ropinirole

REQUIP

ropinirole (as ropinirole hydrochloride)

Tablets
0.25 mg, 1.0 mg, 2.0 mg, 5.0 mg

THERAPEUTIC CLASSIFICATION
AntiParkinsonian Agent / Dopamine Agonist

ACTION AND CLINICAL PHARMACOLOGY
REQUIP (ropinirole hydrochloride) is a non-ergoline dopamine agonist, which activates post-synaptic dopamine receptors.

In vitro studies have shown that ropinirole binds with high affinity to cloned human D_2, D_3 and D_4 receptors. The antiparkinson activity of ropinirole is believed to be due to its stimulatory effects on central post-synaptic dopamine D_2 receptors within the caudate-putamen.

Ropinirole is a potent agonist both *in vitro* and *in vivo* and restores motor function in animal models of Parkinson's disease. Ropinirole has been shown to reverse the motor deficits induced by the neurotoxin 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) in primates.

Neither ropinirole nor its metabolites bind with high affinity to dopamine D_1 receptors. Ropinirole also has very low affinity for 5-HT_1, 5-HT_2, benzodiazepine, $GABA_A$, muscarinic, alpha- or beta-adrenoreceptors. Ropinirole binds to opiate receptors with low affinity, however, studies show that this weak opiate activity has no consequences at pharmacological doses *in vivo*.

In rats, ropinirole binds to melanin-containing tissues (e.g., the eye) to a greater degree than non-pigmented tissues, and tissue levels decline with a half-life of 16-20 days. It is unknown whether or not ropinirole accumulates in these tissues over time.

In healthy normotensive subjects, single oral doses of REQUIP, in the range of 0.01 to 2.5 mg, had little or no effect on supine blood pressure and pulse rate. Upon standing, REQUIP caused decreases in systolic and mainly diastolic blood pressure at doses above 0.25 mg. In some subjects, these changes were associated with the emergence of orthostatic symptoms, bradycardia and, in one case, transient sinus arrest in the context of a severe vasovagal syncope. The effect of repeat dosing and slow titration of REQUIP was not studied in healthy volunteers. The mechanism of REQUIP-induced orthostatic symptoms probably relates to its dopamine D_2-mediated blunting of the noradrenergic response to standing and subsequent decrease in peripheral vascular resistance. Orthostatic signs and symptoms were often accompanied by nausea.

REQUIP had no dose-related effect on ECG wave form and rhythm in young healthy male volunteers.

At doses ≥0.8 mg REQUIP suppressed serum prolactin concentrations in healthy male volunteers.

Pharmacokinetics

Absorption, Bioavailability, and Distribution
Ropinirole is rapidly absorbed with median peak concentrations occurring within 1.5 hours after oral dosing. Despite complete absorption, absolute bioavailability of ropinirole is reduced to approximately 50% as a result of first-pass metabolism. Relative bioavailability from a tablet compared to an oral solution is 85%. Over the therapeutic dose range, C_{max} and AUC values increase in proportion to the increase in dose (see Table 1).

The average oral clearance is approximately 47 L/h (range 17-113 L/h) and is constant over the entire dosage range. The terminal elimination half-life is approximately 6 h (range 2-27 h) and the volume of distribution at steady state is approximately 480 L (range 216-891 L) or 7.0 L/kg (range 3.1-12.9 L/kg).

Table 1: Steady state pharmacokinetic parameters (mean and range) of ropinirole in patients with Parkinson's disease administered ropinirole in a t.i.d. regimen

Unit Dose mg	C_{max} ng/mL	C_{min} ng/mL	T_{max}* h	AUC_{0-8} ng.h/mL
1	5.3 (3.1-9.0)	2.6 (0.9-4.2)	2.0 (0.5-7.0)	27.5 (14.9-46.5)
2	9.8 (5.0-18.0)	4.8 (2.3-10.0)	1.0 (0.6-4.0)	53.8 (23.9-108)
4	23.7 (14.2-40.9)	13.1 (4.8-23.9)	1.0 (1.0-3.0)	136 (66.1-241)

*median

Steady state concentrations are expected to be achieved within 2 days of dosing. There is, on average, a two-fold higher steady-state plasma concentration of ropinirole following the recommended t.i.d. regimen compared to those observed following a single oral dose.

Food delayed the rate of absorption of ropinirole (median T_{max} was increased by 2.6 hours and C_{max} was decreased by 25%) in Parkinsonian patients. However, there was no marked change in the overall systemic availability of the drug. Ropinirole may be given with or without food. While administration of the drug with food may improve gastrointestinal tolerance, in severely fluctuating patients, the morning dose may be given without food in order to avoid a delay in time to switch "ON".

Population pharmacokinetic analyses have shown that frequently co-administered medications, such as levodopa, selegiline, amantadine, anticholinergic drugs, ibuprofen, benzodiazepines and antidepressants did not alter the pharmacokinetics of ropinirole.

Plasma protein binding is low (10 to 40%).

Ropinirole has a blood to plasma ratio of 1.2.

Metabolism
Ropinirole is extensively metabolized by the liver. The N-despropyl metabolite is the major metabolite circulating in the plasma. Based on AUC data, the plasma levels of the metabolite were consistently higher than those of the parent drug suggesting a nonsaturable conversion of ropinirole to the N-despropyl metabolite. The affinity of the N-despropyl metabolite for human cloned D_2 receptors is lower than the affinity of ropinirole. In addition the metabolite does not cross the blood-brain barrier; thus, it is unlikely to contribute to the therapeutic effects of ropinirole. The plasma concentrations of the hydroxylated metabolite are low and account for about 1-5% of the ropinirole concentrations. Although the hydroxylated metabolite was more active than ropinirole in *in vitro* D_2 receptor binding studies, at therapeutic doses it is not expected to contribute to the activity of ropinirole.

In vitro studies indicate that the major cytochrome P450 isozyme involved in the metabolism of ropinirole is CYP1A2. In patients with Parkinson's disease, ciprofloxacin, an inhibitor of CYP1A2, significantly increased the systemic availability of ropinirole, while theophylline, a substrate of CYP1A2, was devoid of such activity (see PRECAUTIONS, Drug Interactions).

Elimination
Recovery of radioactivity after oral and intravenous administration of ^{14}C-ropinirole was approximately 88% and 90% of the dose, respectively. Urinary excretion of unchanged ropinirole is low and represents approximately 5 to 10% of the dose. N-despropyl ropinirole is the predominant metabolite found in the urine (40%), followed by the glucuronide of the hydroxy metabolite (10%), and the carboxylic acid metabolite (10%) formed from N-despropyl ropinirole.

Population Subgroups

Renal and Hepatic Impairment
Based on population pharmacokinetics, no clinically significant differences were observed in the pharmacokinetics of REQUIP in Parkinsonian patients with moderate renal impairment (creatinine clearance between 30 to 50 mL/min; n=18, mean age 74 years) compared to age-matched patients with creatinine clearance above 50 mL/min (n=44, mean age 70 years). Therefore, no dosage adjustment is necessary in Parkinsonian patients with mild to moderate renal impairment (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

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 (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Gender
Population pharmacokinetic analysis indicated that the oral clearance and volume of distribution of REQUIP at steady state were similar in male patients (n=99, mean age 60 years) and female patients who were not taking concomitant estrogens (n=56, mean age 65 years).

Estrogen Replacement Therapy
In women, on long-term treatment with conjugated estrogens (n=16, mean age 63 years), the oral clearance of REQUIP was decreased by an average of 36% compared to the oral clearance in women not receiving supplemental estrogens (n=56, mean age 65 years). The average terminal elimination half-life was 9.0 hours in the estrogen group and 6.5 hours in patients not taking estrogens (see PRECAUTIONS and DOSAGE AND ADMINISTRATION).

Age
Population pharmacokinetic analysis revealed that the oral clearance of REQUIP, seen in patients under the age of 65 years (n=97), was reduced from 62.1 L/h to 45.5 L/h in patients between the ages of 65 and 75 years (n=63). In patients older than 75 years (n=11), oral clearance was similar to that seen in the 65 to 75 year age group (41.7 L/h). However, since the dose of REQUIP is to be individually titrated to clinical response, dosage adjustment is not necessary in the elderly (above 65 years).

Clinical Trials
Up to May 31, 1996, 1599 patients have been exposed to REQUIP, with 481 patients being exposed for over one year and 241 patients being exposed for over two years.

Evidence to support the efficacy of REQUIP in treating the signs and symptoms of Parkinson's disease was obtained in multicentre, double-blind studies. These studies included either patients who had minimal or no prior dopaminergic therapy, or patients who were not optimally controlled with current levodopa-decarboxylase inhibitor therapy. In patients with early disease, REQUIP improved motor function (assessed by the motor component of the UPDRS [Unified Parkinson's Disease Rating Scale]) and delayed the need to initiate treatment with levodopa. In patients with more advanced disease, REQUIP reduced "off" time (based upon patient diaries recording time "on" and "off") and permitted a reduction in levodopa dose. The subsequent section describes some of the studies in which REQUIP was titrated (see DOSAGE AND ADMINISTRATION) to the maximal dose of 8 mg t.i.d.

In clinical trials where dosing was titrated to optimal clinical effect, the mean daily dose of REQUIP at 24 weeks was 9.5 mg in early therapy (n=282) and was 13.5 mg in adjunct therapy (n=303).

In the pivotal clinical trials, including studies where the dose was titrated to the target maximum of 24 mg per day, the mean daily dose of REQUIP at endpoint was 10.7 mg in early therapy (n=458) and 12.5 mg in adjunct therapy (n=456).

In the total patient database (n=1599) over 50% of patients were dosed between 6 and 15 mg of REQUIP per day in both early and adjunct therapy. Less than 22% of patients exceeded a total daily dose of 15 mg.

During the clinical trials, the dose of REQUIP was titrated to optimal clinical response and tolerance. Retrospective analysis showed that female patients required lower doses than male patients but were exposed to REQUIP for similar periods of time.

Early Therapy
In a double-blind, randomized, placebo-controlled, 6-month study, REQUIP-treated patients (n=116) demonstrated a 24% improvement in UPDRS motor scores from baseline, compared to placebo-treated patients (n=125), who demonstrated a 3% worsening in motor scores. On the Clinical Global Impression (CGI) scale, 33% of REQUIP-treated patients and 12% of placebo-treated patients were rated as "very much improved" and "much improved." 'Rescue levodopa' was needed by 11% of REQUIP-treated and 29% of placebo-treated patients. All differences were statistically significant.

In a double-blind, randomized, 5-year study, at the 6 month interim analysis, REQUIP (n=179) was compared to levodopa-benserazide (n=89). The decrease in UPDRS motor scores versus baseline was greater with levodopa than with REQUIP. However, the proportion of 'responders' (UPDRS improvement of at least 30%) did not differ between levodopa and REQUIP. Results on the CGI indicated that there was no difference between REQUIP and levodopa in less severely afflicted patients (Hoehn and Yahr stage I to II) but levodopa was more efficacious in patients with more severe disease.

Adjunct Therapy
In a double-blind, randomized, clinical trial of 6-month duration, REQUIP (n=94) was compared to placebo (n=54) as adjunct therapy to levodopa. The primary efficacy parameter, defined as both a 20% or greater reduction in levodopa dose and a 20% or greater reduction in "off" time, was achieved by 28% of REQUIP-treated patients and 11% of placebo-treated patients. This difference was statistically significant. The daily dose of levodopa was reduced by 19% and 2.8% in the REQUIP and placebo-treated patients, respectively.

Therapeutic Effect – Plasma Concentration
The relationship between efficacy and plasma concentrations of REQUIP was assessed from population pharmacokinetic data obtained in 141 male and female patients who participated in two prospective studies.

In general, the average plasma concentrations of REQUIP at steady state (C_{ss}) were higher in patients classified as responders versus non-responders, although considerable overlap in the range of C_{ss} between the two groups was noted. Mean (±SD) REQUIP C_{ss} for responders and non-responders were 22.8±10.8 ng/mL and 15.1±9.7 ng/mL, respectively.

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.

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

WARNINGS

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
In controlled trials, REQUIP (ropinirole hydrochloride) caused hallucination in 5.1% of patients during early therapy (1.4% in the placebo group) and in 10.1% of patients receiving REQUIP and levodopa (4.2% receiving placebo and levodopa). Hallucination was of sufficient severity that it led to discontinuation in 1.3% and 1.9% of patients during early and adjunct therapy, respectively. The incidence of hallucination was dose-dependent both in early and adjunct therapy studies.

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.

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 (see Pharmacokinetics). 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; see 'Pharmacokinetics').

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
As orthostatic symptoms of dizziness or lightheadedness as well as somnolence may occur during REQUIP therapy patients should be cautioned not to drive a motor vehicle or operate potentially hazardous machinery until they are reasonably certain that REQUIP therapy does not affect their ability to engage in such activities.

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.

The following table 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.

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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 = 208 % 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	a	–
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
Toothache	–	–	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
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 Biliary 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%.

In addition to the events listed in Table 2, the following adverse events were recorded with rates equal to, or more common in, placebo-treated patients:

Early therapy: fever, hot flushes, injury, rigors, ataxia, dyskinesia, dystonia, hyperkinesia, involuntary muscle contractions, paresthesia, aggravated Parkinsonism, tremor, *diarrhea, gingivitis, increased saliva, bradycardia, gout, hyperglycemia, decreased* weight, arthralgia, arthritis, back pain, myalgia, basal cell carcinoma, anxiety, depression, abnormal dreaming, insomnia, nervousness, prostatic disorder, upper respiratory tract infection, coughing, rash, hematuria and leg cramps.

Adjunct therapy: asthenia, chest pain, fatigue, hot flushes, postural hypotension, abnormal gait, hyperkinesia, aggravated Parkinsonism, vertigo, abdominal pain, constipation, back pain, myalgia, depression, insomnia, paronirla (WHO dictionary term for nightmares), viral infection, upper respiratory tract infection, pharyngitis, rhinitis, rash, rash erythematous, taste perversion, hematuria, leg cramps and diplopia, myocardial infarction, extrasystoles supraventricular.

Events Observed During the Premarketing Evaluation of REQUIP: Of the 1599 patients who received REQUIP in therapeutic studies, the following adverse events, which are not included in Table 2 or in the listing above, have been noted up to May 1996. In the absence of appropriate controls in some of the studies, a causal relationship between these events and treatment with REQUIP cannot be determined.

Events are categorized by body system and listed in order of decreasing frequency according to the following definitions: '*frequent*' adverse events are those occurring on one or more occasions in at least 1/100 patients; '*infrequent*' adverse events are those occurring in 1/100 to 1/1,000 patients; '*rare*' events are those occurring in fewer than 1/1,000 patients.

Autonomic Nervous System: *rare,* cold clammy skin.

Body as a Whole: *infrequent,* pallor, allergy, peripheral edema, enlarged abdomen, substernal chest pain, edema, allergic reaction, ascites, precordial chest pain, therapeutic response increased, ischemic necrosis, edema generalised; *rare,* periorbital edema, face edema, halitosis.

Cardiovascular System: *infrequent, cardiac failure, heart disorder, specific abnormal* ECG, aneurysm, cardiomegaly, abnormal ECG, aggravated hypertension; *rare,* cyanosis, fluid overload, heart valve disorder.

Central and Peripheral Nervous System: *frequent,* neuralgia; *infrequent,* hypertonia, speech disorder, choreoathetosis, abnormal coordination, dysphonia, extrapyramidal disorder, migraine, aphasia, coma, convulsions, hypotonia, nerve root lesion, peripheral neuropathy, paralysis, stupor; *rare,* cerebral atrophy, grand mal convulsions, hemiparesis, hemiplegia, hyperreflexia, neuropathy, ptosis, sensory disturbance, hydrocephaly.

Collagen: *rare,* rheumatoid arthritis.

Endocrine System: *infrequent,* gynecomastia, hypothyroidism; *rare,* SIADH (syndrome of inappropriate anti-diuretic hormone secretion), increased thyroxine, goitre, hyperthyroid.

Gastrointestinal System: *frequent,* gastrointestinal disorder (NOS); *infrequent,* gastritis, gastroenteritis, gastroesophageal reflux, increased appetite, esophagitis, peptic ulcer, diverticulitis, hemorrhoids, hiccup, tooth caries, increased amylase, duodenal ulcer, duodenitis, fecal incontinence, GI hemorrhage, glossitis, rectal hemorrhage, melena, pancreatitis, rectal disorder, altered saliva, stomatitis, ulcerative stomatitis, tongue edema, gastric ulcer, tooth disorder; *rare,* esophageal stricture, esophageal ulceration, hemorrhagic gastritis, gingival bleeding, hematemesis, lactose intolerance, salivary duct obstruction, tenesmus, tongue disorder, hemorrhagic duodenal ulcer, aggravated tooth caries.

Hearing: *infrequent,* earache, decreased hearing, vestibular disorder, ear disorder (NOS); *rare,* hyperacusis, deafness.

Heart Rate and Rhythm: *infrequent,* arrhythmia, bundle branch block, cardiac arrest, *supraventricular extrasystoles, ventricular tachycardia; rare, atrioventricular block.*

Liver and Biliary System: *Infrequent,* abnormal hepatic function, increased SGPT, bilirubinemia, cholecystitis, cholelithiasis, hepatocellular damage, increased SGOT; *rare,* biliary pain, aggravated bilirubinemia, gall bladder disorder.

Metabolic and Nutritional Systems: *frequent,* increased blood urea nitrogen; *infrequent,* increased LDH, increased NPN, hyperuricemia, increased weight, hyperphosphatemia, diabetes mellitus, glycosuria, hypercholesterolemia, acidosis, hypokalemia, hyponatremia, thirst, increased creatine phosphokinase, dehydration, aggravated diabetes mellitus, hyperkalemia; *rare,* electrolyte abnormality, enzyme abnormality, hypochloremia, obesity, increased phosphatase acid, decreased serum iron.

Musculoskeletal System: *frequent,* arthrosis; *infrequent,* arthropathy, osteoporosis, tendinitis, bone disorder, bursitis, muscle weakness, polymyalgia rheumatica, skeletal pain, torticollis, *rare,* muscle atrophy, myositis, Dupuytren's contracture, spine malformation.

Myocardial, Endocardial, Pericardial Valve: *frequent,* angina pectoris; *infrequent,* myocardial infarction, aggravated angina pectoris; *rare,* mitral insufficiency.

Neoplasm: *infrequent,* carcinoma, malignant female breast neoplasm, dermoid cyst, malignant skin neoplasm, prostate adenocarcinoma, adenocarcinoma, neoplasm (NOS); *rare,* bladder carcinoma, benign brain neoplasm, breast fibroadenosis, malignant endometrial neoplasm, esophageal carcinoma, malignant larynx neoplasm, malignant lymphoma, malignant neoplasm, neuroma, lipoma, rectal carcinoma, uterine neoplasm.

Platelet Bleeding and Clotting: *infrequent,* purpura, thrombocytopenia, hematoma.

Psychiatric: *frequent,* aggravated depression, agitation; *infrequent,* increased libido, sleep disorder, apathy, dementia, delirium, emotional lability, psychosis, aggressive *reaction, delusion, psychotic depression, euphoria, decreased libido, manic reaction,* neurosis, personality disorder, somnambulism; *rare,* suicide attempt.

Red Blood Cell: *infrequent,* hypochromic anemia, anemia B_{12} deficiency; rare, polycythemia.

Female Reproductive: *infrequent,* amenorrhea, menstrual disorder, vaginal haemorrhage, uterine disorders (NOS); *rare,* female breast enlargement, intermenstrual bleeding, mastitis, uterine hemorrhage, dysmenorrhea.

Male Reproductive: *Infrequent,* epididymitis, balanoposthitis, ejaculation failure, penis disorder, perineal pain male; *rare,* Peyronie's disease, ejaculation disorder, testis disorder.

Resistance mechanism: *frequent,* infection; *infrequent,* herpes zoster, moniliasis, otitis media, sepsis, herpes simplex, fungal infection, abscess, bacterial infection, genital moniliasis; *rare,* poliomyelitis.

Respiratory: *frequent,* pneumonia; *infrequent,* asthma, epistaxis, laryngitis, pleurisy, increased sputum, pulmonary edema; *rare,* hypoxia, respiratory insufficiency, vocal cord paralysis.

Skin and Appendages: *infrequent,* dermatitis, alopecia, skin discoloration, dry skin, skin hypertrophy, skin ulceration, fungal dermatitis, eczema, hyperkeratosis, photosensitivity reaction, psoriasis, maculopapular rash, psoriaform rash, seborrhea, skin disorder, urticaria, furunculosis; *rare,* bullous eruption, nail disorder, nevus, photosensitivity allergic reaction, aggravated psoriasis, skin exfoliation, abnormal skin odor.

Other Special Senses: *rare,* parosmia.

Urinary: *infrequent,* albuminuria, dysuria, nocturia, polyuria, renal calculus, abnormal urine, micturition disorder; *rare,* oliguria, pyelonephritis, renal cyst, acute renal failure, renal pain, uremia, urethral disorder, urinary casts, bladder calculus, nephritis.

Vascular Extracardiac: *infrequent, cerebrovascular disorder, vein disorder, varicose* vein, peripheral gangrene, phlebitis, vascular disorder; *rare,* atherosclerosis, limb embolism, pulmonary embolism, gangrene, superficial phlebitis, subarachnoid hemorrhage, deep thrombophlebitis, leg thrombophlebitis, thrombosis, arteritis.

Vision: *infrequent,* conjunctivitis, blepharitis, abnormal accommodation, blepharospasm, eye pain, glaucoma, photophobia, scotoma; *rare,* blindness, blindness temporary, hemianopia, keratitis, photopsia, macula lutea degeneration, vitreous detachment, retinal disorder.

White Cell and Reticuloendothelial System: *infrequent,* leukocytosis, leukopenia, lymphopenia, lymphedema, lymphocytosis; *rare,* lymphadenopathy, granulocytopenia.

SYMPTOMS AND TREATMENT OF OVERDOSAGE

There were no reports of intentional overdose of REQUIP (ropinirole hydrochloride) in the premarketing clinical trials. A total of 27 patients accidentally took more than their prescribed dose of REQUIP, with 10 patients ingesting more than 24 mg/day. The largest overdose reported in premarketing clinical trials was 435 mg taken over a 7-day period (62.1 mg/day). Of patients who received a dose greater than 24 mg/day, one experienced mild oro-facial dyskinesia, another patient experienced intermittent nausea. *Other symptoms reported with accidental overdoses were:* agitation, increased dyskinesia, grogginess, sedation, orthostatic hypotension, chest pain, confusion, vomiting and nausea.

It is anticipated that the symptoms of REQUIP overdose will be related to its dopaminergic activity. General supportive measures are recommended. Vital signs should be maintained, if necessary. Removal of any unabsorbed material (e.g., by gastric lavage) should be considered.

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 (see 'Pharmacokinetics' section).

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 up to 24 mg per day. Doses greater than 24 mg/day have not been tested in clinical trials. Smaller dose increments are recommended for patients who may be at risk for orthostatic symptoms. In clinical trials, initial benefits were observed with 3 mg/day and higher doses.

	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

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 (see 'Clinical Trials' section).

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.

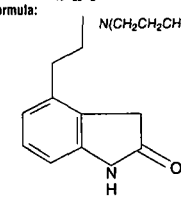
PHARMACEUTICAL INFORMATION

Drug Substance:
Proper Name: Ropinirole Hydrochloride

USAN and Chemical Name:
4-[2-(Dipropylamino)ethyl]-2-indolinone monohydrochloride

Molecular Formula: $C_{16}H_{25}N_2OCl$

Stuctural Formula:



ropinirole hydrochloride

Molecular Weight: 296.84 (260.38 as the free base).

Description: Ropinirole hydrochloride is a white to pale greenish-yellow powder.

Physico-Chemical Properties: *Ropinirole hydrochloride has a melting range of 243°* to 250°C and a solubility of 133 mg/mL in water. The pKa of the protonated tertiary amino group was found to be 9.68 at 25°C and that of the indol-2-one group was found to be 12.43 at 37°C. The distribution coefficients between n-octanol/water and cyclohexane/water at pH 8.4 and 37°C are given by log D values of +2.33 and -0.07 respectively.

Composition: Ropinirole hydrochloride is the active ingredient. Non-medicinal ingredients include: Hydrous lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hydroxypropyl methylcellulose, polyethylene glycol, titanium dioxide, iron oxide yellow (1.0 and 2.0 mg tablets), iron oxide red (2.0 mg tablets), FD&C Blue No. 2 aluminum lake (1.0 and 5.0 mg tablets), polysorbate 80 (0.25 mg tablets), talc (5.0 mg tablets). They do not contain sucrose, tartrazine or any other azo dyes.

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 – pale green imprinted with SB and 4892; 2.0 mg – pale pink *imprinted with SB and 4893; 5.0 mg – pale blue tablets imprinted with SB and 4894.*

REQUIP is available in bottles in the pack size of 100 tablets. It is also available in 0.25 mg as a single unit blister pack of 21 tablets.

Full Product Monograph available to practitioners upon request.

REFERENCES:

1. Product Monograph, 1997.
2. Adler CH, Sethi KD, Hauser RA, *et al.* Ropinirole For The Treatment of Early Parkinson's Disease. Neurology. In press.
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4. Data on file, SB 1036.

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