjects (n=527) who received topiramate in the double-blind trials discontinued due to adverse events, compared to 4% of the subjects (n=216) receiving placebo.

Pediatrics Adverse events associated with the use of topiramate at dosages of 5 to 9 mg/kg/day in worldwide pediatric clinical trials that were seen at greater frequency in topiramate-treated patients were: fatigue, somnolence, anorexia, nervousness, difficulty with concentration/attention, difficulty with memory, aggressive reaction, and weight decrease.

Table 4 lists treatment-emergent adverse events that occurred in at least 2% of children treated with 5 to 9 mg/kg/day topiramate in controlled trials that were numerically more common than in patients treated with placebo.

Table 4

Incidence (%) of Treatment-Emergent Adverse Events in Worldwide Pediatric Clinical Trials Experience (2-16 years of Age) [1]

(Events that Occurred in ≥2% of Topiramate-Treated Patients and Occurred More Frequently in Topiramate-Treated Than Placebo-Treated Patients)

Body System/ Adverse Event	Placebo (N=101)	Topiramate (N=98)
Body as a Whole - General Disorders		
Fatigue	5	16.3
Injury	12.9	14.3
Allergic Reaction	1	2
Central & Peripheral Nervous System Disorders		
Gait Abnormal	5	8.2
Ataxia	2	6.1
Hyperkinesia	4	5.1
Dizziness	2	4.1
Speech Disorders/Related Speech Problems	2	4.1
Convulsions Aggravated	3	3.1
Hyporeflexia	0	2
Gastrointestinal System Disorders		
Nausea	5	6.1
Saliva Increased	4	6.1
Constipation	4	5.1
Gastroenteritis	2	3.1
Metabolic and Nutritional Disorders		
Weight Decrease	1	9.2
Thirst	1	2
Platelet, Bleeding, & Clotting Disorders		
Purpura	4	8.2
Epistaxis	1	4.1
Nervous Disorders		
Somnolence	15.8	25.5
Anorexia	14.9	24.5
Nervousness	6.9	14.3
Personality Disorder (Behavior Problems)	8.9	11.2
Difficulty with Concentration/Attention	2	10.2
Aggressive Reaction	4	9.2
Insomnia	6.9	8.2
Mood Problems	6.9	7.1
Difficulty with Memory NOS	0	5.1
Emotional Lability	5	5.1
Confusion	3	4.1
Psychomotor Slowing	2	3.1
Reproductive Disorders, Female		
Leukorrhea	0.0	2.3
Resistance Mechanism Disorders		
Infection Viral	3.0	7.1
Infection	3.0	3.1
Respiratory System Disorders		
Upper Respiratory Tract Infection	36.6	36.7
Pneumonia	1.0	5.1
Skin and Appendages Disorders		
Skin Disorder	2.0	3.1
Alopecia	1.0	2.0
Dermatitis	0.0	2.0
Hypertrichosis	1.0	2.0
Rash Erythematous	0.0	2.0
Urinary System Disorders		
Urinary Incontinence	2.0	4.1
Vision Disorders		
Eye Abnormality	1.0	2.0
Vision Abnormal	1.0	2.0
White Cell and RES Disorders		
Leukopenia	0.0	2.0

[1] Patients in these add-on trials were receiving 1 to 2 concomitant antiepileptic drugs in addition to TOPAMAX topiramate or placebo.

[2] Values represent the percentage of patients reporting a given adverse event. Patients may have reported more than one adverse event during the study and can be included in more than one adverse event category.

[3] Not Otherwise Specified

None of the pediatric patients who received topiramate adjunctive therapy at 5 to 9 mg/kg/day in controlled clinical trials discontinued due to adverse events. In open extensions of the controlled clinical trials, approximately 9% of the 303 pediatric patients who received topiramate at dosages up to 30 mg/kg/day discontinued due to adverse events. Adverse events associated with discontinuing therapy included aggravated convulsions (2.3%), language problems (1.3%), and difficulty with concentration/attention (1.3%).

In adult and pediatric patients, nephrolithiasis was reported rarely. Isolated cases of thromboembolic events have also been reported; a causal association with the drug has not been established.

When the safety experience of patients receiving TOPAMAX topiramate as adjunctive therapy in both double-blind and open-label trials (1,446 adults and 303 children) was analyzed, a similar pattern of adverse events emerged.

Post-Marketing Adverse Reactions The most frequently reported adverse events in spontaneous post-marketing reports on topiramate include:

Psychiatric: somnolence or sedation, hallucination(s), depression, anorexia, aggressive reaction, psychosis, thinking abnormal, *paranoid reaction, insomnia, emotional lability, suicide attempt, delusion*

Central and Peripheral Nervous System: confusion, convulsions aggravated, paresthesia, agitation, speech disorder, ataxia, dizziness, convulsions, amnesia, headache, hyperkinesia

Metabolic and Nutritional: weight decrease

Autonomic Nervous System: vomiting

Vision: vision abnormal (includes vision decreased, vision blurred, visual disturbance, visual impairment, amblyopia); rarely reported: diplopia, glaucoma, myopia, eye pain.

Gastrointestinal: nausea, diarrhea, abdominal pain, constipation

Body as a Whole - General Disorders: fatigue

Urinary System: renal calculus

Skin and Appendages: rash

SYMPTOMS AND TREATMENT OF OVERDOSAGE

In acute TOPAMAX topiramate overdose, if the ingestion is recent, the stomach should be emptied immediately by lavage or by induction of emesis. Activated charcoal has not been shown to adsorb topiramate *in vitro*. Therefore, its use in overdosage is not recommended. Treatment should be appropriately supportive.

Hemodialysis is an effective means of removing topiramate from the body. However, in the few cases of acute overdosage reported, including doses of over 20 g in one individual, hemodialysis has not been necessary.

DOSAGE AND ADMINISTRATION

General TOPAMAX Tablets or Sprinkle Capsules can be taken without regard to meals. Tablets should not be broken. TOPAMAX Sprinkle Capsules may be swallowed whole or may be administered by carefully opening the capsule and sprinkling the entire contents on a small amount (teaspoon) of soft food. This drug/food mixture should be swallowed immediately and not chewed. It should not be stored for future use. The sprinkle formulation is provided for those patients who cannot swallow tablets, e.g. pediatric and the elderly.

Adults (Age 17 years and older) It is recommended that TOPAMAX topiramate as adjunctive therapy be initiated at 50 mg/day, followed by titration as needed and tolerated to an effective dose. At weekly intervals, the dose may be increased by 50 mg/day and taken in two divided doses. Some patients may benefit from lower initial doses, e.g. 25 mg and/or a slower titration schedule. Some patients may achieve efficacy with once-a-day dosing.

The recommended total daily maintenance dose is 200 mg-400 mg/day in two divided doses. Doses above 400 mg/day have not been shown to improve *responses and have been associated with a greater incidence of adverse events. The maximum recommended dose is 800 mg/day. Daily doses above* 1,600 mg have not been studied.

Children (Ages 2-16 years) It is recommended that TOPAMAX topiramate as adjunctive therapy be initiated at 25 mg (or less, based on a range of 1 to 3 mg/kg/day) nightly for the first week followed by titration as needed and tolerated to an effective dose. The dosage should then be increased at 1- or 2-week intervals by increments of 1 to 3 mg/kg/day (administered in two divided doses). Some patients may benefit from lower initial doses and/or a slower titration schedule.

The recommended total daily maintenance dose is approximately 5 to 9 mg/kg/day in two divided doses. Daily doses up to 30 mg/kg/day have been studied and were generally well tolerated.

Geriatrics See **PRECAUTIONS** section.

Patients with Renal Impairment In renally impaired subjects (creatinine clearance less than 70 mL/min/1.73m²), one-half of the usual adult dose is recommended. Such patients will require a longer time to reach steady-state at each dose.

Patients Undergoing Hemodialysis Topiramate is cleared by hemodialysis at a rate that is 4 to 6 times greater than a normal individual. Accordingly, a prolonged period of dialysis may cause topiramate concentration to fall below that required to maintain an antiseizure effect. To avoid rapid drops in topiramate *plasma concentration during hemodialysis a supplemental dose of topiramate may be required. The actual adjustment should take into account 1) the duration* of dialysis, 2) the clearance rate of the dialysis system being used, and 3) the effective renal clearance of topiramate in the patient being dialyzed.

Patients with Hepatic Disease In hepatically impaired patients, topiramate plasma concentrations are increased approximately 30%. This moderate increase is not considered to warrant adjustment of the topiramate dosing regimen. Initiate topiramate therapy with the same dose and regimen as for patients with normal hepatic function. The dose titration in these patients should be guided by clinical outcome, i.e. seizure control, and avoidance of adverse effects. Such patients will require a longer time to reach steady-state at each dose.

AVAILABILITY OF DOSAGE FORMS

TOPAMAX topiramate is available as embossed tablets in the following strengths as described below:

25 mg: white, round, coated tablets containing 25 mg topiramate.
100 mg: *yellow, round, coated tablets containing 100 mg topiramate.*
200 mg: salmon-coloured, round, coated tablets containing 200 mg topiramate.

TOPAMAX topiramate Sprinkle Capsules contain small white to off-white spheres. The gelatin capsules are white and clear. They are marked as follows:

15 mg: "TOP" and "15 mg" on the side.
25 mg "TOP" and "25 mg" on the side.

Supplied: Bottles of 60 tablets with desiccant.
Bottles of 60 capsules without desiccant.

TOPAMAX is a Schedule F Drug.

Product Monograph available to physicians and pharmacists upon request.

JANSSEN-ORTHO Inc.
Janssen-Ortho Inc., Toronto, Ontario M3C 1L9

Date of Issuance: September 2001
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NEW Reminyl

PRESCRIBING INFORMATION

℞REMINYL*

galantamine hydrobromide tablets

4 mg, 8 mg, 12 mg galantamine base

Cholinesterase Inhibitor

CLINICAL PHARMACOLOGY

Although the etiology of cognitive impairment in Alzheimer's Disease (AD) is not fully understood, it has been reported that acetylcholine-producing neurons degenerate in the brains of patients with Alzheimer's Disease. The degree of this cholinergic loss has been correlated with degree of cognitive impairment and density of amyloid plaques (a neuropathological hallmark of Alzheimer's Disease).

REMINYL (galantamine hydrobromide), a tertiary alkaloid, is a competitive and reversible cholinesterase inhibitor. While the precise mechanism of galantamine's action is unknown, it is postulated to exert its therapeutic effect by enhancing cholinergic function. This is accomplished by increasing the concentration of acetylcholine through reversible cholinesterase inhibition. It has also been postulated, based on *in vitro* data, that galantamine enhances the action of acetylcholine through binding to an allosteric site on the nicotinic receptors (see PRECAUTIONS). The clinical relevance to humans of these *in vitro* findings is unknown.

If these mechanisms are correct, galantamine's effect may lessen as the disease process advances and fewer cholinergic neurons remain functionally intact. There is no evidence that galantamine alters the course of the underlying dementing process.

Pharmacokinetics

Absorption

The summary of related pharmacokinetic parameters in healthy subjects is presented in Table 1. After oral intake of a single 8 mg galantamine solution in 12 healthy males, absorption is rapid, with a peak plasma concentration (C_{max}) of 43 ± 13 ng/mL, which is reached after 1.2 hours (T_{max}), and a mean AUC_{∞} of 427 ± 102 ng.h/mL.

The absolute oral bioavailability of galantamine is 88.5%. Bioavailability of the tablet was the same as the bioavailability of an oral solution in 27 healthy males. Food did not affect the AUC of galantamine but C_{max} decreased by 25% and T_{max} was delayed by 1.5 hours after repeated oral dosing of 12 mg galantamine b.i.d. in 24 healthy elderly subjects.

The maximum inhibition of anticholinesterase activity of about 40% was achieved about one hour after a single oral dose of 8 mg galantamine in healthy male subjects.

Table 1. Pharmacokinetic parameters of galantamine after single or multiple dose administration

	C_{max} (ng/mL)	t_{max} (h)	$C_{ss,av}$ (ng/mL)	C_{min} (ng/mL)	AUC† (ng.h/mL)	$T_{1/2}$ (h)
Single dose, 12 healthy males						
8 mg, solution p.o.	42.6 ± 13.1	1.2 ± 0.6	-	-	427 ± 102	7.3 ± 1.7
8 mg, 1 hr i.v. infusion	-	-	-	-	482 ±112	7.4 ± 1.7
Food effect, single dose, 24 healthy elderly						
Fasted, 8 mg p.o.	57.5 ± 15.8	1.1 ± 0.5	-	-	562 ± 180	9.7 ± 3.1
Non-fasted, 8 mg p.o.	42.5 ± 7.5	2.6 ±1.4	-	-	543 ± 176	9.7 ± 3.3
Multiple oral dose, 27 healthy males						
12 mg b.i.d. tablet	89.4 ± 18.3	1.0 ± 0.6	51.9 ± 12.2	30.7 ± 10.3	623 ± 147	-
12 mg b.i.d. solution	87.6 ± 20.5	1.1 ± 0.5	50.5 ± 13.0	29.8 ± 10.2	606 ± 156	-
Dose-proportionality, multiple oral dose, 18 healthy subjects						
4 mg b.i.d. tablet	30.7 ± 6.2	1.9 ± 0.8	17.7 ± 4.6	10.6 ± 4.0	212 ± 56	-
8 mg b.i.d. tablet	63.8 ± 14.2	1.7 ± 0.8	36.6 ± 9.8	20.6 ± 6.8	439 ± 117	-
12 mg b.i.d. tablet	97.4 ± 31.4	1.9 ± 1.1	53.1 ± 12.7	29.1 ± 9.3	637 ± 152	-
16 mg b.i.d. tablet	137 ± 36	1.7 ± 0.9	76.5 ± 20.3	41.5 ± 14.2	918 ± 244	7.9 ± 0.8

† $AUC = AUC_{\infty}$ after single dose and $AUC = AUC_{\tau}$ after multiple dose

Distribution

Galantamine is a low-clearance drug (plasma clearance of approximately 300 mL/min) with a moderate volume of distribution (average Vd_{ss} of 175 L) after a one-hour i.v. infusion of 8 mg galantamine in 12 healthy males.

The plasma protein binding of galantamine is 18% at therapeutically relevant concentrations. In whole blood, galantamine is mainly distributed to blood cells (52.7%) and plasma water (39.0%), whereas the fraction of galantamine bound to plasma proteins is only 8.4%. The blood-to-plasma concentration ratio of galantamine is 1.2.

Metabolism

Galantamine is metabolized by hepatic cytochrome P450 enzymes, glucuronidated and excreted unchanged in the urine. *In vitro* studies indicate that cytochrome CYP2D6 and CYP3A4 are the major cytochrome P450 isoenzymes involved in the metabolism of galantamine, and inhibitors of both pathways increase oral bioavailability of galantamine modestly (see PRECAUTIONS, Drug-Drug Interactions). O-demethylation, mediated by CYP2D6 is greater in extensive metabolizers of CYP2D6 than in poor metabolizers. In plasma from both poor and extensive metabolizers, however, unchanged galantamine and its glucuronide accounted for most of the sample radioactivity.

Elimination

The elimination of galantamine is bi-phasic, with a terminal half-life on the order of 7-8 hours in young healthy subjects (n=4 males). Two studies in healthy elderly subjects indicated that the terminal half-life of galantamine is 8.5 hours (n=13 males and 16 females) and 9.7 hours (n=10 males and 14 females) after administering a single oral dose of 10 mg galantamine. Up to 8 hours post-dose, unchanged galantamine accounted for 39-77% of the total radioactivity in the plasma, and galantamine glucuronide accounted for 14-24%. Seven days after a single oral dose of 4 mg ^{3}H-galantamine, 93-99% of the radioactivity had been recovered, with about 95% in urine and about 5% in feces. Total urinary recovery of unchanged galantamine accounted for, on average, 32% of the dose, and that of galantamine glucuronide for another 12% on average.

After i.v. and oral administration, about 20% of the dose was excreted as unchanged galantamine in the urine in 24 hours, with a renal clearance of about 65 mL/min, which represents 20-25% of the total plasma clearance of about 300 mL/min.

CYP2D6 Poor Metabolizers

Approximately 7% of the normal population has a genetic variation that leads to reduced levels of activity of the CYP2D6 isozyme. Such individuals have been referred to as poor metabolizers. After a single oral dose of 4 mg or 8 mg galantamine, CYP2D6 poor metabolizers demonstrated a similar C_{max} and about 35% AUC_{∞} increase of unchanged galantamine compared to extensive metabolizers.

A total of 356 patients with Alzheimer's disease enrolled in two phase 3 studies were genotyped with respect to CYP2D6 (n=210 hetero-extensive metabolizers, 126 homo-extensive metabolizers, and 20 poor metabolizers). Population pharmacokinetic analysis indicated that there was a 25% decrease in median clearance in poor metabolizers compared to extensive metabolizers. Dosage adjustment is not necessary in patients identified as poor metabolizers as the dose of drug is individually titrated to tolerability due to observed inter-patient variability.

Hepatic Impairment

Following a single 4 mg dose of galantamine, the pharmacokinetics of galantamine in subjects with mild hepatic impairment (n=8; Child-Pugh score of 5-6) were similar to those in healthy subjects. In patients with moderate hepatic impairment (n=8; Child-Pugh score of 7-9), AUC and half-life of galantamine were increased by about 30% compared to normal subjects (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Renal Impairment

In patients with renal insufficiency, elimination of galantamine decreases with decreasing creatinine clearance. Following a single 8 mg dose of galantamine, AUC increased by 37% and 67% in moderately (n=8; creatinine clearance of 30 to 60 mL/min/1.73 m^2) and severely (n=9; creatinine clearance of 5 to 29 mL/min/1.73 m^2) renal-impaired patients compared to normal volunteers (n=8) (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Patients with Alzheimer's Disease

Data from clinical trials in patients indicate that there is a difference in total clearance after oral administration between patients with Alzheimer's Disease and healthy subjects (13.2 L/h versus 19.4 L/h) based on pooled population analysis. Therefore, the plasma concentrations of galantamine in elderly patients (median age 75) with Alzheimer's Disease are 30-40% higher than in healthy young subjects (median age 28).

Gender and Race

No specific pharmacokinetic study was performed to investigate the gender differences. A population pharmacokinetic analysis (n=539 males and 550 females) suggests that galantamine clearance is about 20% lower in females than in males, which is explained by lower body weight in females.

Pharmacokinetic differences due to race have not been identified in a population pharmacokinetic analysis (n=1029 White, 24 Black, 13 Asian and 23 other).

Clinical Trials

Efficacy data for REMINYL (galantamine hydrobromide) in the symptomatic treatment of patients with Alzheimer's Disease were derived from 4 randomized, double-blind, placebo-controlled clinical trials in patients with probable Alzheimer's Disease [diagnosed by NINCDS-ADRDA criteria, with Mini-Mental State Examination Scores that were ≥10 and ≤24]. Doses studied were 8-32 mg/day given as twice daily doses. In 3 of the 4 studies, patients were started on a low dose of 8 mg, then titrated weekly by 8 mg/day to 24 or 32 mg as assigned (GAL-USA-1, GAL-INT-1, GAL-INT-2). In the fourth study (U.S. 4-week Dose-Escalation Fixed-Dose Study, GAL-USA-10) dose escalation of 8 mg/day occurred over 4 week intervals. The mean age of patients participating in the 4 REMINYL trials was 75 years with a range of 41 to 100. Approximately 62% of patients were women and 38% were men. The racial distribution was White 94%, Black 3% and other races 3%. Two other studies examined a three times daily dosing regimen; these also showed or suggested benefit but did not suggest an advantage over twice daily dosing.

Results for 2 of these studies are presented in this section. The data shown below were obtained from the Intent-To-Treat population (ITT analysis, i.e. all patients who were randomized to treatment, regardless of whether or not they were able to complete the study. For patients unable to complete the study, their last observation while on treatment was carried forward and used at endpoint).

Study Outcome Measures: In each study, the primary efficacy of REMINYL was evaluated using a dual outcome assessment strategy as measured by the Alzheimer's Disease Assessment Scale (ADAS-cog) and the Clinician's Interview Based Impression of Change (CIBIC-plus).

The ability of REMINYL to improve cognitive performance was assessed with the cognitive sub-scale of the Alzheimer's Disease Assessment Scale (ADAS-cog), a multi-item instrument that has been extensively validated in longitudinal cohorts of Alzheimer's Disease patients. The ADAS-cog examines selected aspects of cognitive performance including elements of memory, orientation, attention, reasoning, language and praxis.

The patients recruited as participants in each study had mean scores on the ADAS-cog of approximately 27 units, with a range from 5 to 69. Experience gained in longitudinal studies of ambulatory patients with mild to moderate Alzheimer's Disease suggests that they gain 6 to 12 units a year on the ADAS-cog. Lesser degrees of change, however, are seen in patients with very mild or very advanced disease because the ADAS-cog is not uniformly sensitive to change over the course of the disease. The annualized rate of decline in the placebo patients participating in REMINYL trials was approximately 4.5 units per year.

The ability of REMINYL to produce an overall clinical effect was assessed using a Clinician's Interview Based Impression of Change that required the use of caregiver information, the CIBIC-plus. The CIBIC-plus used in the trials was a semi-structured instrument based on a comprehensive evaluation at baseline and subsequent time-points of 4 major areas of patient function: general, cognitive, behavioural and activities of daily living. Clinical trials for investigational drugs have used a variety of CIBIC formats, each different in terms of depth and structure. As such, results from a CIBIC-plus reflect clinical experience from the trial or trials in which it was used and cannot be compared directly with the results of CIBIC-plus evaluations from other clinical trials.

Among the secondary measures of efficacy, the Alzheimer's Disease Cooperative Study, Activities of Daily Living Inventory (ADCS/ADL) was used. The ADCS/ADL is a caregiver-rated evaluation which yields a compound score derived from a categorical scale of 23 items concerning participation in activities of daily living.

U.S. Twenty-One-Week Fixed-Dose Study (GAL-USA-10)

In a study of twenty-one weeks' duration, 978 patients were randomized to doses of 8, 16, or 24 mg of REMINYL per day, or to placebo, each given in 2 divided doses. Treatment was initiated at 8 mg/day for all patients randomized to REMINYL, and increased by 8 mg/day every 4 weeks. Therefore, the maximum dose-escalation phase was 8 weeks and the minimum maintenance phase was 13 weeks (in patients randomized to 24 mg/day of REMINYL).

Effects on the ADAS-cog: Figure 1 illustrates the time course for the change from baseline in ADAS-cog scores for all four dose groups over the 21 weeks of the study. At 21 weeks of treatment, the mean differences in the ADAS-cog change scores for the REMINYL-treated patients compared to the patients on placebo were 0.8, 2.9 and 2.9 units for the 8, 16 and 24 mg/day treatments, respectively. The 16 mg/day and 24 mg/day treatments were statistically significantly superior to placebo and to the 8 mg/day treatment. There was no statistically significant difference between the 16 mg/day and 24 mg/day dose groups.

Figure 1: Time-course of the Changes from Baseline in ADAS-cog Score (ITT Population)

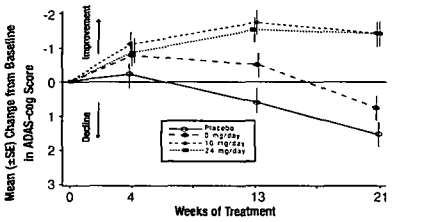
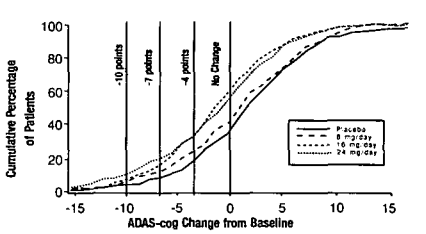


Figure 2 illustrates the cumulative percentages of patients from each of the four treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X-axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to galantamine and placebo have a wide range of responses, but that the REMINYL groups are more likely to show the greater improvements.

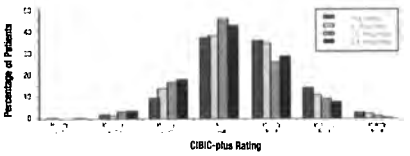
Figure 2: Cumulative percentage of Patients with Specified Changes from Baseline in ADAS-cog Scores (ITT Population)



Treatment	Change in ADAS-cog			
	-10	-7	-4	0
Placebo	3.7%	7.8%	19.0%	43.9%
8 mg/day	4.5%	11.4%	22.7%	47.7%
16 mg/day	6.4%	15.0%	33.1%	67.3%
24 mg/day	8.8%	19.8%	32.4%	62.6%

Effects on the CIBIC-plus: Figure 3 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the four treatment groups. The REMINYL-placebo differences for these groups of patients in mean rating were 0.10, 0.32 and 0.38 units for the 8,16 and 24 mg/day treatments, respectively. The 16 mg/day and 24 mg/day treatments were statistically significantly superior to placebo. The differences vs. the 8 mg/day treatment for the 16 and 24 mg/day treatments were 0.22 and 0.28, respectively. There were no statistically significant differences between the 16 mg/day and 24 mg/day dose groups.

Figure 3: Distribution of CIBIC-plus Ratings at Week 21 (ITT Population)



Effects on ADCS/ADL Inventory: The Alzheimer's Disease Cooperative Study, Activities of Daily Living Inventory was used as a secondary efficacy measure. At baseline, mean ADCS/ADL scores (mean ± SE) were for the placebo group: 52.3 ± 0.89 units; for the 16 mg/day group: 51.6 ± 0.93 units; for the 24 mg/day group: 51.9 ± 0.98 units. At Week 21, the placebo group declined an average of 3.9 ± 0.55 units, and the 16 mg/day and 24 mg/day groups deteriorated minimally at 1.0 ± 0.51 units and 1.6 ± 0.56 units, respectively. The difference between the placebo group and the galantamine treatment groups (16 mg/day or 24 mg/day) was statistically significant.

U.S. Twenty-Six-Week Fixed-Dose Study (GAL-USA-1)

In a study of 26 weeks' duration, 636 patients were randomized to either a dose of 24 mg or 32 mg of REMINYL per day, or to placebo, each given in two divided doses. The 26-week study was divided into a 3-week dose-escalation phase and a 23-week maintenance phase.

Effects on the ADAS-cog: Figure 4 illustrates the time course for the change from baseline in ADAS-cog score for all three dose groups over the 26 weeks of the study. At 26 weeks of treatment, the mean difference in the ADAS-cog change scores for the REMINYL-treated patients compared to the patients on placebo were 3.2 and 2.8 units for the 24 mg/day and 32 mg/day treatments, respectively. Both treatments were statistically significantly superior to placebo, but were not statistically significantly different from each other.

Figure 4: Time course of the Changes from Baseline in ADAS-cog Score (ITT Population)

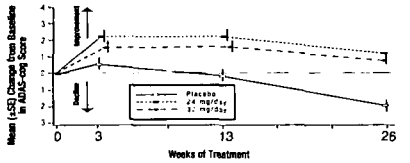
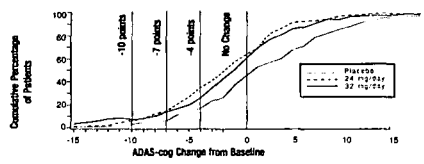


Figure 5 illustrates the cumulative percentages of patients from each of the three treatment groups who had attained at least the measure of improvement in ADAS-cog score shown on the X-axis. Three change scores (10-point, 7-point and 4-point reductions) and no change in score from baseline have been identified for illustrative purposes, and the percent of patients in each group achieving that result is shown in the inset table.

The curves demonstrate that both patients assigned to galantamine and placebo have a wide range of responses, but that the REMINYL groups are more likely to show the greater improvements. Curve for an effective treatment would be shifted to the left of the curve for placebo, while an ineffective or deleterious treatment would be superimposed upon, or shifted to the right of the curve for placebo, respectively.

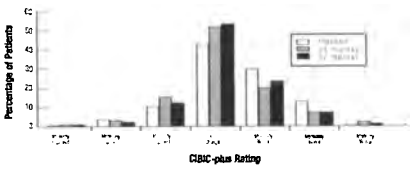
Figure 5: Cumulative Percentage of Patients with Specified Changes from Baseline in ADAS-cog Scores (ITT Population)



Treatment	Change in ADAS-cog			
	-10	-7	-4	0
Placebo	2.3%	5.6%	16.4%	45.5%
24 mg/day	5.8%	14.0%	34.3%	63.8%
32 mg/day	7.7%	13.4%	25.8%	61.2%

Effects on the CIBIC-plus: Figure 6 is a histogram of the percentage distribution of CIBIC-plus scores attained by patients assigned to each of the three treatment groups. The mean REMINYL-placebo differences for these groups of patients in the mean rating were 0.22 and 0.17 units for 24 and 32 mg/day of REMINYL, respectively. The mean ratings for both groups were statistically significantly superior to placebo, but were not significantly different from each other.

Figure 6: Distribution of CIBIC-plus Ratings Week 26 (ITT Population)



Age, gender and race: Patient's age, gender or race did not predict outcome of treatment.

INDICATIONS AND CLINICAL USE

REMINYL (galantamine hydrobromide) is indicated for the symptomatic treatment of patients with mild to moderate dementia of the Alzheimer's type. REMINYL has not been studied in controlled clinical trials for longer than 6 months.

REMINYL should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's Disease.

CONTRAINDICATIONS

REMINYL (galantamine hydrobromide) is contraindicated in patients with known hypersensitivity to galantamine hydrobromide, other tertiary alkaloid derivatives or to any excipients used in the formulation.

WARNINGS

Anesthesia

REMINYL (galantamine hydrobromide), as a cholinesterase inhibitor, is likely to exaggerate succinylcholine-type muscle relaxation during anesthesia.

Neurological Conditions

Seizures: In placebo-controlled trials with REMINYL, cases of seizure were reported; there was no increase in incidence compared with placebo. Cholinomimetics are believed to have some potential to cause generalized convulsions. However, seizure activity may also be a manifestation of Alzheimer's Disease. The risk/benefit of REMINYL treatment for patients with a history of seizure disorder must therefore be carefully evaluated.

REMINYL has not been studied in patients with moderately severe or severe Alzheimer's Disease, non-Alzheimer dementias or individuals with Parkinson's Disease features. The efficacy and safety of REMINYL in these patient populations is unknown.

Pulmonary Conditions

Like other cholinomimetic drugs, REMINYL should be prescribed with care for patients with a history of asthma or obstructive pulmonary disease.

Cardiovascular Conditions

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 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, and it 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.

Gastrointestinal Conditions

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 REMINYL, patients with symptomatic peptic ulceration were excluded. Clinical studies of REMINYL have shown no increase, relative to placebo, in the incidence of either peptic ulcer disease or gastrointestinal bleeding (see ADVERSE REACTIONS).

REMINYL, 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.

Weight Loss

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.

Genitourinary

Although not observed in clinical trials of REMINYL, cholinomimetics may cause bladder outflow obstruction.

PRECAUTIONS

Concomitant Use with Other Drugs

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 REMINYL (galantamine hydrobromide) clinical trials received neuroleptics, antidepressants or anticonvulsants, there is thus limited information concerning the interaction of REMINYL with these drugs.

Use in Patients ≥85 Years Old

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 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 REMINYL treatment in patients with mild to moderate Alzheimer's Disease and serious/significant comorbidity. The use of REMINYL 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.

Renally and Hepatically Impaired Patients

There is limited information on the pharmacokinetics of REMINYL in renally and hepatically impaired patients (see CLINICAL PHARMACOLOGY, Pharmacokinetics). It is therefore recommended that dose escalation with REMINYL in Alzheimer's Disease patients with renal impairment (creatinine clearance of 9 to 60 mL/min) or hepatic impairment be undertaken with caution and under conditions of close monitoring for adverse effects (see DOSAGE AND ADMINISTRATION, Special Populations). In patients with a creatinine clearance of less than 9 mL/min and in patients with severe hepatic impairment (Child-Pugh score of 10-15), the use of REMINYL is not recommended.

Drug-Drug Interactions

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.

Effect of Other Drugs on the Metabolism of REMINYL

Pharmacokinetic studies to assess the potential of REMINYL 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 2° and 3° 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 (see CLINICAL PHARMACOLOGY).

Carcinogenesis, Mutagenesis and Impairment of Fertility

In a 24-month oral carcinogenicity study in rats, a slight increase in endometrial adenocarcinomas was observed at 10 mg/kg/day (4 times the Maximum Recommended Human Dose [MRHD] on a mg/m² basis or 6 times on an exposure [AUC] basis), and 30 mg/kg/day (12 times the MRHD on a mg/m² basis or 19 times on an AUC basis). No increase in neoplastic changes was observed in females at 2.5 mg/kg/day (equivalent to the MRHD on a mg/m² basis or 2 times on an AUC basis) or in males up to the highest dose tested of 30 mg/kg/day (12 times the MRHD on a mg/m² and AUC basis).

Galantamine was not carcinogenic in a 6-month oral carcinogenicity study in transgenic (P 53-deficient) mice up to 20 mg/kg/day, or in a 24-month oral carcinogenicity study in male and female mice up to 10 mg/kg/day (2 times the MRHD on a mg/m² basis and equivalent on an AUC basis).

Galantamine produced no evidence of genotoxic potential when evaluated in the *in vitro* Ames *S. typhimurium* or *E. coli* reverse mutation assay, *in vitro* mouse lymphoma assay, *in vivo* micronucleus test in mice, or *in vitro* chromosome aberration assay in Chinese hamster ovary cells.

No impairment of fertility was seen in rats given up to 16 mg/kg/day (7 times the MRHD on a mg/m² basis) for 14 days prior to mating in females and for 60 days prior to mating in males.

Pregnancy

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 in pregnant women has not been established. REMINYL 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 Mothers

It is not known whether REMINYL is excreted in human breast milk and therefore REMINYL should not be used in nursing mothers.

Pediatric Use

The safety and effectiveness of REMINYL in any illness occurring in pediatric patients have not been established.

ADVERSE REACTIONS

A total of 2287 patients with mild to moderate Alzheimer's Disease were treated with REMINYL (galantamine hydrobromide) 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 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: Most frequent adverse events leading to discontinuation in a placebo-controlled, double-blind trial with a 4-week dose-escalation schedule (GAL-USA-10)

	Recommended 4-week dose escalation		
Adverse Events	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 2. These events were primarily gastrointestinal and tended to occur at a lower rate with 16 mg/day, the initial recommended maintenance dose.

Table 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)

	Week 1-12*			Week 13-21		
Adverse Event	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%

* 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 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 3 were derived from trials using a 1-week or the recommended 4-week dose-escalation period.

Table 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† (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%
Gastro-intestinal 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%

† 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).

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. 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.

Cardiovascular System Disorders: *Frequent*: hypertension; *Infrequent*: hypotension postural, hypotension, edema dependent, cardiac failure.

Central & Peripheral Nervous System Disorders: *Infrequent*: vertigo, hypertonia, convulsions, muscle contractions involuntary, paraesthesia, ataxia, hypokinesia, hyperkinesia, apraxia, aphasia.

Gastrointestinal System Disorders: *Frequent*: flatulence; *Infrequent*: gastritis, melena, dysphagia, hemorrhage rectum, mouth dry, saliva increased, diverticulitis, gastroenteritis, hiccup; *Rare*: esophageal perforation

Heart Rate & Rhythm Disorders: *Infrequent*: AV block, palpitation, fibrillation atrial, QT prolonged, bundle branch block, tachycardia supraventricular, T-wave inversion, tachycardia ventricular.

Metabolic & Nutritional Disorders: *Infrequent*: hyperglycemia, phosphatase alkaline increased, NPN increased.

Platelet, Bleeding & Clotting Disorders: *Infrequent*: purpura, epistaxis, thrombocytopenia.

Psychiatric Disorders: *Infrequent*: apathy, paroniria, paranoid reaction, libido increased, delirium.

Urinary System Disorders: *Frequent*: incontinence; *Infrequent*: hematuria, micturition frequency, cystitis, urinary retention, nocturia, renal calculi.

SYMPTOMS AND TREATMENT OF 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.

Treatment

REMINYL (galantamine hydrobromide) has a plasma half-life of approximately 7-8 hours. It is recommended that, in case of asymptomatic overdose, no further dose of REMINYL 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 REMINYL 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 REMINYL 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 AND ADMINISTRATION

REMINYL (galantamine hydrobromide) tablets should only be prescribed by (or following consultation with) clinicians who are experienced in the diagnosis and management of Alzheimer's Disease.

Adults

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 given in a b.i.d. regimen. 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 of REMINYL is 4 mg twice a day (8 mg/day). After a minimum of 4 weeks of treatment, if this dose is well tolerated, the dose should be increased to 8 mg twice a day (16 mg/day). A further increase to 12 mg twice a day (24 mg/day) after a minimum of 4 weeks at the previous dose may be considered following appropriate assessment of clinical benefit and tolerability.

REMINYL should be administered twice a day, preferably with morning and evening meals.

Patients and caregivers should be warned that 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.

The abrupt withdrawal of REMINYL 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 are lost, however, when the drug is discontinued.

Concomitant Treatment

In patients treated with potent CYP2D6 or CYP3A4 inhibitors, dose reductions can be considered.

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), dosing should proceed cautiously and should not exceed 8 mg twice a day (16 mg/day). In patients with severe hepatic impairment (Child-Pugh score of 10-15), the use of REMINYL is not recommended (see PRECAUTIONS).

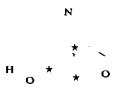
Renal Impairment

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. In patients with a creatinine clearance less than 9 mL/min, the use of REMINYL is not recommended (see PRECAUTIONS).

In a population of cognitively-impaired individuals, safe use of this and all other medications may require supervision.

PHARMACEUTICAL INFORMATION

Drug Substance

Trade Name:	REMINYL
Common Name:	galantamine hydrobromide
Chemical Name:	(4a*S*,6*R*,8a*S*)-4a,5,9,10,11,12-hexahydro-3-methoxy-11-methyl-6*H*-benzofuro[3a,3,2-*ef*][2]benzazepin-6-ol hydrobromide
Structural Formula:	 [4aS-(4aα,6β,8aR*)] Hydrobromide (1:1)
Molecular Formula:	$C_{17}H_{21}NO_3 \cdot HBr$
Molecular Weight:	368.27
Ionization Constant:	pKa=8.2 (azepine moiety)
Partition Coefficient:	log *P*=1.09, between *n*-octanol and an aqueous buffer solution at pH=12.0
Melting Point:	257.3°C
Description:	Galantamine hydrobromide is a white to almost white powder. It is freely soluble in water (pH=5.2), 0.1 N hydrochloric acid (pH=1.0) and 0.1 N sodium hydroxide (pH=8.3).

Composition

REMINYL (galantamine hydrobromide) tablets are available in three strengths containing 4, 8, 12 mg of galantamine per tablet, as galantamine hydrobromide. The inactive ingredients are lactose monohydrate, microcrystalline cellulose, colloidal anhydrous silica, crospovidone, magnesium stearate, hydroxypropyl methylcellulose, propylene glycol, talc, and titanium dioxide. The 4 mg tablet also contains yellow ferric oxide. The 8 mg tablet also contains red ferric oxide. The 12 mg tablet also contains red ferric oxide and FD & C yellow #6 (also known as orange yellow S aluminum lake).

Stability and Storage Recommendations

REMINYL tablets should be stored between 15°C-30°C.

AVAILABILITY OF DOSAGE FORMS

REMINYL (galantamine hydrobromide), expressed as galantamine base, is available as film-coated tablets in the following strengths:

4 mg tablets which are off-white, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G4" on the other side;

8 mg tablets which are pink, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G8" on the other side;

12 mg tablets which are orange-brown, circular, biconvex tablets with the inscription "JANSSEN" on one side and "G12" on the other side.

The tablets are packaged in a blister card that holds 14 tablets. There are 4 cards per carton.

Product Monograph available to healthcare professionals upon request.

JANSSEN-ORTHO Inc.
19 Green Belt Drive, Toronto, ON M3C 1L9

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FUTURE MEETINGS OF THE CANADIAN CONGRESS OF NEUROLOGICAL SCIENCES

June 17-21, 2003 Quebec City

June 8-12, 2004 Calgary

June 14-18, 2005 Ottawa

June 13-17, 2006 Montreal

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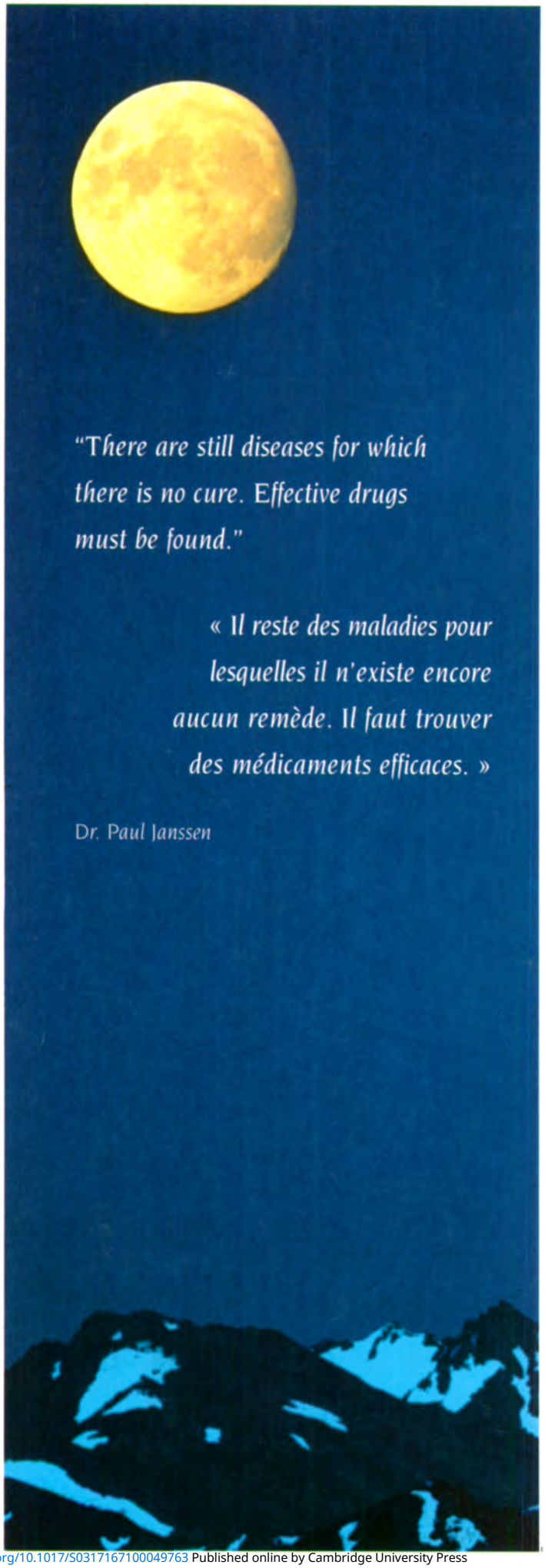

"There are still diseases for which there is no cure. Effective drugs must be found."

« Il reste des maladies pour lesquelles il n'existe encore aucun remède. Il faut trouver des médicaments efficaces. »

Dr. Paul Janssen

SOME GOALS
SEEM DISTANT
AND REMOTE.

SOMEONE HAS
TO BELIEVE THEY CAN BE
REACHED.

IL Y A DES BUTS QUI
SEMBLENT LOINTAINS
ET DIFFICILES
À ATTEINDRE.

IL FAUT Y CROIRE.

We do.

Effective treatments and cures are needed. We're working as hard as we can to find them.

Our motivation is simple – improving and even saving peoples' lives.

Remember, the smallest step today can lead to a giant leap tomorrow.

C'est ce que nous faisons.

Des traitements et des remèdes efficaces sont indispensables. Nous travaillons incessamment pour les découvrir.

Notre motivation est simple – améliorer la qualité de vie et même sauver des vies humaines.

N'oublions pas : un tout petit pas aujourd'hui peut permettre un grand bond en avant demain.

Good health above all.

JANSSEN-ORTHO

La santé avant tout

Member
R&D
Membre

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