**REQUIP™ PD 24 HOUR**
Ropinirole

1. **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Each prolonged release tablet contains ropinirole hydrochloride equivalent to 2, 4 or 8 mg ropinirole free base.

2. **PHARMACEUTICAL FORM**
Film-coated, capsule-shaped tablets for oral administration. The tablet strengths are distinguished by colour and debossing;
- 2 mg: pink, capsule-shaped, film coated tablet 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.

3. **CLINICAL PARTICULARS**

3.1 **Indications**
*REQUIP PD 24 HOUR* may be used as:
- Monotherapy, alone (without levodopa) in idiopathic Parkinson's disease or
- Adjunctive therapy in addition to levodopa to control "on-off" fluctuations which might permit a reduction in the total daily dose of levodopa.

3.2 **Dosage and Administration**
When switching treatment from another dopamine agonist to *REQUIP PD 24 HOUR*, the manufacturer's guidance on discontinuation should be followed before initiating *REQUIP PD 24 HOUR*.
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.

- **Adults**
*REQUIP PD 24 HOUR* 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, *REQUIP PD 24 HOUR* may be taken with or without food.

**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>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total daily dose (mg)</td>
<td>2</td>
<td>4</td>
<td>6</td>
<td>8</td>
</tr>
</tbody>
</table>
Therapeutic regimen
If sufficient symptomatic control is not achieved or maintained after the initial titration period, as described above, the daily dose may then be increased by increments of up to 4 mg once every one to two week, as necessary. The dose may be adjusted depending on the therapeutic response. 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 REQUIP PD 24 HOUR is 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 recieving REQUIP PD 24 HOUR concurrently. In patients with advanced Parkinson's disease receiving REQUIP PD 24 HOUR in combination with L-dopa, dyskinesias can occur during the initial titration of REQUIP PD 24 HOUR. In clinical trials it was shown that a reduction of L-dopa dose may ameliorate dyskinesia (see Adverse Reactions). As with other dopamine agonists, REQUIP PD 24 HOUR should be discontinued gradually by reducing the daily dose over the period of one week. If treatment is interrupted for one day or more, re-initiation by dose titration should be considered (see above)

- Elderly
The clearance of ropinirole is decreased in patients over 65 years of age, but the dose of REQUIP PD 24 HOUR for elderly patients can be titrated in the normal manner.

-Children and Adolescents
There are no data available on the use of ropinirole in patients under 18 years of age therefore, REQUIP PD 24 HOUR is not recommended for use in patients within this age group.

- Renal and hepatic impairment
In patients with mild to moderate renal impairment (creatinine clearance 30-50 ml/min) no change in the clearance of ropinirole was observed, indicating that no dosage adjustment is necessary in this population. The use of ropinirole in patients with severe renal impairment (creatinin clearance < 30 ml/min) or hepatic impairment has not been studied. Administration of REQUIP PD 24 HOUR to such patients is not recommended.

3.3 Contraindications
Hypersensitivity to ropinirole or to any of the excipients. In light of the results of animal studies and the lack of studies in human pregnancy, ropinirole is contraindicated in pregnancy, lactation and in women of child-bearing potential unless adequate contraception is used.

3.4 Warning and Precautions
Due to the pharmacological action of ropinirole, patients with cardiovascular disease should be treated with caution. Patients with a history or presence of, major psychotic disorders should only be treated with dopamine agonists if the potential benefits outweigh the risk. Impulse control symptoms including compulsive behaviors such as pathological gambling and hypersexuality have been reported in patients treated with dopaminergic agents, including ropinirole. As described in the literature, such behaviors 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. 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 same cases without awareness or warning signs, has been reported uncommonly. Patient 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.

Patient with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose mal absorption should not take this medicine.

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

### 3.5 Interactions

Neuroleptics and other centrally active dopamine antagonists, such as sulpiride or metoclopramide, may diminish the effectiveness of ropinirole and, therefore, concomitant use of the drugs with **REQUIP PD 24 HOUR** should be avoided.

There is no pharmacokinetic interaction between ropinirole and L-dopa or domperidone which would necessitate dosage adjustment of the drugs. No interaction has been seen between ropinirole and other drugs commonly used to treat Parkinson’s disease, but, as is common practice, care should be taken when adding a new to a treatment regimen. Other dopamine agonists may be used with caution.

In a study in parkinsonian patients receiving concurrent digoxin, no interaction was seen which would require dosage adjustment. Ropinirole is principally metabolised by the cytochrome P450 enzyme CYP1A2. A pharmacokinetic study in Parkinson’s patients revealed that ciprofloxacin increased the Cmax and AUC of ropinirole by approximately 60% and 84% respectively. Hence, in patients already receiving **REQUIP PD 24 HOUR**, the dose of the **REQUIP PD 24 HOUR** may need to be adjusted when drugs known to inhibit CYP1A2, e.g. ciprofloxacin, enoxacin or fluvoxamine, are introduced or withdrawn.

A pharmacokinetic interaction study in Parkinson’s patients between ropinirole and theophylline, as representative of substrates of CYP1A2, revealed no change in the pharmacokinetics of either ropinirole or theophylline. Hence, change in ropinirole pharmacokinetics following coadministration with other substrates of CYP1A2 are not expected. Increased plasma concentrations of ropinirole have been observed in patients treated with high doses of oestrogens. In patients already receiving hormone replacement therapy (HRT), **REQUIP PD 24 HOUR** 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 *REQUIP PD 24 HOUR* with alcohol. Smoking is known to induce CYP1A2 metabolism, therefore if patients stop or start smoking during treatment with *REQUIP PD 24 HOUR*, adjustment of dose may be required.

### 3.6 Pregnancy and Lactation
It is recommended that *REQUIP PD 24 HOUR* is not used during pregnancy unless the potential benefit to the patient outweighs the potential risk to the foetus (see *Non-Clinical Safety Data*). *REQUIP PD 24 HOUR* should not be used in nursing mothers as it may inhibit lactation.

In animal studies, administration of ronipirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg (approximately three times the AUC of the maximum dose in man), increased foetal death at 90 mg/kg (~x5) and digit malformations at 150 mg/kg (~x9). There was no teratogenic effect in the rat at 120 mg/kg (~ x7) and no indication of an effect on development in the rabbit. There have been no studies of ropinirole in human pregnancy.

### 3.7 Effects on Ability to Drive and Use Machines
No data are available on the effect of ropinirole on the ability to drive or use machinery. Patients should be cautioned about their ability to drive or operate machinery whilst taking *REQUIP PD 24 HOUR* because of the possibility of somnolence and of dizziness (including vertigo).

Patients should be informed about very rare cases of sudden onset of sleep without any prior warning or apparent daytime somnolence (see *Adverse Reactions*), which have primarily been observed in patients with Parkinson's disease, and should be cautioned that their safety and that of others is at risk should this happen when driving or operating machinery. If patients develop significant daytime sleepiness or episodes of falling asleep during activities that require active participation, patients should be told not to drive and to avoid other potentially dangerous activities.

### 3.8 Adverse Reaction
Adverse reactions are tabulated below according to the indication. The overall safety profile of ropinirole comprises adverse reactions from all indications from clinical trial data and from post-marketing experience.

### 3.9 Clinical Trial Data
**Adverse Drug Reactions Reported from Patients with Parkinson’s Disease**

Unless otherwise indicated, the data in the following table was observed with both immediate release and prolonged release formulations.

<table>
<thead>
<tr>
<th></th>
<th>Use in monotherapy studies</th>
<th>Use in adjunct therapy studies:</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, confusion¹</td>
</tr>
<tr>
<td><strong>Nervous system disorders</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Adverse Drug Reactions Reported During Clinical Trials in Patients with Restless Legs Syndrome

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
<th>Nervousness</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Nervousness</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
<th>Dizziness (including vertigo), somnolence, syncope</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
<td>Dizziness (including vertigo), somnolence, syncope</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Gastrointestinal disorders</th>
<th>Nausea, vomiting</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Nausea, vomiting</td>
</tr>
<tr>
<td>Common</td>
<td>Nausea, vomiting, dyspepsia, constipation</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>General disorders and administrative site conditions</th>
<th>Oedema peripheral (including leg oedema)</th>
<th>Oedema peripheral</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very common</td>
<td>Oedema peripheral (including leg oedema)</td>
<td>Oedema peripheral</td>
</tr>
</tbody>
</table>

1. Immediate release clinical trials data
2. Prolonged release clinical trials data
3. In patients with advanced Parkinson's disease, dyskinesias can occur during the initial titration of REQUIP PD 24 HOUR. In clinical trials it was shown that a reduction of the L-dopa may ameliorate dyskinesia (see Dosage and Administration)
Post Marketing Data

<table>
<thead>
<tr>
<th>Immune system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td>Hypersensitivity reactions (including urticaria, angioedema, rash, pruritus)</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Psychiatric disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Uncommon</td>
</tr>
<tr>
<td>Psychotic reactions (other than hallucinations) including delusion, paranoia, delirium. Patients treated with dopamine agonists for treatment of Parkinson's disease, including ropinirole, especially at high doses, have been reported a exhibiting signs of pathological gambling, increased libido and hypersexuality, generally reversible upon reduction of the dose or treatment discontinuation.</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Nervous system disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Very rare</td>
</tr>
<tr>
<td>Extreme somnolence, sudden onset of sleep*</td>
</tr>
</tbody>
</table>

*As with other dopaminergic therapies, extreme somnolence and 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.

<table>
<thead>
<tr>
<th>Vascular disorders</th>
</tr>
</thead>
<tbody>
<tr>
<td>Common</td>
</tr>
<tr>
<td>Hypotension, postural hypotension</td>
</tr>
</tbody>
</table>

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

3.10 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.

4. PHARMACOLOGICAL PROPERTIES

4.1 Pharmacodynamics
ATC Code
N04BC04

Mechanism of action
Ropinirole is a potent, non-ergoline D2/D3 dopamine agonist. Parkinson's disease is characterized by a marked dopamine deficiency in the nigral striatal system. Ropinirole alleviates this deficiency by stimulating striatal dopamine receptors.

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

**4.2 Pharmacokinetics**
The pharmacokinetics of ropinirole are consistent between healthy volunteers, Parkinson's disease patients and patients with Restless Legs Syndrome. Wide inter-individual variability in the pharmacokinetic parameters has been seen. Bioavailability of ropinirole is approximately 50% (36 to 57%).

**Absorption**
Following oral administration of ropinirole PR, plasma concentrations increase slowly, with a median time to $C_{\text{max}}$ of 6 h. The bioavailability of ropinirole following administration of ropinirole PR was similar in both the fed and fasted state.

**Distribution**
Plasma protein binding of the drug is low (10 to 40%). Consistent with its high lipophilicity, ropinirole exhibits a large volume of distribution (approx. 7 L/kg).

**Metabolism**
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 6 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.

**Special Patient Populations**

**Elderly:**
Oral clearance of ropinirole is reduced 30% in elderly patients (above 65 years) compared to younger patients. Dosing adjustment is not necessary in the elderly, as the dose of *REQUIP PD 24 HOUR* is to be individually titrated to clinical response.

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

**Clinical Studies**
A 36-week, double-blind, three-period crossover study conducted in 161 patients compared the efficacy and safety of ropinirole prolonged release tablets and ropinirole immediate release tablets as monotherapy in subjects
with early phase Parkinson's disease. The primary endpoint of this non-inferiority study was the treatment difference in change from baseline in the Unified Parkinson's Disease Rating Scale (UPDRS) motor score (a 3-point non-inferiority margin was defined). Ropinirole prolonged release was demonstrated to be non-inferior to ropinirole immediate release on the primary endpoint, the adjusted mean difference between ropinirole prolonged release and ropinirole immediate release 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 indication of worsened adverse event profile and less than 3% of patients required a dose adjustment (by increasing one dose level).

A 24-week double-blind, placebo-controlled, parallel group study evaluated the efficacy and safety of ropinirole PR as adjunctive therapy in patients with Parkinson's disease who were not optimally controlled on L-dopa. Ropinirole PR demonstrated a clinically relevant and statistically significant superiority over placebo on the primary endpoint, change from baseline in awake time "off" (adjusted mean treatment difference -1.7 hours (95% CI: (-2.34, -1.09), p<0.0001). The odds of ropinirole PR patients being a responder on the CGI global improvement scale were more than 4 times the odds of a placebo patients (PR 42% : IR 14%) (odds ratio 4.4 (95% CI: (2.63, 7.20), p<0.001). The odds of a ropinirole PR patient being a responder on the composite endpoint of 20% reduction from baseline in both L-dopa dose and "off" time were also more than 4 times that of a placebo patient (PR 54%: IR 20%) (odds ratio 4.3 (95% CI: [2.73, 6.78], p<0.001) while the odds of a ropinirole PR patient requiring reinstatement of L-dopa following a dose reduction were 5 times lower than a placebo patient (PR 7%: IR 28%) (odds ratio 0.2 (95% CI: [0.09, 0.34], p<0.001). The results on the primary endpoint were supported by clinically meaningful and statistically significant superiority over placebo on secondary efficacy parameters of 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.

At week 24 the mean dose of investigational product was 18.8 mg/day for ropinirole PR and 20.0 mg/day of placebo equivalent.

4.3 Pre-clinical Safety Data

Carcinogenesis, mutagenesis

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

Reproductive toxicology

Infertility studies in rats, effects were seen on implantation due to the prolactin-lowering effect of ropinirole. In humans, chorionic gonadotropin, not prolactin, is essential for implantation in females. No effects were seen on male fertility. Administration of ropinirole to pregnant rats at maternally toxic doses resulted in decreased foetal body weight at 60 mg/kg, increased foetal death at 90 mg/kg and digit malformations at 150 mg/kg. There was no teratogenic effect in the rat at 120 mg/kg and no indication of an effect on development in the rabbit. There have been no
Animal toxicology and/or pharmacology
Ropinirole caused no serious or irreversible toxicity in laboratory animals at 15 mg/kg (monkey), 20 mg/kg (mouse) or 50 mg/kg (rat). The toxicology profile is principally determined by the pharmacological activity of the drug (behavioural changes, hyperprolactinaemia, and decrease in blood pressure and heart rate, ptosis and salivation).

5. PHARMACEUTICAL PARTICULARS

5.1 List of excipients
**Tablet cores:** hypromellose 2208, hydrogenated castor oil, carboxymethylcellulose sodium, povidone, maltodextrin, magnesium stearate, lactose monohydrate, colloidal silicon dioxide, mannitol (E421), ferric oxide yellow (E172), glyceryl behenate.

**Film Coats:**

<table>
<thead>
<tr>
<th>Tablet Colour</th>
<th>Tablet Strength (mg) and colour</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>2 Pink</td>
</tr>
<tr>
<td>Hypromellose 2910</td>
<td>√</td>
</tr>
<tr>
<td>Titanium dioxide (E171)</td>
<td>√</td>
</tr>
<tr>
<td>Polyethylene glycol/Macrogol 400</td>
<td>√</td>
</tr>
<tr>
<td>Ferric oxide yellow (E172)</td>
<td>√</td>
</tr>
<tr>
<td>Ferric oxide black (E172)</td>
<td></td>
</tr>
<tr>
<td>Ferric oxide red (E172)</td>
<td>√</td>
</tr>
<tr>
<td>Sunset yellow FCF, Aluminium Lake (E110)</td>
<td></td>
</tr>
<tr>
<td>Indigo carmine, Aluminium Lake (E132)</td>
<td></td>
</tr>
<tr>
<td>Carmine (E120)</td>
<td></td>
</tr>
</tbody>
</table>

5.2 Incompatibilities
None known

5.3 Shelf Life
The Expiry date is indicated on the packaging.

5.4 Special Precautions for Storage
Store below 25°C. Store in the original package.
5.5 Nature and Contents of Container
PVC/PCTFE blister pack or HDPE bottle.

5.6 Instructions for Use/Handling
No special instructions. Further information is available on request.
Not all presentations are available in every country.

*REQUIP™ PD* and *REQUIP PD* logo are trademarks of the GlaxoSmithKline group of companies.

**HARUS DENGAN RESEP DOKTER**

Packaging available:

**Starter Pack:**
REQUIP PD 24 HOUR 2 mg, 3 blister @ 14 tablets, Reg. No. xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

**Trade Pack:**
REQUIP PD 24 HOUR 2 mg, 2 blister @ 14 tablets, Reg. No. xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
REQUIP PD 24 HOUR 2 mg, 6 blister @ 14 tablets, Reg. No. xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
REQUIP PD 24 HOUR 4 mg, 2 blisters @ 14 tablets, Reg. No. xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
REQUIP PD 24 HOUR 4 mg, 6 blisters @ 14 tablets, Reg. No. xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
REQUIP PD 24 HOUR 8 mg, 2 blisters @ 14 tablets, Reg. No. xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx
REQUIP PD 24 HOUR 8 mg, 6 blisters @ 14 tablets, Reg. No. xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx

Manufactured by
SmithKline Beecham plc
(trading as SmithKline Beecham Pharmaceuticals)
Crawley, United Kingdom

Imported by
PT. Glaxo Wellcome Indonesia
Jakarta, Indonesia

PI based on version GDS19/IP110 (Date of issue 13-Feb-2008)