REQUIP XL
Professional Information

SCHEDULING STATUS:

S4

1. NAME OF THE MEDICINE:

REQUIP XL 2 mg Prolonged Release tablets

REQUIP XL 4 mg Prolonged Release tablets

REQUIP XL 8 mg Prolonged Release tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION:

REQUIP XL 2 mg: Each tablet contains 2,0 mg ropinirole as the hydrochloride.

Contains sugar (lactose 46,32 mg\tablet, mannitol 73,16 mg\tablet and maltodextrin 7,50 mg\tablet)

REQUIP XL 4 mg: Each tablet contains 4,0 mg ropinirole as the hydrochloride.

Contains sugar (lactose 44,04 mg\tablet, mannitol 73,16 mg\tablet and maltodextrin 7,50 mg\tablet)

REQUIP XL 8 mg: Each tablet contains 8,0 mg ropinirole as the hydrochloride.

Contains sugar (lactose 39,48 mg\tablet, mannitol 73,16 mg\tablet and maltodextrin 7,50 mg\tablet)

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM:

REQUIP XL 2 mg: Pink, film-coated, biconvex capsule-shaped tablet, debossed with 'GS' on one face and ‘3V2’ on the other face.

REQUIP XL 4 mg: Light brown (tan), film-coated, biconvex capsule-shaped tablet, debossed with 'GS' on one face and ‘WXG’ on the other face.

REQUIP XL 8 mg: Red, film-coated, biconvex capsule-shaped tablet, debossed with 'GS' on one face and '5CC' on the other face.

4. CLINICAL PARTICULARS:

4.1 Therapeutic indications:

REQUIP XL is indicated

- as early therapy in patients with Parkinson's disease requiring dopaminergic therapy.
- as adjunctive treatment to L-dopa in patients with Parkinson's disease, REQUIP XL 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:

Individual dose titration against efficacy and tolerability is recommended.

REQUIP XL 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.

REQUIP XL tablets 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:

	Week			
	1	**2**	**3**	**4**
Total daily dosage (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.

Doses above 24 mg/day have not been investigated in clinical trials.

When REQUIP XL 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 REQUIP XL tablets concurrently.

In patients with advanced Parkinson's disease receiving REQUIP XL in combination with L-dopa, dyskinesias can occur.

In clinical trials it was shown that a reduction of the L-dopa dose may ameliorate dyskinesia (see section 4.4).

REQUIP XL 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).

Switching from ropinirole immediate release tablets to REQUIP XL tablets:

Patients may be switched overnight from ropinirole immediate release tablets to REQUIP XL tablets. The dose of REQUIP XL tablets should be based on the total daily dose of ropinirole immediate release tablets that the patient was taking.

The table below shows the recommended dose of REQUIP XL tablets for patients switching from ropinirole immediate release tablets:

Ropinirole immediate release tablets total daily dose (mg)	REQUIP XL tablets total daily dose (mg)
0,75-2,25	2,0
3,0-4,5	4,0
6,0	6,0
7,5-9,0	8,0
12,0	12,0

Ropinirole immediate release tablets total daily dose (mg)	REQUIP XL tablets total daily dose (mg)
15,0-18,0	16,0
21,0	20,0
24,0	24,0

After switching to REQUIP XL tablets, the dose may be adjusted depending on the therapeutic response (see 'Treatment initiation' and 'Therapeutic regimen' above).

Switching from other dopamine agonists to REQUIP XL:

When switching treatment from another dopamine agonist to REQUIP XL, the manufacturer's guidance on discontinuation should be followed before initiating REQUIP XL.

When stopping REQUIP XL:

REQUIP XL should be discontinued gradually by reducing the number of daily doses over the period of one week (see section 4.4).

Children and Adolescents:

The safety and efficacy of REQUIP XL has not been established in patients under 18 years of age. Therefore, REQUIP XL is not recommended for use in patients within this age group.

Elderly:

Although the clearance of ropinirole is decreased in patients aged 65 years or above, the dose of REQUIP XL for elderly patients can be titrated in the normal manner.

Renal Impairment:

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

A study into the use of REQUIP XL 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 XL 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 REQUIP XL in patients with severe renal impairment (creatinine clearance less than 30 ml/min) without regular dialysis has not been studied (see section 4.3).

Hepatic Impairment:

The use of REQUIP XL in patients with hepatic impairment has not been studied, administration of REQUIP XL to such patients is not recommended (see section 4.4).

4.3 Contraindications:

Hypersensitivity to ropinirole or to any of the excipients of REQUIP XL.

Pregnancy and lactation (see section 4.6).

Severe renal impairment, except when on haemodialysis.

4.4 Special warnings and precautions for use:

Falling Asleep During Activities of Daily Living:

Patients treated with REQUIP XL have reported falling asleep while engaged in activities of daily living, including the driving of motor vehicles, which has resulted in accidents. Although many of these patients reported somnolence while on REQUIP XL, 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 one year after initiation of treatment.

Somnolence is a common occurrence in patients receiving REQUIP XL. Many clinical experts believe that falling asleep while engaged in activities of daily living always occurs in a setting of pre-existing 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 REQUIP XL, patients and their caregivers should be advised of the potential to develop drowsiness and be specifically questioned about factors that may increase the risk with REQUIP XL, such as use of concomitant sedating medicines, the presence of sleep disorders and use of concomitant medicines that increase ropinirole plasma levels (e.g. ciprofloxacin – see sections 4.5 and 4.8). If a patient develops significant daytime sleepiness or episodes of falling asleep during activities that require active participation (e.g. conversations, eating, etc.), REQUIP XL should ordinarily be discontinued (see section 4.2 for guidance in discontinuing REQUIP XL).

If a decision is made to continue REQUIP XL, 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.

Because of the additive sedative effects, caution should also be exercised when patients are taking alcohol or other CNS depressants (e.g. benzodiazepines, antipsychotics, and antidepressants) in combination with REQUIP XL.

REQUIP XL tablets gradually release ropinirole over a 24-hour period. Therefore, if rapid gastrointestinal transit occurs, there may be risk of incomplete release of medication and of medication residue being passed in the stool.

Pathological Gambling and Hypersexuality: Impulse control symptoms including compulsive behaviours (including pathological gambling, hypersexuality, aggression, compulsive shopping and binge eating) and mania may occur in patients treated with REQUIP XL (see section 4.8).

These were generally reversible upon dose reduction or treatment discontinuation. The caregivers of patients taking REQUIP XL, should be informed of these possible effects.

Syncope: Syncope, sometimes associated with bradycardia, was observed in association with REQUIP XL in both early Parkinson's disease (without L-dopa) patients and advanced Parkinson's disease (with L-dopa) patients. Most of these cases of syncope occurred more than four weeks after initiation of therapy with REQUIP XL and were usually associated with a recent increase in dose.

Postural hypotension: Dopamine agonists such as REQUIP XL impair the systemic regulation of blood pressure, with resulting postural hypotension, especially during dose escalation. Parkinson's disease patients, in addition, may have an impaired capacity to respond to a postural challenge. Parkinson's patients being treated with REQUIP XL therefore require careful monitoring for signs and symptoms of postural hypotension, especially during dose escalation and should be informed of this risk (see section 4.4).

Postural hypotension: Patients and their caregivers should be advised that they may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, syncope and sweating. Hypotension and/or orthostatic symptoms may occur during initial therapy or with an increase in dose or at any other time. Accordingly, patients should be cautioned against rising rapidly after sitting or lying down, especially if they have been doing so for prolonged periods and especially at the initiation of treatment with REQUIP XL.

Hallucinations: Patients and their caregivers should be warned that hallucinations can occur and that the elderly are at a higher risk than younger patients with Parkinson's disease.

Dyskinesia: REQUIP XL may potentiate the dopaminergic side effects of L-dopa and may cause and/or exacerbate pre-existing dyskinesia. Decreasing the dose of L-dopa may ameliorate this side effect.

Cardiac conditions: Due to the pharmacological action of ropinirole, patients with severe cardiovascular disease should be treated with caution.

Psychotic disorders: Patients with major psychotic disorders should only be treated with dopamine agonists such as REQUIP XL, if the potential benefits outweigh the risks (also see section 4.5).

Events reported with dopaminergic therapy:

Withdrawal emergent hyperpyrexia and confusion: Although not reported with REQUIP XL, a symptom complex resembling the neuroleptic malignant syndrome (characterised by elevated temperature, muscular rigidity, altered consciousness and autonomic instability) with no other obvious etiology has been reported in association with rapid dose reduction, withdrawal of, or changes in anti-Parkinsonian therapy.

Therefore, it is recommended to discontinue treatment gradually.

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

Dopamine agonist withdrawal syndrome (DAWS)*:* The dose of REQUIP XL should be reduced gradually when discontinuing treatment (see section 4.2). 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 severe and/or persistent withdrawal symptoms, temporary re-administration of ropinirole at the lowest effective dose may be considered.

Retinal pathology: Retinal degeneration was observed pre-clinically in albino rats in a two year carcinogenicity study at all doses. Similar changes were not observed in albino mice, rats or monkeys treated for one year. The potential significance of this effect in humans has not been established.

Binding to melanin: Pre-clinical studies show REQUIP XL binds to melanin-containing tissues (i.e. eyes and skin). After a single dose, long-term retention of the medicine was demonstrated, with a half-life in the eye of 20 days. It is not known if REQUIP XL accumulates in these tissues over time.

Hepatic impairment: The pharmacokinetics of ropinirole has not been studied in hepatically impaired patients. These patients may have higher plasma levels and lower clearance of ropinirole than patients with normal hepatic function. REQUIP XL should be titrated with caution in patients with hepatic impairment.

Contains lactose: Patients with rare hereditary problems of galactose intolerance e.g. galactosaemia, the Lapp lactase deficiency or glucose-galactose malabsorption should not take REQUIP XL (see section 2).

Prolonged release tablets: The REQUIP XL 4 mg tablets contain the azo colouring agent sunset yellow (E110), which may cause allergic reactions (see section 2).

4.5 Interaction with other medicines and other forms of interaction:

Neuroleptics and other centrally active dopamine antagonists, such as sulpiride or metoclopramide, may diminish the effectiveness of REQUIP XL and, therefore, concomitant use of these medicines with REQUIP XL should be avoided.

No pharmacokinetic interaction has been seen between REQUIP XL and L-dopa or domperidone, which would necessitate dosage adjustment of either medicine.

No interaction has been seen between ropinirole and other medicines commonly used to treat Parkinson's disease.

In a study in Parkinsonian patients receiving concurrent digoxin, no interaction was seen that would require dosage adjustment.

It has been established from *in vitro* experiments that ropinirole is metabolised by the cytochrome P450 enzyme CYP1A2.

There is, therefore, the potential for an interaction between ropinirole and substrates (such as theophylline) or inhibitors (such as ciprofloxacin) of this enzyme. In patients already receiving REQUIP XL, the dose of REQUIP XL may need to be adjusted when these medicines are introduced or withdrawn.

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 XL treatment may be initiated in the normal manner. However, if HRT is stopped or introduced during treatment with REQUIP XL, dosage adjustment may be required.

P450 Interaction: *In vitro* metabolism studies showed that CYP1A2 was the major enzyme responsible for the metabolism of ropinirole. Thus, there is a potential for inhibitors or substrates of this enzyme to alter its clearance when co-administered with ropinirole. Therefore, if therapy with a medicine known to be a potent inhibitor of CYP1A2 is stopped or started during treatment with ropinirole, adjustment of the ropinirole dose may be required.

4.6 Fertility, pregnancy and lactation:

Pregnancy:

There are no adequate and well-controlled studies of ropinirole in pregnant women. Ropinirole concentrations may gradually increase during pregnancy (see section 5.2). Studies in animals have shown embryo-foetal toxicity.

REQUIP XL should not be used during pregnancy

Fertility:

There is no data on the effects of ropinirole on human fertility. In female fertility studies in rats, effects were seen on implantation. No effects were seen on male fertility in rats.

Lactation:

There is no data regarding the excretion of ropinirole in human milk. Ropinirole has been detected in rat milk. REQUIP XL should not be used during lactation.

4.7 Effects on the ability to drive and use machines:

REQUIP XL may cause somnolence. Patients should be advised to neither drive a car nor operate other complex machinery, until they have gained sufficient experience of REQUIP XL to gauge whether or not, it adversely affects their mental and/or motor performance (see section 4.4).

4.8 Undesirable effects:

During the pre-marketing development of ropinirole immediate release, patients received ropinirole immediate release either without L-dopa (early Parkinson's disease studies) or as concomitant therapy with L-dopa (advanced Parkinson's disease studies). Because these two populations may have differential risks for various adverse events, the adverse events for the two populations have been separated.

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥ 1/10), common (≥ 1/100 to 1/10), uncommon (≥ 1/1 000 to 1/100), rare (≥ 1/10 000 to 1/1 000) very rare (<1/10 000), including isolated reports.

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

Clinical trial data:

	Use in Monotherapy Studies	Use in Adjunct Therapy Studies
Psychiatric disorders		
common	hallucinations	confusion, hallucinations [1]
Nervous system disorders		
very common	somnolence, syncope [1]	dyskinesia [3]
common	dizziness, including vertigo [2], sudden onset of sleep[2]	somnolence [2], dizziness (including vertigo), sudden onset of sleep[2]
Vascular disorders		
common		postural hypotension[2,4], hypotension[2,4]
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		
common	oedema peripheral (including leg oedema)	peripheral oedema[2]
very rare	drug withdrawal syndrome[5]	

1 Ropinirole immediate release clinical trials data

2 REQUIP XL clinical trials data

3 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 L-dopa dose may ameliorate dyskinesia (see section 4.2).

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

5 Dopamine agonist withdrawal syndrome (including insomnia, apathy, anxiety, depression, fatigue, sweating and pain).

Post-marketing data:

Immune system disorders:

hypersensitivity reactions (including urticaria, angioedema, rash, pruritus)

Psychiatric disorders:

psychotic reactions (other than hallucinations) including delusion, paranoia, delirium. Impulse control symptoms, increased libido including hypersexuality, pathological gambling, compulsive shopping, binge eating, mania, aggression# (see section 4.4)

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

Nervous system disorders:

extreme somnolence, sudden onset of sleep*

* Extreme somnolence and/or sudden onset of sleep may occur (see section 4.4). Patients experiencing this phenomenon cannot resist the urge to sleep and on wakening may be unaware of any tiredness prior to the sleep. Where data are available, all such cases recovered after down-titration or withdrawal of REQUIP XL

Vascular disorders:

hypotension, postural hypotension

Dopamine agonists such as REQUIP XL appear to impair the systemic regulation of blood pressure, with resulting postural hypotension, especially during dose escalation. Parkinson's disease patients, in addition, appear to have an impaired capacity to respond to a postural challenge. Parkinson's patients being treated with REQUIP XL therefore require careful monitoring for signs and symptoms of postural hypotension, especially during dose escalation and should be informed of this risk (see section 4.4).

Other adverse events observed during clinical trials:

	Adverse events occurring frequently in Parkinson's disease patients in REQUIP clinical trials		Adverse events occurring less frequently in patients in all clinical trials
	Early Parkinson's Disease (without L-dopa)	**Advanced Parkinson's Disease (with L-dopa)**	
Infections and infestations	viral infection, pharyngitis, urinary tract infections, upper respiratory infection	upper respiratory infection, viral infection, urinary tract infection, virus infections, rhinitis, pharyngitis	cellulitis, diverticulitis, herpes zoster, herpes simplex, fungal infection, genital moniliasis, otitis, laryngitis media, fungal dermatitis, furunculosis, mastitis, pyelonephritis, sepsis, abscess
Neoplasms benign, malignant and unspecified (including cysts nd polyps)	basal cell carcinoma	-	malignant breast neoplasm, bladder carcinoma, benign brain neoplasm, esophageal carcinoma, lipoma, rectal carcinoma, uterine neoplasm, uraemia, (malignant) laryngeal neoplasm
Blood and lymphatic system disorders	-	-	thrombocytopenia, hypochromic anaemia, eosinophilia, leukocytosis, leukopenia, lymphocytosis, lymphopenia
Endocrine disorders	-	-	hypothyroidism, hyperthyroidism, goiter, SIADH
Metabolism and nutrition disorders	hyperglycaemia, gout	-	hypoglycaemia, hyperphosphataemia, hyperuricaemia, diabetes mellitus, hypokalaemia, hypercholesterolaemia, hyperkalaemia, acidosis, hyponatraemia, dehydration, vitamin B12 deficiency, hypochloraemia
Psychiatric disorders	confusion, hallucinations, insomnia, anxiety, depression, nervousness, abnormal dreams	insomnia, hallucinations, confusion, anxiety, depression	dysphoria, increased libido, agitation, apathy, depersonalization, paranoid reaction, personality disorder, euphoria, delirium, delusion, emotional lability, decreased libido, manic reaction, somnambulism, aggressive reaction, neurosis, suicide attempt
Nervous system disorders	dizziness, somnolence, headache, syncope, tremor, dyskinesias, aggravated Parkinsonism, dystonia	dizziness, somnolence, headache, aggravated Parkinsonism, tremor, hypokinesia, paresthesia, hyperkinesias, dyskinesia	neuralgia, involuntary muscle contractions, hypertonia, abnormal coordination, extrapyramidal disorder, migraine, choreoathetosis, coma, stupor, aphasia, hypotonia, convulsions, peripheral neuropathy, paralysis, impaired concentration, dementia, torticollis, grand mal convulsions, hemiparesis, hemiplegia, subarachnoid haemorrhage
Eye disorders	abnormal vision	-	abnormal lacrimation, conjunctivitis, blepharitis, glaucoma, abnormal accommodation, blepharospasm, eye pain, photophobia, scotoma
Ear and labyrinth disorders	-	vertigo, tinnitis	tinnitus, earache, decreased hearing
Cardiac disorders	bradycardia	myocardial infarction	cardiac failure, bradycardia, tachycardia, supraventricular tachycardia, angina pectoris, bundle

	Adverse events occurring frequently in Parkinson's disease patients in REQUIP clinical trials		Adverse events occurring less frequently in patients in all clinical trials
	Early Parkinson's Disease (without L-dopa)	**Advanced Parkinson's Disease (with L-dopa)**	
			branch block, cardiac arrest, cardiomegaly, mitral insufficiency, ventricular tachycardia
Vascular disorders	hot flushes, orthostatic symptoms	orthostatic symptoms, hot flushes	aneurysm, varicose veins, phlebitis, peripheral gangrene, haematoma, limb embolism, gangrene, deep thrombophlebitis, leg thrombophlebitis, thrombosis, lymphoedema
Respiratory, thoracic and mediastinal	cough	-	hiccups, asthma, epistaxis, pleurisy, pulmonary oedema, pulmonary embolism
Gastrointestinal disorders	nausea, vomiting, dyspepsia, constipation, abdominal pain, diarrhoea, increased salivation, gingivitis	nausea, abdominal pain, vomiting, constipation, dry mouth, dyspepsia	enlarged abdomen, precordial chest pain, colitis, dysphagia, peridentitis, faecal incontinence, gastroesophageal reflux, haemorrhoids, toothache, eructation, gastritis, esophagitis, duodenal ulcer, gastric ulcer, melaena, duodenitis, gastrointestinal haemorrhage, glossitis, rectal haemorrhage, pancreatitis, stomatitis, ulcerative stomatitis, tongue oedema, haemorrhagic gastritis, haematemesis, salivary duct obstruction, ascites,
Hepatobiliary disorders	-	-	bilirubinaemia, cholecystitis, cholelithiasis, biliary pain
Skin and subcutaneous tissue disorders	increased sweating, rash	increased sweating	purpura, pruritus, dermatitis, eczema, skin ulceration, alopecia, skin hypertrophy, skin discolouration, urticaria, hyperkeratosis, photosensitivity reactions, psoriasis, maculapapular rash, psoriasiform rash, seborrhoea
Musculoskeletal and connective tissue disorders	arthralgia, back pain, myalgia, leg cramps, paresthesias, arthritis, muscle spasm, arthrosis	arthralgia, myalgia, back pain, leg cramps	aggravated arthritis, tendonitis, osteoporosis, bursitis, polymyalgia, muscle weakness, skeletal pain, rheumatica (rheumatics), Dupuytren's contracture (requiring surgery)
Renal and urinary disorders	haematuria	haematuria	glycosuria, dysuria, micturition frequency, albuminuria, nocturia, polyuria, renal calculus, acute renal failure
Reproductive system and breast disorders	-	-	gynaecomastia, amenorrhoea, vaginal haemorrhage, penile (penis) disorder, prostatic disorder, balanoposthitis, epididymitis, perineal pain, breast enlargement, uterine haemorrhage, ejaculation disorder, Peyronie's disease
General disorders and administrative site conditions	fatigue, pain, asthaenia, leg oedema, rigors	pain, asthenia, fatigue, chest pain, leg oedema, abnormal gait	peripheral oedema, fever, influenza-like symptoms, generalized oedema, thirst

	Adverse events occurring frequently in Parkinson's disease patients in REQUIP clinical trials		Adverse events occurring less frequently in patients in all clinical trials
	Early Parkinson's Disease (without L-dopa)	**Advanced Parkinson's Disease (with L-dopa)**	
Investigations	weight loss	increased drug level	increased hepatic enzymes, increased BUN, increased alkaline phosphatase, increased LDH, weight increased, increased CPK
Injury, poisoning and procedural complications	falls	injury, falls	-

4.9 Overdose:

It is anticipated that the symptoms of ropinirole overdose will be related to its dopaminergic activity. Side effects will be evoked and exacerbated (see section 4.8). These symptoms may be alleviated by appropriate treatment with dopamine antagonists such as neuroleptics or metoclopramide.

5. PHARMACOLOGICAL PROPERTIES:

5.1 Pharmacodynamic properties:

A 5.4.1 Anti-Parkinsonism preparations.

Ropinirole is a non-ergoline 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.

5.2 Pharmacokinetic properties:

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

Wide inter-individual variability in the pharmacokinetic parameters has been seen. Bioavailability of ropinirole is approximately 50 % for prolonged release tablets.

Following oral administration of ropinirole prolonged release formulation, 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 compared to when taking ropinirole prolonged release in the fasted state. However, in clinical studies, patients were instructed to take study medication without regard to food intake.

Metabolism of ropinirole is extensive. Wide inter-individual variability in the pharmacokinetic parameters has been seen but, overall, there is a proportional increase in the systemic exposure (C_{max} and AUC) to the medicine with an increase in dose, over the therapeutic dose range.

Consistent with its high lipophilicity, ropinirole exhibits a large volume of distribution (approx. 8 ℓ/kg) and is cleared from the systemic circulation with an average elimination half-life of about 6 hours. Plasma protein binding of ropinirole is low (10-40 %). Ropinirole is metabolised primarily by oxidative metabolism and ropinirole 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. No change in the clearance of ropinirole is observed following single and repeated oral administration. As expected for a medicine being administered approximately every half-life, there is, on average, 2-fold higher steady-state plasma concentrations of ropinirole following the recommended three times daily regimen compared to those observed following a single oral dose.

Renal impairment: There was no change in the pharmacokinetics of ropinirole in Parkinson's disease patients with mild to moderate renal impairment (CrCl more than 30 ml/min).

In patients with end stage renal disease also receiving regular dialysis, oral clearance of ropinirole is reduced by approximately 30 %.

Hepatic impairment: The pharmacokinetics of ropinirole has not been studied in hepatically impaired patients. These patients may have higher plasma levels and lower clearance of the medicine than patients with normal hepatic function. Ropinirole should be titrated with caution in this population.

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).

6. PHARMACEUTICAL PARTICULARS:

6.1 List of Excipients:

Tablet core: 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 coat: The tablet strengths of REQUIP XL are distinguished by colour therefore, the composition of the film coat varies. All film coats contain hydroxypropyl methylcellulose, titanium oxide and polyethylene glycol, other variations are shown below:

2 mg: ferric oxide yellow (E172) and ferric oxide red (E172).

4 mg: sunset yellow (E110) and indigo carmine (E132).

8 mg: ferric oxide yellow (E172), ferric oxide black (E172), and ferric oxide red (E172).

REQUIP XL 4 mg tablets contain the azo colouring called sunset yellow (see section 4.4).

6.2 Incompatibilities:

N/A

6.3 Shelf-life:

REQUIP XL 2 mg: 24 months

REQUIP XL 4 mg and 8 mg: 36 months

6.4 Special precautions for storage:

Store at or below 25 ºC. Store in original package.

6.5 Nature of contents and container:

REQUIP XL 2 mg: Cartons of 28 or 84 tablets packed in opaque PVC/PCTFE/PVC blisters.

REQUIP XL 4 mg: Cartons of 28 or 84 tablets packed in opaque PVC/PCTFE/PVC blisters.

REQUIP XL 8 mg: Cartons of 28 or 84 tablets packed in opaque PVC/PCTFE/PVC blisters.

7. HOLDER OF CERTIFICATE OF REGISTRATION:

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

Epping Industria 1, 7460

8. REGISTRATION NUMBERS

REQUIP XL 2 mg: 41/5.4.1/0604

REQUIP XL 4 mg: 41/5.4.1/0606

REQUIP XL 8 mg: 41/5.4.1/0607

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION:

Date of registration: 15 August 2008

10. DATE OF REVISION OF TEXT:

Date of most recent revision: 13 September 2021

GDS-36

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