1. NAME OF THE MEDICINAL PRODUCT

Requip Modutab™ 8 mg
Requip Modutab™ 4 mg
Requip Modutab™ 2 mg

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

2 / 4 / 8 mg ropinirole (as hydrochloride).

Excipient(s) with known effect:

Lactose

Sunset yellow (E110) - 4 mg only

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Prolonged-release tablet.

2 mg: Pink capsule-shaped, film-coated tablets marked "GS" on one side and "3V2" on the other.

4 mg: Light brown capsule-shaped, film-coated tablets marked "GS" on one side and "WXG" on the other.

8 mg: Red capsule-shaped, film-coated tablets marked "GS" on one side and "5CC" on the other.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

- Ropinirole is indicated for the treatment of Parkinson's disease.
- Ropinirole is effective as early therapy in patients requiring dopaminergic therapy.
- As adjunctive treatment to L-dopa, ropinirole enhances the efficacy of L-dopa, including control of "on-off" fluctuations and "end of dose" effects associated with chronic L-dopa therapy and permits reduction in daily L-dopa dose.
4.2. Posology and method of administration

When switching treatment from another dopamine agonist to ropinirole, the manufacturer's guidance on discontinuation should be followed before initiating ropinirole. Individual dose titration against efficacy and tolerability is recommended. Patients should be down-titrated if they experience disabling somnolence at any dose level. For other adverse events, down-titration followed by more gradual up-titration has been shown to be beneficial.

Populations

- Adults

Ropinirole prolonged release tablets should be taken as a single daily dose and should be taken at a similar time each day. The tablet(s) must be swallowed whole, and must not be chewed, crushed or divided. Ropinirole prolonged release tablets may be taken with or without food (see section 5.2.).

Treatment initiation

The dose should be titrated according to the individual clinical response. The recommended initial dose is 2 mg once daily for one week. A guide for the titration regimen for the first four weeks of treatment is given in the table below:

<table>
<thead>
<tr>
<th>Week</th>
<th>Total daily dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>6</td>
</tr>
<tr>
<td>4</td>
<td>8</td>
</tr>
</tbody>
</table>

Therapeutic regimen

If sufficient symptomatic control is not maintained after switching to a dose of less than 8 mg once daily of ropinirole prolonged-release tablets, the daily dose may be increased by 2 mg at weekly or longer intervals up to a dose of 8 mg once daily of ropinirole prolonged-release tablets.

If sufficient symptomatic control is not achieved or maintained at a dose of 8 mg or greater once daily of ropinirole prolonged-release tablets, the daily dose may be increased by 2 mg at two weekly or longer intervals.

Individual dose titration against efficacy and tolerability is recommended.

Patients should be maintained on the lowest dose of ropinirole prolonged-release tablets that achieves symptomatic control.

The dose may be increased up to a maximum of 24 mg once daily. The safety and efficacy of doses above 24 mg/day have not been established.

When ropinirole PR tablets are given as adjunct therapy to L-dopa, it may be possible to reduce gradually the L-dopa dose, depending on the clinical response. In clinical trials, the L-dopa dose was reduced gradually by approximately 30% in patients receiving ropinirole PR tablets concurrently. In patients with advanced Parkinson's disease receiving ropinirole in combination with L-dopa, dyskinesias can occur during the initial titration of ropinirole. In clinical trials it was shown that a reduction of the L-dopa dose may ameliorate dyskinesia (see section 4.8.).

The dose in patients experiencing disabling somnolence should be down titrated; for some other adverse events, down-titration followed by more gradual up-titration has been shown to be beneficial.
As with other dopamine agonists, ropinirole should be discontinued gradually by reducing the
daily dose over the period of one week (see section 4.4).
If treatment is interrupted for one day or more, re-initiation by dose titration should be considered
(see above).

**Switching from ropinirole immediate release tablets (IR) to ropinirole prolonged release
tablets (PR)**

Patients should be considered for switching to ropinirole prolonged-release tablets only after they
have achieved sufficient symptomatic control on ropinirole immediate release tablets.

Patients may be switched overnight from ropinirole IR tablets to ropinirole PR tablets. The dose of
ropinirole PR tablets should be based on the total daily dose of ropinirole IR tablets that the patient
was taking.

The table below shows the recommended dose of ropinirole PR tablets for patients switching from
ropinirole IR tablets:

<table>
<thead>
<tr>
<th>Ropinirole immediate release tablets total daily dose (mg)</th>
<th>Ropinirole prolonged release tablets total daily dose (mg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.75 – 2.25</td>
<td>2.0</td>
</tr>
<tr>
<td>3.0 – 4.5</td>
<td>4.0</td>
</tr>
<tr>
<td>6.0</td>
<td>6.0</td>
</tr>
<tr>
<td>7.5 – 9.0</td>
<td>8.0</td>
</tr>
<tr>
<td>12.0</td>
<td>12.0</td>
</tr>
<tr>
<td>15.0 – 18.0</td>
<td>16.0</td>
</tr>
<tr>
<td>21.0</td>
<td>20.0</td>
</tr>
<tr>
<td>24.0</td>
<td>24.0</td>
</tr>
</tbody>
</table>

After switching to ropinirole PR tablets, the dose may be adjusted depending on the therapeutic
response (see “Treatment initiation” and “Therapeutic regimen” above).

**Dose interruption or discontinuation**

If treatment is interrupted for one day or more, re-initiation by dose titration on ropinirole immediate
release tablets should be considered.

If it is necessary to discontinue ropinirole treatment, this should be done gradually by reducing the
daily dose over the period of one week.

When switching treatment from another dopamine agonist to ropinirole, the manufacturer's guidance
on discontinuation should be followed before initiating ropinirole immediate release tablets according
to the recommended titration regimen. Patients can be switched to ropinirole prolonged-release
tablets once sufficient symptomatic control is achieved (see ‘Starting dose’).
- **Elderly**

The clearance of ropinirole is decreased by approximately 15% in patients aged 65 years or above. Although a dose adjustment is not required, ropinirole dose should be individually titrated, with careful monitoring of tolerability, to the optimal clinical response. In patients aged 75 years and above, slower titration during treatment initiation may be considered.

- **Children and Adolescents**

The safety and efficacy of ropinirole have not been established in patients under 18 years of age; therefore ropinirole is not recommended for use in patients within this age group.

- **Renal impairment**

In patients with mild to moderate renal impairment (creatinine clearance 30 to 50mL/min), no change in the clearance of ropinirole was observed indicating that no dosage adjustment is necessary in this population.

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 ropinirole PR is 2 mg once daily. Further dose escalations should be based on tolerability and efficacy. The recommended maximum dose is 18 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. Administration of ropinirole to such patients is not recommended.

**Hepatic impairment**

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

### 4.3. Contraindications

Hypersensitivity to ropinirole or to any of the excipients listed in section 6.1.

Severe renal impairment (creatinine clearance <30 ml/min) without regular haemodialysis.

Hepatic impairment.

### 4.4. Special warnings and precautions for use

Due to the risk of hypotension, blood pressure monitoring is recommended, particularly at the start of treatment, in patients with severe cardiovascular disease (in particular coronary insufficiency).

**Psychotic-like Behavior**

Postmarketing reports indicate that patients may experience new or worsening mental status and behavioral changes, which may be severe, including psychotic-like behavior during treatment with ropinirole or after starting or increasing the dose of ropinirole. Other drugs prescribed to improve the symptoms of Parkinson's disease can have similar effects on thinking and behavior. This abnormal thinking and behavior can consist of one or more of a variety of manifestations including paranoid ideation, delusions, hallucinations, confusion, psychotic-like behavior, disorientation, aggressive behavior, agitation, and delirium.
Patients with a major psychotic disorder should ordinarily not be treated with Requip Modutab because of the risk of exacerbating the psychosis. In addition, certain medications used to treat psychosis may exacerbate the symptoms of Parkinson’s disease and may decrease the effectiveness of Requip Modutab (see section 4.5).

**Impulse control disorders**
Patients should be regularly monitored for the development of impulse control disorders. Patients and carers should be made aware that behavioural symptoms of impulse control disorders including pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including Requip Modutab. Dose reduction/tapered discontinuation should be considered if such symptoms develop. Impulse control disorders were reported especially at high doses and were generally reversible upon reduction of the dose or treatment discontinuation. Risk factors such as a history of compulsive behaviours were present in some cases (see section 4.8).

Ropinirole has been associated with somnolence and episodes of sudden sleep onset, particularly in patients with Parkinson’s disease. Sudden onset of sleep during daily activities, in some cases without awareness or warning signs, has been reported (see section 4.8). Patients must be informed of this and advised to exercise caution while driving or operating machines during treatment with ropinirole. Patients who have experienced somnolence and/or an episode of sudden sleep onset must refrain from driving or operating machines. Furthermore, a reduction of dosage or termination of therapy may be considered.

**Neuroleptic malignant syndrome**
Symptoms suggestive of neuroleptic malignant syndrome have been reported with abrupt withdrawal of dopaminergic therapy. Therefore it is recommended to taper treatment (see section 4.2).

Requip Modutab tablets are designed to release medication over a 24hr period. If rapid gastrointestinal transit occurs, there may be risk of incomplete release of medication, and of medication residue being passed in the stool.

This medicinal product also contains lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

The 4 mg tablets contain the azo colouring agent sunset yellow (E110), which may cause allergic reactions.

**Elevation of blood pressure and changes in heart rate**
In the placebo-controlled trial in advanced Parkinson’s disease, there were no clear effects of Requip Modutab on average changes in blood pressure or heart rate compared with placebo. Elevation of blood pressure and/or changes in heart rate in patients taking Requip Modutab should be considered when treating patients with cardiovascular disease.

**Withdrawal-emergent Hyperpyrexia and Confusion**
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 dopaminergic therapy. Therefore, it is recommended that the dose be tapered at the end of treatment with Requip Modutab as a prophylactic measure.

**Melanoma**
Epidemiological studies have shown that patients with Parkinson’s disease have a higher risk (2- to approximately 6-fold higher) of developing melanoma than the general population. Whether the increased risk observed was due to Parkinson’s disease or other factors, such as drugs used to
treat Parkinson’s disease, is unclear. In the clinical development program (N = 613), one patient treated with Requip Modutab and also levodopa/carbidopa developed melanoma.

For the reasons stated above, patients and providers are advised to monitor for melanomas frequently and on a regular basis when using Requip Modutab. Ideally, periodic skin examinations should be performed by appropriately qualified individuals (e.g., dermatologists).

**Fibrotic Complications**

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 reactions are believed to be related to the ergoline structure of these compounds, whether other, non-ergot-derived dopamine agonists, such as ropinirole, can cause them is unknown.

Cases of possible fibrotic complications, including pleural effusion, pleural fibrosis, interstitial lung disease, and cardiac valvulopathy have been reported in the development program and postmarketing experience for ropinirole. In the clinical development program (N = 613), 2 patients treated with Requip Modutab had pleural effusion. While the evidence is not sufficient to establish a causal relationship between ropinirole and these fibrotic complications, a contribution of ropinirole cannot be excluded.

4.5. Interaction with other medicinal products and other forms of interaction

There is no pharmacokinetic interaction between ropinirole and L-dopa or domperidone which would necessitate dosage adjustment of these drugs. Neuroleptics and other centrally active dopamine antagonists, such as sulpiride or metoclopramide, may diminish the effectiveness of ropinirole and therefore, concomitant use of these medicinal products should be avoided.

Ropinirole is principally metabolised by the cytochrome P450 enzyme CYP1A2. A pharmacokinetic study (with a ropinirole film-coated (immediate-release) tablet dose of 2 mg, three times a day) in Parkinson's disease patients, revealed that ciprofloxacin increased the Cmax and AUC of ropinirole by 60% and 84% respectively, with a potential risk of adverse events. Hence, in patients already receiving ropinirole, the dose of ropinirole may need to be adjusted when medicinal products known to inhibit CYP1A2, e.g. ciprofloxacin, enoxacin, cimetidine or fluvoxamine, are introduced or withdrawn.

A pharmacokinetic interaction study in patients with Parkinson's disease between ropinirole (with a ropinirole film-coated (immediate-release) tablet dose of 2 mg, three times a day) and theophylline, a substrate of CYP1A2, revealed no change in the pharmacokinetics of either ropinirole or theophylline.

In a study in patients with Parkinson's disease receiving concurrent digoxin, no interaction was seen which would require dosage adjustment.

Increased plasma concentrations of ropinirole have been observed in patients treated with high doses of oestrogens. In patients already receiving hormone replacement therapy (HRT), ropinirole treatment may be initiated in the normal manner. However, if HRT is stopped or introduced during treatment with ropinirole, dosage adjustment may be required.

No information is available on the potential for interaction between ropinirole and alcohol. As with other centrally active medications, patients should be cautioned against taking ropinirole with alcohol.
Smoking is known to induce CYP1A2 metabolism, therefore if patients stop or start smoking during treatment with ropinirole, adjustment of dose may be required.

4.6. **Fertility, pregnancy and lactation**

**Pregnancy**
There are no adequate data from the use of ropinirole in pregnant women. Studies in animals have shown reproductive toxicity (see section 5.3). As the potential risk for humans is unknown, it is recommended that ropinirole is not used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the foetus.

**Breast-feeding**
Ropinirole should not be used in nursing mothers as it may inhibit lactation. No human fertility data are available.

4.7. **Effects on ability to drive and use machines**

Ropinirole may have a major effect on the ability to drive and use machines. Patients being treated with ropinirole and presenting with somnolence and/or sudden sleep episodes 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 also section 4.4).

4.8. **Undesirable effects**

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1,000, <1/100), rare (>1/10,000, <1/1,000), very rare (<1/10,000), not known (cannot be estimated from the available data).

During clinical trials, the most commonly reported undesirable effects for ropinirole prolonged-release tablets were during monotherapy and dyskinesia during adjunctive therapy with levodopa.

The following adverse events were reported during clinical trials with Requip Modutab up to 24 mg/day.

<table>
<thead>
<tr>
<th>System Organ Class</th>
<th>In monotherapy</th>
<th>In adjunct therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Psychiatric disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td>Hallucinations</td>
<td>Hallucinations</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Very common</td>
<td>Somnolence</td>
<td>Dyskinesia</td>
</tr>
<tr>
<td></td>
<td></td>
<td>In patients with advanced Parkinson's disease, dyskinesias can occur during the initial titration of ropinirole. In clinical trials it was shown that a reduction of the levodopa dose may ameliorate dyskinesia (see section 4.2).</td>
</tr>
<tr>
<td>Common</td>
<td>Dizziness (including vertigo)</td>
<td>Somnolence, dizziness</td>
</tr>
<tr>
<td></td>
<td>Sudden onset of sleep</td>
<td>(including vertigo), Sudden onset of sleep</td>
</tr>
<tr>
<td><strong>Vascular disorders</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Common Postural hypotension, hypotension

Uncommon Postural hypotension, hypotension

Gastrointestinal disorders
Very common Nausea
Common Constipation Nausea, constipation

General disorders and administrative site conditions
Common Oedema peripheral Oedema peripheral

Additional adverse events were reported during clinical trial in advanced stage Parkinson's disease (with L-dopa): abdominal pain/discomfort, diarrhea, dry mouth, fall (dose related), back pain, anxiety, hypertension (dose related), abnormal dreams, chest pain, bronchitis and nasopharyngitis.

Additional adverse events were reported during clinical trial in early stage Parkinson's disease (without L-dopa): abdominal pain/discomfort, headache, vomiting, fall, diarrhea, pyrexia, flatulence, myalgia, sleep disorders, muscle spasms, insomnia, cough and nasopharyngitis.

In addition to the above adverse drug reactions, the following events have been reported with Requip film-coated (immediate-release) tablets in patients with Parkinson’s disease during clinical trials (at doses up to 24 mg/day) and/or post-marketing reports.

<table>
<thead>
<tr>
<th></th>
<th>In monotherapy</th>
<th>In adjunct therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immune system disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not known</td>
<td>Hypersensitivity reactions (including urticaria, angioedema, rash, pruritus).</td>
<td></td>
</tr>
<tr>
<td>Psychiatric disorders</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Common</td>
<td></td>
<td>Confusion</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Psychotic reactions (other than hallucinations) including delirium, delusion, paranoia.</td>
<td>Psychotic reactions (other than hallucinations) including delirium, delusion, paranoia.</td>
</tr>
<tr>
<td>Not known</td>
<td>Aggression*</td>
<td>Dopamine dysregulation syndrome</td>
</tr>
</tbody>
</table>

* Aggression has been associated with psychotic reactions as well as compulsive symptoms

Not known Impulse control disorders including pathological gambling, compulsive shopping, binge eating and hypersexuality and increased libido, have been reported in post marketing reports (see section 4.4)

Nervous system disorders

<table>
<thead>
<tr>
<th></th>
<th>In monotherapy</th>
<th>In adjunct therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Syncope</td>
<td>Somnolence</td>
</tr>
<tr>
<td>Uncommon</td>
<td>Sudden onset of sleep, excessive daytime somnolence</td>
<td>Sudden onset of sleep, excessive daytime somnolence</td>
</tr>
</tbody>
</table>

Ropinirole is associated with somnolence and has been associated uncommonly with excessive daytime somnolence and sudden sleep onset episodes.

Vascular disorders
Uncommon | Postural hypotension or hypotension is rarely severe
---|---

**Gastrointestinal disorders**

<table>
<thead>
<tr>
<th>Very common</th>
<th>Nausea</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Vomiting, heartburn, abdominal pain</td>
</tr>
</tbody>
</table>

**Hepatobiliary disorders**

| Not known | Hepatic reactions, mainly increased liver enzymes |

**General disorders and administrative site conditions**

| Common | Leg oedema |

Additional adverse events observed during clinical trial with Requip film-coated (immediate-release) tablets in patients in early stage Parkinson’s disease: dyskinesia, dizziness, hallucinations, headache and increased sweating.

Additional adverse events observed during clinical trial with Requip film-coated (immediate-release) tablets in patients in advanced stage Parkinson’s disease: dizziness, asthenic condition and viral infection.

Other adverse events were reported but their frequency is not known (see section 4.4. ‘Special warnings and precautions for use’):

- Impulse control disorders
  Pathological gambling, increased libido, hypersexuality, compulsive spending or buying, binge eating and compulsive eating can occur in patients treated with dopamine agonists including Requip Modutab (see section 4.4.).

- Elevation of Blood Pressure and Changes in Heart Rate.

- Withdrawal-emergent Hyperpyrexia and Confusion.

- Melanoma.

- Fibrotic Complications.

**Reporting of suspected adverse reactions**

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@moh.health.gov.il). Additionally, you should also report to GSK Israel (il.safety@gsk.com).

**4.9. Overdose**

The symptoms of ropinirole overdose are generally related to its dopaminergic activity. These symptoms may be alleviated by appropriate treatment with dopamine antagonists such as neuroleptics or metoclopramide.
5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Pharmacotherapeutic group

Dopamine agonist.

ATC code: N04BC04

Mechanism of action

Parkinson's disease is characterised by a marked dopamine deficiency in the nigrostriatal system. Ropinirole is a non-ergoline D2/D3 dopamine agonist that alleviates this deficiency by stimulating striatal dopamine receptors.

Ropinirole acts in the hypothalamus and pituitary to inhibit the secretion of prolactin.

Clinical efficacy

A 36-week, double-blind, three-period crossover study, in monotherapy with a primary end point of change from period baseline in Unified Parkinson's Disease Rating Scale (UPDRS) total motor score was conducted in 161 patients with early phase Parkinson’s disease. A subgroup analysis of patients initiated on monotherapy treatment with ropinirole immediate release tablets and switched overnight to the nearest equivalent dose of ropinirole prolonged-release tablets was consistent with similar efficacy from equivalent mg for mg doses. The adjusted mean difference between ropinirole prolonged-release tablets and Requip film-coated (immediate-release) tablets at study-endpoint was 0.7 points (95% CI: [-1.51, 0.10], p=0.0842).

Following the overnight switch to a similar dose of the alternative tablet formulation, there was no difference in the adverse event profile and less than 3% of patients required a dose adjustment (all dose adjustments were increases by one dose level. No patients required a dose increase).

A 24-week, double-blind, placebo-controlled, parallel group study in patients with Parkinson’s disease who were not optimally controlled on levodopa demonstrated that adjunctive therapy of ropinirole prolonged-release tablets results in clinically relevant and statistically significant superiority over placebo in a change from baseline in awake time “off” (adjusted mean treatment difference -1.7 hours (95% CI: [-2.34, -1.09], p<0.0001). This was supported by secondary efficacy parameters of change from baseline in total awake time “on” (+1.7 hours (95% CI [1.06, 2.33], p<0.0001) and total awake time “on” without troublesome dyskinesias (+1.5 hours (95% CI: [0.85, 2.13], p<0.0001). Importantly, there was no indication of an increase from baseline in awake time “on” with troublesome dyskinesias, either from diary card data or from the UPDRS items.

Study of the effect of ropinirole on cardiac repolarisation

A thorough QT study conducted in male and female healthy volunteers who received doses of 0.5, 1, 2 and 4 mg of ropinirole film-coated (immediate release) tablets once daily showed a maximum increase of the QT interval duration nat the 1 mg dose of 3.46 milliseconds (point estimate) as compared to placebo. The upper bound of the one sided 95% confidence interval for the largest mean effect was less than 7.5 milliseconds. The effect of ropinirole at higher doses has not been systematically evaluated.

The available clinical data from a thorough QT study do not indicate a risk of QT prolongation at doses of ropinirole up to 4 mg/day. A risk of QT prolongation cannot be excluded as a thorough QT study at doses up to 24 mg/day has not been conducted.
5.2. Pharmacokinetic properties

Absorption

Bioavailability of ropinirole is approximately 50% (36–57%). Following oral administration of ropinirole prolonged-release tablets, plasma concentrations of ropinirole increase slowly, with a median time to Cmax of between six and ten hours. In a steady-state study in Parkinson’s disease patients receiving 12 mg of Requip Modutab once daily, a high fat meal increased the systemic exposure to ropinirole as shown by an average 20% increase in AUC (90% CI [1.12, 1.28]) and an average 44% increase in Cmax (90% CI [1.34, 1.56]). Tmax was delayed by 3.0 hours. However, in the studies that established the safety and efficacy of Requip Modutab, patients were instructed to take study medication without regard to food intake.

The systemic exposure to ropinirole is comparable for ropinirole prolonged-release tablets and ropinirole film-coated (immediate-release) tablets based on the same daily dose.

Distribution

Plasma protein binding of the drug is low (10–40%). Consistent with its high lipophilicity, ropinirole exhibits a large volume of distribution (approximately 7 l/kg).

Biotransformation

Ropinirole is primarily cleared by CYP1A2 metabolism and its metabolites are mainly excreted in the urine. The major metabolite is at least 100-times less potent than ropinirole in animal models of dopaminergic function.

Elimination

Ropinirole is cleared from the systemic circulation with an average elimination half-life of about six hours. The increase in systemic exposure (Cmax and AUC) to ropinirole is approximately proportional over the therapeutic dose range. No change in the oral clearance of ropinirole is observed following single and repeated oral administration. Wide inter-individual variability in the pharmacokinetic parameters has been observed. Following steady-state administration of ropinirole prolonged-release tablets, the inter-individual variability of Cmax was between 30% and 55% and for AUC was between 40% and 70%.

Special Patient Populations

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

In patients with end stage renal disease receiving regular dialysis, oral clearance of ropinirole is reduced by approximately 30%. Oral clearance of the metabolites SKF-104557 and SKF-89124 were also reduced by approximately 80% and 60%, respectively. Therefore, the recommended maximum dose is limited to 18 mg/day in these patients with Parkinson’s disease.

5.3. Preclinical safety data

Reproductive toxicity

Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg/day (approximately twice the AUC at the maximum dose in humans), increased foetal death at 90 mg/kg/day (approximately 3 times the AUC at the maximum dose in humans) and digit malformations at 150 mg/kg/day (approximately 5 times the AUC at the maximum dose in humans). There were no teratogenic effects in the rat at 120 mg/kg/day (approximately 4
times the AUC at the maximum dose in humans) and no indication of an effect on development in the rabbit.

**General toxicology**

The toxicology profile is principally determined by the pharmacological activity of the drug (behavioural changes, hypoprolactinaemia, decrease in blood pressure and heart rate, ptosis and salivation). In the albino rat only, retinal degeneration was observed in a long term study at the highest dose (50 mg/kg/day), and was probably associated with an increased exposure to light.

**Genotoxicity**

Genotoxicity was not observed in a battery of *in vitro* and *in vivo* tests.

**Carcinogenicity**

Two-year studies have been conducted in the mouse and rat at dosages up to 50 mg/kg. The mouse study did not reveal any carcinogenic effect. In the rat, the only drug-related lesions were Leydig cell hyperplasia/adenoma in the testis resulting from the hypoprolactinaemic effect of ropinirole. These lesions are considered to be a species specific phenomenon and do not constitute a hazard with regard to the clinical use of ropinirole.

**Safety pharmacology**

*In vitro* studies have shown that ropinirole inhibits hERG-mediated currents. The IC$_{50}$ is 5-fold higher than the expected maximum plasma concentration in patients treated at the highest recommended dose (24 mg/day), see section 5.1.

6. **PHARMACEUTICAL PARTICULARS**

6.1. **List of Excipients**

**Tablet core**

Hypermellose 2208, glycerol dibehenate, mannitol (E421), lactose monohydrate, povidone K29-32, carmellose sodium, hydrogenated castor oil, maltodextrin, magnesium stearate, anhydrous colloidal silica and ferric oxide yellow (E172).

**Film coat**

2 mg: Hypermellose 2910, titanium dioxide (E171), macrogol 400, ferric oxide red (E172) and ferric oxide yellow (E172).

4 mg: Hypermellose 2910, titanium dioxide (E171), macrogol 400, sunset yellow (E110) and indigo carmine (E132).

8 mg: Hypermellose 2910, titanium dioxide (E171), macrogol 400, ferric oxide red (E172), ferric oxide black (E172) and ferric oxide yellow (E172).

6.2. **Incompatibilities**

Not applicable.

6.3. **Shelf life**

The expiry date of the product is indicated on the label and packaging.
6.4. Special precautions for storage

Do not store above 25°C. Store in the original package.

6.5. Nature and contents of container

PVC/PCTFE/Aluminium or PVC/PE/PVdC/Aluminium/Paper child-resistant blister packs.

Packs of 28 or 84 prolonged-release tablets.

Not all pack sizes may be marketed.

6.6. Special precautions for disposal

No special requirements.

7. MANUFACTURER

Glaxo Wellcome S.A., Burgos, Spain.

8. LICENSE HOLDER AND IMPORTER

GlaxoSmithKline (Israel) Ltd., 25 Basel St., Petach Tikva.

9. LICENSE NUMBERS

Requip Modutab 2 mg 141-62-31838
Requip Modutab 4 mg 141-64-31839
Requip Modutab 8 mg 141-63-31840

Req MT DR v7.1