REQUIP PD 24 HOUR
Ropinirole prolonged release tablets

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

2. CLINICAL INFORMATION
2.1 Indications
REQUIP PD 24 HOUR may be used as:
- Monotherapy, alone (without levadopa) in idiopathic Parkinson's disease or
- As adjunctive therapy in addition to levadopa to control "on-off" fluctuations which might permit a reduction in the total daily dose of levadopa.

2.2 Dosage and Administration
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 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.

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 (*see Pharmacokinetics*).

- **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:

	Week			
	1	2	3	4
Total daily dose (mg)	2	4	6	8

- **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 weeks, 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 receiving *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 the 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 (*see Warning and Precautions*).

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 aged 65 years or above, but the dose of *REQUIP PD 24 HOUR* for elderly patients can be titrated in the normal manner.

Children and Adolescents
The safety and efficacy of ropinirole have not been established in patients under 18 years of age, therefore, *REQUIP PD 24 HOUR* is not recommended for use in patients within this age group.

Renal 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.

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 *REQUIP PD 24 HOUR* 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.

Hepatic Impairment
The use of ropinirole in patients with hepatic impairment has not been studied. Administration of *REQUIP PD 24 HOUR* to such patients is not recommended.

2.3 Contraindications
Hypersensitivity to ropinirole or to any of the excipients.

2.4 Warnings and Precautions
Due to the pharmacological action of ropinirole, patients with severe 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 risks.

Impulse control symptoms including compulsive behaviours (including pathological gambling, hypersexuality, compulsive shopping and binge eating) and mania have been reported in patients treated with dopaminergic agents, including ropinirole (*see Adverse Reactions – Post-marketing Data*). These 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.

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

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

The dose of ropinirole should be reduced gradually when discontinuing treatment (*see Dosage and Administration*). Non-motor adverse effects may occur when tapering or discontinuing dopamine agonists, including ropinirole. Symptoms include insomnia, apathy, anxiety, depression, fatigue, sweating and pain which may be severe. Patients should be informed about this before dose reduction and monitored regularly thereafter. In case of persistent symptoms, it may be necessary to increase the ropinirole dose temporarily (*see Adverse Reactions*).

Excipients
REQUIP PD 24 HOUR 4 mg tablets contain sunset yellow FCF (E110 or FD&C Yellow No 6) which may cause allergic-type reactions.

2.5 Interactions
Neuroleptics and other centrally active dopamine antagonists, such as sulpiride or metoclopramide, may diminish the effectiveness of ropinirole and, therefore, concomitant use of these 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 these 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 drug 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 C_{max} and AUC of ropinirole by approximately 60% and 84% respectively. Hence, in patients already receiving *REQUIP PD 24 HOUR*, the dose of *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, changes in ropinirole pharmacokinetics following co-administration 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.

2.6 Pregnancy and Lactation

Fertility
There are no data on the effects of ropinirole on human fertility. In female fertility studies in rats, effects were seen on implantation *(see Non-clinical Information).* No effects were seen on male fertility in rats.

Pregnancy
There are no adequate and well-controlled studies of ropinirole in pregnant women. Ropinirole concentrations may gradually increase during pregnancy (*see Pharmacokinetics*). Studies in animals have shown embryo-foetal toxicity *(see Non-clinical Information).* 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.

Lactation
There are no data regarding the excretion of ropinirole in human milk. Ropinirole has been detected in rat milk *(see Non-clinical Information). REQUIP PD 24 HOUR* should not be used in nursing mothers as it may inhibit lactation.

2.7 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 the possibility of sudden onset of sleep without any prior warning or apparent daytime somnolence (*see Adverse Reactions*), which has 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.

2.8 Adverse Reactions
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.

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), including isolated reports.

Clinical Trial Data
The tables below list the adverse drug reactions reported at a higher rate with ropinirole than placebo or a higher or comparable rate to comparator in clinical trials.

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.

	Use in monotherapy studies	**Use in adjunct therapy studies**
Psychiatric disorders		
Common	Hallucinations	Hallucinations, confusion[1]
Nervous system disorders		
Very common	Somnolence, syncope[1]	Dyskinesia[3]
Common	Dizziness (including vertigo), sudden onset of sleep[2]	Somnolence[2], dizziness (including vertigo), sudden onset of sleep[2]
Vascular disorders		
Common		Postural hypotension[2], hypotension[2]
Uncommon	Postural hypotension[2], hypotension[2]	

Gastrointestinal disorders		
Very common	Nausea	
Common	Abdominal pain[1], vomiting[1], dyspepsia[1], constipation[2]	Nausea, constipation[2]
General disorders and administrative site conditions		
Very common	Oedema peripheral (including leg oedema)	Oedema peripheral[2]
[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 dose may ameliorate dyskinesia* (*see Dosage and Administration*)*.*		

Adverse Drug Reactions Reported During Clinical Trials in Patients with Restless Legs Syndrome

Psychiatric disorders	
Common	Nervousness
Nervous system disorders	
Common	Dizziness (including vertigo), somnolence, syncope
Gastrointestinal disorders	
Very common	Nausea, vomiting
Common	Abdominal pain
General disorders and administrative site conditions	
Common	Fatigue

Post-marketing Data

Immune system disorders	
Very rare	Hypersensitivity reactions (including urticaria, angioedema, rash, pruritus).
Psychiatric disorders	
Uncommon	Psychotic reactions (other than hallucinations) including delusion, paranoia, delirium. Impulse control symptoms, increased libido including hypersexuality, pathological gambling, compulsive shopping, binge eating (*see Warnings and Precautions*). Aggression*
Very rare	Mania
*Aggression has been associated with psychotic reactions as well as compulsive symptoms.	
Nervous system disorders	
Very rare	Extreme somnolence, sudden onset of sleep[†]
[†]As with other dopaminergic therapies, extreme somnolence and sudden onset of sleep have been reported, primarily in Parkinson's disease. 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 from post-marketing reports were available, patients had recovered after down titration or on withdrawal of the drug. In most cases the patients received concomitant medication with potential sedating properties.	
Vascular disorders	
Common	Hypotension, postural hypotension**
**As with other dopamine agonists, hypotension including postural hypotension has been observed with ropinirole treatment.	
General disorders and administrative site conditions	
Very rare	Drug withdrawal syndrome[††]
[††]Dopamine agonist withdrawal syndrome (including insomnia, apathy, anxiety, depression, fatigue, sweating and pain).	

2.9 Overdose

Symptoms and Signs

The symptoms of ropinirole overdose are generally related to its dopaminergic activity.

Treatment
These symptoms may be alleviated by appropriate treatment with dopamine antagonists such as neuroleptics or metoclopramide.

3. PHARMACOLOGICAL PROPERTIES
3.1 Pharmacodynamics
ATC Code
N04BC04.

Mechanism of Action
Ropinirole is a potent, non-ergoline D2/D3 dopamine agonist.

Parkinson's disease is characterised 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.

3.2 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_{max} of 6 hours. In a steady-state study in Parkinson's disease patients receiving 12 mg of ropinirole PR once daily, a high fat meal increased the systemic exposure to ropinirole as shown by an average 20% increase in AUC and an average 44% increase in C_{max}. T_{max} was delayed by 3.0 hours. However, in the studies that established the safety and efficacy of ropinirole PR, patients were instructed to take study medication without regard to food intake.

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 (C_{max} 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 15% in elderly patients (above 65 years) compared to younger patients. Dosing adjustment is not necessary in the elderly.

- **Renal impairment**

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

In patients with end stage renal disease receiving regular dialysis, oral clearance of ropinirole is reduced by approximately 30%. The recommended maximum dose is limited to 18 mg/day in patients with Parkinson's disease (*see Dosage and Administration, Renal Impairment*).

- **Pregnancy**

Physiological changes in pregnancy (including decreased CYP1A2 activity) are predicted to gradually lead to an increased maternal systemic exposure of ropinirole (reaching an approximate 2-fold increase by the third trimester based on physiologically based pharmacokinetic modelling).

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 patient (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.

3.3 Non-clinical Information

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
In fertility 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 (3.4, 5.1 and 8.5 times the mean human AUC at the Maximum Recommended Human Dose (MRHD)). There was no teratogenic effect in the rat at 120 mg/kg (6.8 times the mean human AUC at the MRHD) and no indication of an effect during organogenesis in the rabbit when given alone at 20 mg/kg (9.5 times the mean human C_{max} at the MRHD). However, ropinirole at 10 mg/kg (4.8 times the mean human C_{max} at the MRHD) administered to rabbits in combination with oral L-dopa produced a higher incidence and severity of digit malformations than L-dopa alone.

Ropinirole-related material was shown to transfer into the milk of lactating rats in small amounts (approximately 0.01% of the dose per pup).

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); 0.9, 0.4 and 2.8 times the mean human AUC at the MRHD. 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).

4. PHARMACEUTICAL INFORMATION

4.1 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:

Tablet colour	**Tablet strength (mg) and colour**		
	2 Pink	4 Light Brown	8 Red
Hypromellose 2910	✓	✓	✓
Titanium dioxide (E171)	✓	✓	✓
Polyethylene glycol/Macrogol 400	✓	✓	✓
Ferric oxide yellow (E172)	✓		✓
Ferric oxide black (E172)			✓
Ferric oxide red (E172)	✓		✓
Sunset yellow FCF (*see Warnings and Precautions*), Aluminium Lake (E110)		✓	
Indigo carmine, Aluminium Lake (E132)		✓	

4.2 Shelf Life

The expiry date is indicated on the packaging.

4.3 Storage

Do not store above 30°C. Store in original package.

4.4 Nature and Contents of Container
Cold form child-resistant double foil blister.

4.5 Incompatibilities
None known.

4.6 Use and Handling
No special instructions. Further information is available on request.

Not all presentations are available in every country.

HARUS DENGAN RESEP DOKTER

Packaging available:

Trade pack:
REQUIP PD 24 HOUR 2 mg, 7 blisters @ 4 tablets, Reg. No. DKI1291600614A1
REQUIP PD 24 HOUR 4 mg, 7 blisters @ 4 tablets, Reg. No. DKI1291600614B1
REQUIP PD 24 HOUR 8 mg, 7 blisters @ 4 tablets, Reg. No. DKI1291600614C1

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