# REQUIP® XL

**SCHEDULING STATUS:**

S4

**PROPRIETARY NAME AND DOSAGE FORM:**

**REQUIP® XL 2 mg** Prolonged Release tablets

**REQUIP® XL 4 mg** Prolonged Release tablets

**REQUIP® XL 8 mg** Prolonged Release tablets

**COMPOSITION:**

REQUIP XL 2 mg: Each tablet contains 2,0 mg ropinirole as the hydrochloride and sugar (lactose 46,32 mg and mannitol 73,16 mg).

REQUIP XL 4 mg: Each tablet contains 4,0 mg ropinirole as the hydrochloride and sugar (lactose 44,04 mg and mannitol 73,16 mg).

REQUIP XL 8 mg: Each tablet contains 8,0 mg ropinirole as the hydrochloride and sugar (lactose 39,48 mg and mannitol 73,16 mg).

**Excipients:**

***Tablet core:*** Hypromellose 2208, hydrogenated castor oil, carboxymethylcellulose sodium, povidone, maltodextrin, magnesium stearate, lactose monohydrate (see above), colloidal silicon dioxide, mannitol (E421) (see above), 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).

See WARNINGS AND SPECIAL PRECAUTIONS.

**PHARMACOLOGICAL CLASSIFICATION:**

A 5.4.1 Anti-Parkinsonism preparations

**PHARMACOLOGICAL ACTION:**

Ropinirole is a non-ergoline 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.

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

For both the immediate and prolonged release formulations, wide inter-individual variability in the pharmacokinetic parameters has been seen. Bioavailability of ropinirole is approximately 50 % for immediate and 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.

**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.

**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.

**INDICATIONS:**

**Treatment of Parkinson's Disease:**

- REQUIP XL is indicated as early therapy in patients requiring dopaminergic therapy.
- As adjunctive treatment to L-dopa, 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.

**CONTRA-INDICATIONS:**

Hypersensitivity to ropinirole or to any of the excipients.

Pregnancy and lactation.

Severe renal impairment, except when on haemodialysis.

**WARNINGS AND SPECIAL PRECAUTIONS:**

**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 operation of motor vehicles which sometimes 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 should be advised of the potential to develop drowsiness and specifically asked about factors that may increase the risk with REQUIP XL such as concomitant sedating medications, the presence of sleep disorders and concomitant medications that increase ropinirole plasma levels (e.g. ciprofloxacin – see INTERACTIONS). 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 DOSAGE AND DIRECTIONS FOR USE 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 used when patients are taking alcohol or other CNS depressants (e.g. benzodiazepines, antipsychotics, and antidepressants) in combination with REQUIP XL.

**Pathological Gambling and Hypersexuality:** Impulse control symptoms including compulsive behaviours such as pathological gambling and hypersexuality have been reported in patients treated with REQUIP XL. Such behaviours have been reported principally in Parkinson's disease patients treated with dopaminergic agents, especially at higher doses and were generally reversible upon dose reduction or treatment discontinuation.

**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.

**Symptomatic 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 WARNINGS AND SPECIAL PRECAUTIONS).

**Postural hypotension:** Patients should be advised that they may develop postural (orthostatic) hypotension with or without symptoms such as dizziness, nausea, syncope and sometimes sweating. Hypotension and/or orthostatic symptoms may occur more frequently during initial therapy or with an increase in dose or at any 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 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 if the potential benefits outweigh the risks (see also INTERACTIONS).

**Events reported with dopaminergic therapy:**

***Withdrawal emergent hyperpyrexia and confusion***: Although not reported with REQUIP XL, a symptom complex resembling the neuroleptic 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 anti-Parkinsonian therapy.

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

**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.

**Driving and using machinery:** REQUIP XL may cause somnolence. Patients should be advised neither to drive a car nor operate other complex machinery, until they have

gained sufficient experience on REQUIP XL to gauge whether or not, it affects their mental and/or motor performance adversely.

**Contains lactose:** Patients with the rare hereditary conditions of galactose intolerance e.g. galactosaemia, Lapp lactase deficiency or glucose-galactose malabsorption should not take REQUIP XL (see COMPOSITION). Lactose may have an effect on the glycaemic control of patients with diabetes mellitus.

**Contains azo colouring**: The REQUIP XL 3 mg and 4 mg tablets contain the azo colouring agent sunset yellow (E110), which may cause allergic reactions (see COMPOSITION).

**INTERACTIONS:**

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 which would require dosage adjustment.

It has been established from *in vitro* experiments that ropinirole is metabolized 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.

**PREGNANCY AND LACTATION:**

REQUIP XL should not be used during pregnancy and lactation.

**DOSAGE AND DIRECTIONS FOR USE:**

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 WARNINGS AND SPECIAL PRECAUTIONS).

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 REQUIP tablets to REQUIP XL tablets:***

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

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

| REQUIP 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 |
| 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:***

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.

**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 CONTRA-INDICATIONS).

**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.

**SIDE EFFECTS:**

During the pre-marketing development of REQUIP, patients received REQUIP 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, <1/10), uncommon (≥1/1 000, <1/100), rare (≥1/10 000, <1/1 000) very rare (<1/10 000), including isolated reports.

Unless otherwise indicated, the data in the following table was observed with both REQUIP 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] | somnolence [2], dizziness (including vertigo) |
| ***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] |

| | Use in Monotherapy Studies | Use in Adjunct Therapy Studies |
|---|---|---|
| ***General disorders and administrative site conditions*** | | |
| common | oedema peripheral (including leg oedema) | oedema peripheral[2] |

1 REQUIP 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 DOSAGE AND DIRECTIONS FOR USE).

**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 (see WARNINGS AND SPECIAL PRECAUTIONS)

***Nervous system disorders:*** extreme somnolence, sudden onset of sleep*

* Extreme somnolence and/or sudden onset of sleep may occur (see WARNINGS AND SPECIAL PRECAUTIONS). 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 WARNINGS AND SPECIAL PRECAUTIONS).

**Other adverse events observed during clinical trials:**

The frequencies of the following adverse events listed in the following table are unknown.

| | **Adverse events occurring in ≥1 % Parkinson's disease patients in REQUIP clinical trials** | | **Adverse events occurring in <1 % 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 and 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, hallucinations, | dysphoria, increased libido, agitation, apathy, depersonalization, paranoid |

| | **Adverse events occurring in ≥1 % Parkinson's disease patients in REQUIP clinical trials** | | **Adverse events occurring in <1 % patients in all clinical trials** |
|---|---|---|---|
| | **Early Parkinson's Disease (without L-dopa)** | **Advanced Parkinson's Disease (with L-dopa)** | |
| | insomnia, anxiety, depression, nervousness, abnormal dreams | confusion, anxiety, depression | 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 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, |

| | **Adverse events occurring in ≥1 % Parkinson's disease patients in REQUIP clinical trials** | | **Adverse events occurring in <1 % patients in all clinical trials** |
|---|---|---|---|
| | **Early Parkinson's Disease (without L-dopa)** | **Advanced Parkinson's Disease (with L-dopa)** | |
| ***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 |
| ***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 | - |

## KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:

It is anticipated that the symptoms of ropinirole overdose will be related to its dopaminergic activity. These symptoms may be alleviated by appropriate treatment with dopamine antagonists such as neuroleptics or metoclopramide.

**IDENTIFICATION:**

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.

**PRESENTATION:**

REQUIP XL 2 mg: White blister packs (PVC/PCTFE/PVC blister film backed with white, hard tempered aliminium foil) of 28 or 84 tablets or opaque blister packs (PVC/PE/PvdC thermoform blisters and sealed with silver, child-resistant aluminium lidding foil) of 28 tablets (2 blisters of 14 tablets).

Three week starter pack containing 42 tablets in opaque PVC/PCTFE/PVC blisters.

REQUIP XL 4 mg: White blister packs (PVC/PCTFE/PVC blister film backed with white, hard tempered aliminium foil) of 28 or 84 tablets or opaque blister packs (PVC/PE/PvdC thermoform blisters and sealed with silver, child-resistant aluminium lidding foil) of 28 tablets (2 blisters of 14 tablets).

REQUIP XL 8 mg**:** White blister packs (PVC/PCTFE/PVC blister film backed with white, hard tempered aliminium foil) of 28 or 84 tablets or opaque blister packs (PVC/PE/PvdC thermoform blisters and sealed with silver, child-resistant aluminium lidding foil) of 28 tablets (2 blisters of 14 tablets).

**STORAGE INSTRUCTIONS:**

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

Keep out of reach of children.

**REGISTRATION NUMBER:**

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

**NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION:**

GlaxoSmithKline South Africa (Pty) Ltd

39 Hawkins Avenue

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**DATE OF PUBLICATION OF THE PACKAGE INSERT:**

Last approval: 01 March 2013

Date compliant with Regulation 11: 02 February 2016

**History:**

Proposed: 15 March 2006 (Inclusion of Prolonged-release tablets for Parkinson's disease)
Amended: 10 August 2007 (in-line with CCC recommendations dated 26/04/2007)
Amended: 24 January 2008 (in line with CCC recommendations dated 14/12/2007)
Amended: 25 March 2008 (new proprietary name proposed for prolonged release tablets – REQUIP XL)
Amended:31 March 2008 (response to CCC recommendations dated 22/02/2008) – compliant pi
Amended: 21 April 2009 (In line with GCT versions 17, 19 - 21)
Amended: 2 February 2010 (Correction of spelling errors as highlighted in CCC recommendation 13 August 2009 for RLS) – Included as Attachment 1
Amended: 05 October 2010 (in response to CCC recommendations dated 27/07/2010 – Response D2010-4334)
Amended: 28-07-2010 Cape town address details reflected
Amended: 04 October 2012 (compliant response to CCC recommendations dated 05/09/2012) Approved: 01 March 2013
Amended: 30 April 2013 (applicant address to CT, amendment to blister material)
Amended: 02 February 2016 (Implementation of Regulation 9 and 10)

**Amended: 06 September 2018 (to bring presentation in line with amended m3.2.P.7, reference to Requip XL 3 mg has been deleted as the license has been cancelled)**