REPREVE® PRODUCT INFORMATION
(ropinirole)

NAME OF THE MEDICINE

REPREVE tablets contain ropinirole hydrochloride equivalent to 0.25, 0.5, 1.0 or 2.0 mg ropinirole free base.

Ropinirole hydrochloride is an orally administered dopamine receptor agonist. The compound is identified chemically as 4-[2-(dipropylamino)ethyl]-1,3-dihydro-2H-indol-2-one hydrochloride. The molecular weight of ropinirole hydrochloride is 296.84 (260.38 free base) and has a molecular formula of C_{16}H_{24}N_{2}0.HCl.

![Ropinirole Hydrochloride]

CAS Registry Number: 91374-20-8

DESCRIPTION

Ropinirole hydrochloride is a white to pale greenish-yellow powder. It is highly soluble in water (133 mg/mL).

REPREVE tablets contain the following excipients: lactose, microcrystalline cellulose, croscarmellose sodium, magnesium stearate, hypromellose, macrogol 400 and titanium dioxide (CI77891). The 0.25 mg tablets also contain polysorbate 80.

Colouring agents are also contained in the film coating as follows:
- 0.25 mg tablet (white) contains titanium dioxide (CI77891).
- 0.5 mg tablets (pale yellow) contains iron oxide yellow (CI77492), iron oxide red (CI77491) and indigo carmine (CI73015) and aluminum.
- 1.0 mg tablets (green) contains iron oxide yellow (CI77492) and indigo carmine (CI73015) and aluminum.
- 2.0 mg tablets (pale yellowish pink) contains iron oxide yellow (CI77492), and iron oxide red (CI77491).

REPREVE tablets do not contain sucrose, tartrazine, or any other azo dyes.

PHARMACOLOGY

Ropinirole hydrochloride is a potent, non-ergoline D_{2}/D_{3} dopamine agonist.
Studies with human cloned receptors *in vitro* show that ropinirole binds with high affinity to cloned human D₂, D₃ and D₄ receptors. Neither ropinirole hydrochloride nor its metabolites bind with high affinity to dopamine D₁ receptors. Ropinirole hydrochloride also has very low affinity for 5-HT₁, 5-HT₂, benzodiazepine, GABA, muscarinic, alpha- or beta-adrenoceptors. Ropinirole hydrochloride is a potent dopamine agonist *in vitro* and *in vivo*. The pathophysiology of Restless Legs Syndrome is thought to be a result of dopaminergic deficiency, such as a reduction in the synthesis of dopamine and/or D2 receptor density in the striatum. Neuropharmacological evidence suggests primary dopaminergic system involvement and possibly other neurotransmitter systems. Furthermore, evidence from Positron Emmision Tomography (PET) studies show that a mild striatal pre-synaptic dopaminergic dysfunction may be involved.

D₂ receptors are found in the central nervous system, cardiovascular system, hypothalamic-pituitary axis and gastrointestinal tract. Ropinirole hydrochloride acts in the hypothalamus and pituitary to inhibit the secretion of prolactin.

In healthy subjects, mean uric acid excretion decreased after acute dosing with 0.2 mg and 0.4 mg of ropinirole. This was not associated with changes in serum uric acid level measured 24 hours after dosing and is not likely to be of clinical significance. There is no information available on the effect of ropinirole on uric acid excretion in healthy elderly subjects or on those with mild to moderate renal impairment.

**PHARMACOKINETICS**

**Absorption**
Oral absorption of ropinirole hydrochloride is rapid and essentially complete with first pass metabolism by the liver. Bioavailability of ropinirole hydrochloride may be up to approximately 46% and average peak concentrations of the drug are achieved at a median time of 1.5 hours post dose. Wide inter-individual variability in the pharmacokinetic parameters has been seen and the increase in systemic exposure (Cmax and AUC) to the drug is proportional to the increase in dose, over the therapeutic dose range. The bioavailability of a tablet formulation is 86% relative to an oral solution. Ropinirole is mainly metabolised by the liver, and it has been shown that the enzyme predominantly responsible for its clearance is CYP1A2.

**Distribution**
Consistent with its high lipophilicity, ropinirole exhibits a large volume of distribution (approx. 7 L/kg) and is cleared from the systemic circulation with an average elimination half life of about 6 hours. Plasma protein binding of the drug is low (10-40%).

**Metabolism**
Ropinirole hydrochloride is primarily cleared by CYP1A2 metabolism and its metabolites are mainly excreted in urine. The major metabolite (N-despropyl derivative) is at least 100 times less potent than ropinirole in animal models of dopaminergic function. The active metabolite (SK&F 89124) represents a much smaller proportion of circulating dose-derived material and would not notably contribute to the pharmacological activity of ropinirole.

Administration of ropinirole hydrochloride with food delayed the rate of absorption (prolonged median Tmax by 2.6 hours and 25% decrease in Cmax); however, there was no marked change in overall systemic availability of the drug.

**Elimination**
No change in the oral clearance of ropinirole is observed following single and repeated oral administration.
In patients with mild to moderate renal impairment, no change in the clearance of ropinirole hydrochloride was observed by population kinetics.

The pharmacokinetics of ropinirole are consistent between healthy volunteers and patients with Restless Legs Syndrome.

**CLINICAL TRIALS**

The effectiveness of REPREVE in the treatment of primary RLS was demonstrated in 2 randomised, double-blind, placebo-controlled 12-week studies in adults diagnosed with RLS using the International Restless Legs Syndrome Study Group diagnostic criteria. Patients were required to have a history of a minimum of 15 RLS episodes/month during the previous month and a total score of $\geq 15$ on the International RLS Rating Scale (IRLS scale) at baseline.

Patients with RLS secondary to other conditions (e.g., pregnancy, renal failure, and anemia) were excluded.

Both studies employed flexible dosing, with patients initiating therapy at 0.25 mg REPREVE once daily. Patients were titrated based on clinical response and tolerability over 7 weeks to a maximum of 4 mg once daily. All doses were taken between 1 and 3 hours before bedtime.

A variety of measures were used to assess the effects of treatment, including the IRLS Scale and Clinical Global Impression (CGI) scores. The IRLS Scale contains 10 items designed to assess the severity of sensory and motor symptoms, sleep disturbance, daytime somnolence, and impact on activities of daily living and mood associated with RLS. The range of scores is 0 to 40, with 0 being absence of RLS symptoms and 40 the most severe symptoms. Both studies utilised the change from baseline in the IRLS Scale at the week 12 endpoint as the primary efficacy outcome.
### Table 1 Summary of Studies 190 and 194

<table>
<thead>
<tr>
<th>Study 190</th>
<th>Study 194</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Ropinirole</strong></td>
<td><strong>Placebo</strong></td>
</tr>
<tr>
<td>N=146</td>
<td>N=138</td>
</tr>
<tr>
<td>Change from Baseline in IRLS Scale Total Score Week 12 LOCFIN=144 n=135</td>
<td>n=128 n=131</td>
</tr>
<tr>
<td>Adjusted mean change from Baseline (SE)</td>
<td>-11.0 (0.72) -11.2 (0.76)</td>
</tr>
<tr>
<td>-8.0 (0.73) -8.7 (0.75)</td>
<td></td>
</tr>
<tr>
<td>Adjusted Treatment Difference</td>
<td>-3.0 -2.5</td>
</tr>
<tr>
<td>95% CI</td>
<td>-5.0, -1.0 -4.6, -0.4</td>
</tr>
<tr>
<td>P- Value</td>
<td>0.0036 0.0197</td>
</tr>
<tr>
<td>Patients with a score of (1) or (2) on the CGI-I Scale Week 12 LOCFIN=146 n=137</td>
<td>n=131 n=134</td>
</tr>
<tr>
<td>Responders % (n)</td>
<td>53.4 (78) 59.5 (78)</td>
</tr>
<tr>
<td>40.9 (56) 39.6 (53)</td>
<td></td>
</tr>
<tr>
<td>Adjusted Odds Ratio</td>
<td>1.7 2.3</td>
</tr>
<tr>
<td>1.0, 2.7 1.4, 3.8</td>
<td></td>
</tr>
<tr>
<td>95% CI</td>
<td>0.0416 0.0010</td>
</tr>
</tbody>
</table>
| P- Value | Across the 2 studies, the mean duration of RLS was 16 to 22 years (range of 0 to 64 years), mean age was approximately 55 years (range of 28 to 79 years), and approximately 61% were women. The mean dose at week 12 was approximately 2 mg/day for both studies.

A third study [191] (12-week placebo-controlled polysomnography study) in 65 patients who had periodic leg movements of sleep (PLMS) associated with their Restless Legs Syndrome examined the effect of treatment with REPREVE on PLMS (per hour of sleep) and on PLMS associated with arousal from sleep. The mean reduction from baseline in PLMS (per hour of sleep) at Week 12 was 32.9 in the REPREVE treated group, compared to a reduction of 5.7 for the placebo group. The treatment difference showed that REPREVE was statistically superior to placebo at Week 12 (p<0.0001). A significant reduction from baseline to week 12 in PLMS associated with arousal from sleep was also observed in the group treated with REPREVE (mean reduction of 3.3) compared to the group treated with placebo (mean increase of 1.1, p = 0.0096).
Long-term maintenance of efficacy [study 188] in the treatment of RLS was demonstrated in a 36-week study 188. Following a 24-week single-blind treatment phase (flexible doses of REPREVE of 0.25 to 4 mg once daily), patients who were responders (defined as a decrease of >6 points on the IRLS Scale total score relative to baseline) were randomized in double-blind fashion to placebo or continuation of REPREVE for an additional 12 weeks. Relapse was defined as an increase of at least 6 points on the IRLS Scale total score to a total score of at least 15, or withdrawal due to lack of efficacy. For patients who were responders at week 24 the mean dose of ropinirole was 2.0 mg (range 0.25 to 4 mg). Patients continued on REPREVE demonstrated a significantly lower relapse rate compared with patients randomized to placebo (32.6% vs 57.8%, p = 0.0156).

INDICATIONS

REPREVE is indicated for the treatment of primary restless legs syndrome, including the reduction of associated periodic limb movement and episodes of nocturnal arousal.

CONTRAINDICATIONS

Hypersensitivity to ropinirole hydrochloride or any of the listed excipients.

Pregnancy and lactation.

PRECAUTIONS

Repreve should not be used in the treatment of patients with neuroleptic induced akathisia.

Cardiovascular conditions: Due to the peripheral dopaminergic action of ropinirole hydrochloride, patients with severe cardiovascular disease should be treated with caution.

Psychotic disorders: Patients with a history or presence of, major psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risks (see Interactions).

Impulsive control symptoms, including compulsive behaviours such as pathological gambling and hypersexuality, have been reported in patients treated with dopaminergic agents, including ropinirole. As described in the literature, such behaviours have been reported principally in Parkinson’s disease patients treated with dopaminergic agents, especially at higher doses, and were generally reversible upon dose reduction or treatment discontinuation. In some ropinirole cases, other factors were present such as a history of compulsive behaviours or concurrent dopaminergic treatment.

Paradoxical worsening of Restless Legs Syndrome symptoms described as augmentation (either earlier onset, increased intensity, or spread of symptoms to previously unaffected limbs), or early morning rebound (reoccurrence of symptoms in the early morning hours), have been observed during treatment with ropinirole. If this occurs, treatment review may be required in some cases. The latter could be in the form of drug discontinuation, dose increment, change in dose regimen or changing to alternative treatment modality.

Sudden Onset of Sleep: Patients treated with REPREVE have reported falling asleep while engaged in activities of daily living, including the operation of motor vehicles, which sometimes resulted in accidents. Although many of these patients reported somnolence while on REPREVE, some perceived that they had no warning signs such as excessive
drowsiness, and believed that they were alert immediately prior to the event. Some of these events have been reported as late as 1 year after initiation of treatment.

In controlled clinical trials, somnolence was a common occurrence in patients receiving REPREVE and is more frequent in Parkinson’s disease (up to 40% REPREVE, 6% placebo) than in Restless Legs Syndrome (12% REPREVE, 6% placebo). Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of preexisting somnolence, although patients may not give such a history. For this reason, prescribers should continually reassess patients for drowsiness or sleepiness, especially since some of the events occur well after the start of treatment. Prescribers should also be aware that patients may not acknowledge drowsiness or sleepiness until directly questioned about drowsiness or sleepiness during specific activities.

Before initiating treatment with REPREVE, patients should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with REPREVE such as concomitant sedating medications, the presence of sleep disorders (other than Restless Legs Syndrome), and concomitant medications that increase ropinirole plasma levels (e.g., ciprofloxacin – see PRECAUTIONS: Interactions). If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g., conversations, eating, etc), REPREVE should ordinarily be discontinued. (See DOSAGE and ADMINISTRATION for guidance on discontinuing REPREVE). If a decision is made to continue REPREVE, patients should be advised to not drive and to avoid other potentially dangerous activities. There is insufficient information to establish that dose reduction will eliminate episodes of falling asleep while engaged in activities of daily living.

Fibrotic complications: Repreve is a non-ergot derived dopaminergic agent. Cases of retroperitoneal fibrosis, pulmonary infiltrates, pleural effusion, pleural thickening, pericarditis and cardiac valvulopathy have been reported in some patients treated with ergot-derived dopaminergic agents. While these complications may resolve when the drug is discontinued, complete resolution does not always occur. Although these adverse events are believed to be related to the ergoline structure of these compounds, whether other, non-ergot derived dopamine agonists can cause them is unknown.

Driving or operating machinery: Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes or dizziness (including vertigo) must be informed to refrain from driving or engaging in activities where impaired alertness may put themselves or others at risk of serious injury or death (e.g. operating machines) until such recurrent episodes and somnolence have resolved (see Precautions, Sudden Onset of Sleep.).

Carcinogenicity: Two-year carcinogenicity studies were conducted in mice and rats at oral doses up to 50 mg/kg/day (6 times (in the mouse) and 27 times (in the rat) the systemic exposure at the maximum recommended clinical dose, based on AUC). In the male rat, there was a significant increase in testicular Leydig cell adenomas at doses of 15 mg/kg and above. This finding is thought to be due to the effects of hypoprolactinaemia in rats and not relevant to humans. In the female mouse there was an increase in benign uterine endometrial polyps at a dose of 50 mg/kg/day (equivalent to the systemic exposure at the maximum recommended clinical dose, based on AUC). No drug-related carcinogenic effects were seen in male mice or female rats.

Mutagenicity: Ropinirole was not genotoxic in a series of assays for gene mutations and chromosomal damage.

Effects on Fertility: When administered to female rats prior to, during mating and throughout pregnancy, ropinirole caused reduced implantation at oral doses of 10 mg/kg/day
or greater. This effect is thought to be due to the prolactin-lowering effect of ropinirole. In humans, chorionic gonadotrophin, not prolactin, is essential for implantation. In rat studies using low doses of ropinirole (5 mg/kg) during the prolactin-dependent phase of early pregnancy (gestation days 0-8), oral doses of ropinirole, up to 100 mg/kg/day, did not affect female fertility. There was no effect on fertility in male rats dosed at 125 mg/kg/day for ten weeks.

Use in Pregnancy (Category B3): REPREVE should not be used during pregnancy. In animal studies, oral administration of ropinirole to pregnant rats at maternotoxic doses resulted in abortion at 40 mg/kg/day, decreased fetal body weight at 60 mg/kg/day, increased fetal death at 90 mg/kg/day and fetal malformations (predominantly digital malformations) at 120 mg/kg/day. There was no teratogenic effect in rats at 90 mg/kg/day and no indication of an effect on fetal development in rabbits at 20 mg/kg/day. In rabbits, ropinirole on combination with levodopa (10/250 mg/kg/day) increased the incidence of malformations (predominantly digital malformations). There have been no studies of ropinirole in human pregnancy.

Use in Lactation: REPREVE should not be used in breast-feeding mothers as it may inhibit lactation. Animal studies showed that ropinirole is excreted in the milk of lactating rats.

Use in Children and Adolescents (age <18 years): The safety and efficacy of ropinirole have not been established in patients with Restless Legs Syndrome under 18 years of age; therefore ropinirole is not recommended for use in patients within this age group.

INTERACTIONS WITH OTHER MEDICINES

Because of the possible additive sedative effects, caution should also be used when patients are taking CNS depressants (eg., benzodiazepines, antipsychotics, antidepressants, etc) in combination with REPREVE.

Dopamine antagonists
Neuroleptics and other centrally active dopamine antagonists, such as sulpiride or metoclopramide, may diminish the effectiveness of ropinirole hydrochloride and, therefore, concomitant use of these drugs with ropinirole hydrochloride should be avoided.

Domperidone is a peripherally active dopamine antagonist and as such may be useful in managing peripheral dopaminergic adverse events. No pharmacokinetic interaction has been seen between ropinirole hydrochloride and domperidone which would necessitate dosage adjustment of either drug.

Drugs metabolised by Cytochrome P450 1A2
It has been established from in vitro experiments that ropinirole is principally metabolised by the cytochrome P450 enzyme CYP1A2. There is therefore the potential for an interaction between ropinirole hydrochloride and substrates (such as theophylline) or inhibitors (such as ciprofloxacin, enoxacin or fluvoxamine) of this enzyme. In patients already receiving ropinirole hydrochloride, the dose of ropinirole hydrochloride may need to be adjusted when drugs known to inhibit CYP1A2 are introduced or withdrawn.

Hormone replacement therapy (HRT)
Increased plasma concentrations of ropinirole hydrochloride have been observed in patients treated with high doses (0.6 - 3 mg) of oestrogens, predominantly conjugated oestrogens, with ropinirole clearance reduced by, on average, 33 % (range 26% - 39%) in post-menopausal women receiving HRT. In patients already receiving hormone replacement therapy (HRT), ropinirole hydrochloride treatment maybe initiated in the normal manner.
However, if HRT is stopped or introduced during treatment with ropinirole hydrochloride, dosage adjustment may be required.

**Alcohol**
No information is available on the potential for interaction between ropinirole hydrochloride and alcohol. As with other centrally active medications, patients should be cautioned against taking ropinirole hydrochloride with alcohol.

**Smoking**
The effect of smoking on the oral clearance of ropinirole has not been systematically evaluated. Smoking is expected to increase the clearance of ropinirole since CYP1A2 is known to be induced by smoking. Therefore if patients stop or start smoking during treatment with ropinirole, adjustment of dose may be required.

**ADVERSE EFFECTS**

In RLS clinical trials the most common adverse event was nausea occurring in approximately 38% of patients. Adverse events were normally mild to moderate and experienced at the start of therapy or on increase of dose and few patients withdrew from the clinical studies due to adverse events. Dose reduction should be considered if patients experience significant adverse events. If the adverse event abates, gradual up-titration can be re-instituted. Table 2 lists the adverse reactions reported for ropinirole in the 12-week clinical trials at ≥2.0% above the placebo rate.
Table 2: Number (%) of Patients Reporting Adverse Events at Greater than or equal to 2% in the Ropinirole Treatment Group and Greater than Placebo During the On-Treatment Phase
(Safety Population: 12-Week Efficacy Studies 190, 194, 191, Combined)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Ropinirole N=309</th>
<th>Placebo N=307</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n (%)</td>
<td>n (%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>117 (37.9)</td>
<td>25 (8.1)</td>
</tr>
<tr>
<td>Headache</td>
<td>69 (22.3)</td>
<td>64 (20.8)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>40 (12.9)</td>
<td>5 (1.6)</td>
</tr>
<tr>
<td>Dizziness</td>
<td>38 (12.3)</td>
<td>14 (4.6)</td>
</tr>
<tr>
<td>Somnolence</td>
<td>36 (11.7)</td>
<td>20 (6.5)</td>
</tr>
<tr>
<td>Upper Resp Tract Infection</td>
<td>33 (10.7)</td>
<td>27 (8.8)</td>
</tr>
<tr>
<td>Fatigue</td>
<td>32 (10.4)</td>
<td>18 (5.9)</td>
</tr>
<tr>
<td>Abdominal Pain</td>
<td>22 (7.1)</td>
<td>16 (5.2)</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>19 (6.1)</td>
<td>9 (2.9)</td>
</tr>
<tr>
<td>Injury</td>
<td>19 (6.1)</td>
<td>17 (5.5)</td>
</tr>
<tr>
<td>Mouth Dry</td>
<td>15 (4.9)</td>
<td>8 (2.6)</td>
</tr>
<tr>
<td>Pain</td>
<td>15 (4.9)</td>
<td>9 (2.9)</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>14 (4.5)</td>
<td>10 (3.3)</td>
</tr>
<tr>
<td>Vertigo</td>
<td>11 (3.6)</td>
<td>5 (1.6)</td>
</tr>
<tr>
<td>Myalgia</td>
<td>10 (3.2)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>9 (2.9)</td>
<td>6 (2.0)</td>
</tr>
<tr>
<td>Sweating increased</td>
<td>9 (2.9)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Coughing</td>
<td>8 (2.6)</td>
<td>5 (1.6)</td>
</tr>
<tr>
<td>Infection Viral</td>
<td>8 (2.6)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Migraine</td>
<td>8 (2.6)</td>
<td>4 (1.3)</td>
</tr>
<tr>
<td>Rhinitis</td>
<td>8 (2.6)</td>
<td>7 (2.3)</td>
</tr>
<tr>
<td>Sinusitis</td>
<td>7 (2.3)</td>
<td>2 (0.7)</td>
</tr>
</tbody>
</table>

Table 3 lists the adverse reactions reported for ropinirole in the 12-week clinical trials at ≥1.0% above the placebo rate, for which a possible causal relationship with ropinirole has been established. Adverse reactions are listed by system organ class and frequency. Frequencies from clinical trials are determined as excess incidence over placebo and are classed as very common (>1/10) or common (>1/100, <1/10).
Table 3: Adverse Drug Reactions Reported in 12-week restless legs syndrome Clinical Trials (ropinirole n=309, placebo n=307)

<table>
<thead>
<tr>
<th>Psychiatric system disorders</th>
<th>Nervous system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>common</td>
<td>nervousness</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td></td>
</tr>
<tr>
<td>common</td>
<td>dizziness (including vertigo), somnolence, syncope Augmentation*, Early morning rebound#</td>
</tr>
</tbody>
</table>

*Paradoxical worsening of Restless Legs Syndrome symptoms described as augmentation (either earlier onset, increased intensity, or spread of symptoms to previously unaffected limbs), or early morning rebound (reoccurrence of symptoms in the early morning hours), have been observed during treatment with ropinorole (see Precautions).

Gastrointestinal disorders
- very common nausea, vomiting
- common abdominal pain

General disorders and administrative site conditions
- common fatigue

Post-marketing

As with other dopaminergic therapies, extreme somnolence and/or sudden onset of sleep have been reported very rarely primarily in Parkinson's Disease, during post-marketing experience. Patients experiencing sudden onset of sleep cannot resist the urge to sleep, and on waking may be unaware of any tiredness prior to the sleep. Where data are available, all cases have recovered after down titration or on withdrawal of the drug. In most cases the patients received concomitant medication with potential sedating properties.

As with other dopamine agonists, hypotension including postural hypotension has been observed with ropinirole treatment.

*Psychiatric disorders* – uncommon.

Psychotic reactions including hallucinations, delusion, paranoia, delirium, impulse control symptoms, increased libido including hypersexuality, pathological gambling (see Precautions).

Hypersensitivity reactions (including urticaria, angioedema, rash, pruritis) have been reported very rarely.

**DOSAGE AND ADMINISTRATION**

Individual dose titration against efficacy and tolerability is recommended. Ropinirole should be taken once-daily before bedtime, however the dose can be taken up to 3 hours before retiring. Repreve may be taken with or without food (see Pharmacokinetics).
Treatment Initiation (Week 1)

The recommended initial dose is 0.25mg once daily for 2 days. If this dose is well tolerated the dose may be increased to 0.5mg once daily for the remainder of Week 1.

Therapeutic Regimen (Week 2 onwards)

Following treatment initiation, the daily dose can be increased according to the regimen below until optimal therapeutic response is achieved.

<table>
<thead>
<tr>
<th>Week</th>
<th>Dose (mg)/once daily</th>
</tr>
</thead>
<tbody>
<tr>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>3</td>
<td>1.5</td>
</tr>
<tr>
<td>4</td>
<td>2</td>
</tr>
<tr>
<td>5</td>
<td>2.5</td>
</tr>
<tr>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>7</td>
<td>4</td>
</tr>
</tbody>
</table>

First signs of a response can be anticipated after one week of treatment in some patients, although further titration to achieve optimal effect is likely to be required. The mean daily dose in clinical trials was 2mg/day. Doses above 4mg/day have not been investigated in patients with Restless Legs Syndrome.

If treatment is interrupted for more than a few days it should be re-initiated by dose titration carried out as above.

Renal Impairment

No dosage adjustment is necessary in patients with mild to moderate renal impairment (creatinine clearance 30-50 mL/min).

In patients with end stage renal disease receiving regular dialysis, exposure to ropinirole as measured by the AUC is increased by approximately 27%. The recommended maximum dose is limited to 3 mg/day in patients with Restless Legs Syndrome.

A study into the use of ropinirole in patients with end stage renal disease (patients on haemodialysis) has shown that a dose adjustment in these patients is required as follows: The recommended initial dose of REPREVE is 0.25 mg once daily. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose is 3 mg/day in patients receiving regular dialysis. Supplemental doses after dialysis are not required.

The use of ropinirole in patients with severe renal impairment (creatinine clearance less than 30 mL/min) without regular dialysis has not been studied.

There was no change observed in the pharmacokinetics of ropinirole in Parkinson’s disease patients with mild to moderate renal impairment.

Hepatic Impairment

The use of REPREVE in patients with hepatic impairment has not been studied. Administration of REPREVE to such patients is not recommended.

Elderly:
Oral clearance of ropinirole is reduced by approximately 15% in elderly patients (65 years or above) compared to younger patients. Dosing adjustment is not necessary in the elderly.

OVERDOSAGE

There have been no incidences of intentional overdose with REPREVE in clinical trials. The symptoms of REPREVE overdose are related to its dopaminergic activity. These symptoms maybe alleviated by appropriate treatment with dopamine antagonists such as neuroleptics or metoclopramide.

Symptomatic supportive therapy and cardiovascular monitoring are recommended.

Contact the Poisons Information Centre (telephone 13 11 26) for advice on overdose management.

PRESENTATION AND STORAGE CONDITIONS

Store in a dry place at or below 25°C.

REPREVE are pentagonal film-coated "Tiltab" tablets with beveled edges and a raised pentagonal flattened tilt feature offset on each face. The tablet strengths are distinguished by colour and contain the following quantities of ropinirole (present as hydrochloride): 0.25 mg (white) marked “SB” on one side and “4890” on the other, 0.5 mg (pale yellow) marked “SB” on one side and “4891” on the other, 1.0 mg (green) marked “GS” on one side and “SJG” on the other, and 2.0 mg (pale yellowish pink) marked “SB” on one side and “4893” on the other.

The 0.25mg tablet strength is provided in blister packs of 2 and 12 tablets. The other strengths 0.5 mg, 1.0 mg, 2.0 mg are provided in blister packs of 28 and 84 tablets.

Not all strengths or pack sizes are being distributed in Australia.

POISON SCHEDULE OF THE MEDICINE: S4

NAME AND ADDRESS OF THE SPONSOR

GlaxoSmithKline Australia Pty Ltd
Level 4, 436 Johnston Street
Abbotsford, Victoria, 3067

DATE OF FIRST INCLUSION ON THE AUSTRALIAN REGISTER OF THERAPEUTIC GOODS (THE ARTG): 5 October 2004

DATE OF MOST RECENT AMENDMENT: 3 August 2012

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Version 6.0