

GLAXOSMITHKLINE SOUTH AFRICA (PTY) LIMITED	Submission Date	06 SEPTEMBER 2018	Type	B
REQUIP XL	Implementation Date	06 OCTOBER 2018	Category	3
PROLONGED RELEASE TABLET 2 mg/4 mg/8 mg			Reference	D2017-2019, v0004

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**REQUIP® XL**

4 **SCHEDULING STATUS:**

5 **S4**

6

7 **PROPRIETARY NAME AND DOSAGE FORM:**

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

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

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

11

12 **COMPOSITION:**

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

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

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

19 **Excipients:**

20 **Tablet core:** Hypromellose 2208, hydrogenated castor oil, carboxymethylcellulose  
21 sodium, povidone, maltodextrin, magnesium stearate, lactose monohydrate (see above),  
22 colloidal silicon dioxide, mannitol (E421) (see above), ferric oxide yellow ( E172),  
23 glyceryl behenate.

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

27 2 mg: ferric oxide yellow (E172) and ferric oxide red (E172).

28 4 mg: sunset yellow (E110) and indigo carmine (E132).

29 8 mg: ferric oxide yellow (E172), ferric oxide black (E172), and ferric oxide red (E172).

30 See WARNINGS AND SPECIAL PRECAUTIONS.

31

**32 PHARMACOLOGICAL CLASSIFICATION:**

33 A 5.4.1 Anti-Parkinsonism preparations

34

**35 PHARMACOLOGICAL ACTION:**

36 Ropinirole is a non-ergoline dopamine agonist.

37 Parkinson's disease is characterized by a marked dopamine deficiency in the nigral  
38 striatal system. Ropinirole alleviates this deficiency by stimulating striatal dopamine  
39 receptors.

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

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

44 Following oral administration of ropinirole prolonged release formulation, plasma  
45 concentrations increase slowly, with a median time to C<sub>max</sub> of 6 hours.

46 In a steady-state study in Parkinson's disease patients receiving 12 mg of ropinirole PR  
47 once daily, a high fat meal increased the systemic exposure to ropinirole as shown by

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48 an average 20 % increase in AUC and an average 44 % increase in  $C_{max}$ .  $T_{max}$  was  
49 delayed by  
50 3,0 hours compared to when taking ropinirole prolonged release in the fasted state.  
51 However, in clinical studies, patients were instructed to take study medication without  
52 regard to food intake.

53 Metabolism of ropinirole is extensive. Wide inter-individual variability in the  
54 pharmacokinetic parameters has been seen but, overall, there is a proportional increase  
55 in the systemic exposure ( $C_{max}$  and AUC) to the medicine with an increase in dose, over  
56 the therapeutic dose range. Consistent with its high lipophilicity, ropinirole exhibits a  
57 large volume of distribution (approx. 8 l/kg) and is cleared from the systemic circulation  
58 with an average elimination half-life of about 6 hours. Plasma protein binding of  
59 ropinirole is low (10-40 %). Ropinirole is metabolised primarily by oxidative metabolism  
60 and ropinirole and its metabolites are mainly excreted in the urine. The major  
61 metabolite is at least 100 times less potent than ropinirole in animal models of  
62 dopaminergic function. No change in the clearance of ropinirole is observed following  
63 single and repeated oral administration. As expected for a medicine being administered  
64 approximately every half-life, there is, on average, 2-fold higher steady-state plasma  
65 concentrations of ropinirole following the recommended three times daily regimen  
66 compared to those observed following a single oral dose.

67

**68 P450 Interaction:**

69 *In vitro* metabolism studies showed that CYP1A2 was the major enzyme responsible for  
70 the metabolism of ropinirole. Thus there is a potential for inhibitors or substrates of this  
71 enzyme to alter its clearance when co-administered with ropinirole. Therefore, if therapy

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72 with a medicine known to be a potent inhibitor of CYP1A2 is stopped or started during  
73 treatment with ropinirole, adjustment of the ropinirole dose may be required.

74

**75 Renal impairment:**

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

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

80

**81 Hepatic impairment:**

82 The pharmacokinetics of ropinirole has not been studied in hepatically impaired patients.

83 These patients may have higher plasma levels and lower clearance of the medicine than  
84 patients with normal hepatic function. Ropinirole should be titrated with caution in this  
85 population.

86

**87 INDICATIONS:**

**88 Treatment of Parkinson's Disease:**

- 89 • REQUIP XL is indicated as early therapy in patients requiring dopaminergic therapy.
- 90 • As adjunctive treatment to L-dopa, REQUIP XL enhances the efficacy of L-dopa,  
91 including control of 'on-off' fluctuations and 'end-of-dose' effects associated with  
92 chronic L-dopa therapy and permits reduction in daily L-dopa dose.

93

**94 CONTRA-INDICATIONS:**

95 Hypersensitivity to ropinirole or to any of the excipients.

96 Pregnancy and lactation.

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97 Severe renal impairment, except when on haemodialysis.

98

99 **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.**

100

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

104

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

111

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

117

118 **Symptomatic hypotension:** Dopamine agonists such as REQUIP XL appear to impair  
119 the systemic regulation of blood pressure, with resulting postural hypotension, especially  
120 during dose escalation. Parkinson's disease patients, in addition, appear to have an  
121 impaired capacity to respond to a postural challenge. Parkinson's patients being treated  
122 with REQUIP XL therefore require careful monitoring for signs and symptoms of  
123 postural hypotension, especially during dose escalation and should be informed of this  
124 risk (see WARNINGS AND SPECIAL PRECAUTIONS).

125

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

133

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

136

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

140

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

143

144 **Psychotic disorders:** Patients with major psychotic disorders should only be treated  
145 with dopamine agonists if the potential benefits outweigh the risks (see also  
146 INTERACTIONS).

147

148 **Events reported with dopaminergic therapy:**

149 ***Withdrawal emergent hyperpyrexia and confusion:*** Although not reported with  
150 REQUIP XL, a symptom complex resembling the neuroleptic syndrome

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151 (characterized by elevated temperature, muscular rigidity, altered consciousness and  
152 autonomic instability) with no other obvious etiology has been reported in association  
153 with rapid dose reduction, withdrawal of, or changes in anti-Parkinsonian therapy.

154

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

162

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

167

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

172

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

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

177

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

182

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

186

187 **INTERACTIONS:**

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

191 No pharmacokinetic interaction has been seen between REQUIP XL and L-dopa or  
192 domperidone, which would necessitate dosage adjustment of either medicine. No  
193 interaction has been seen between ropinirole and other medicines commonly used to  
194 treat Parkinson's disease.

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

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

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

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

208

**209 PREGNANCY AND LACTATION:**

210 REQUIP XL should not be used during pregnancy and lactation.

211

**212 DOSAGE AND DIRECTIONS FOR USE:**

213 Individual dose titration against efficacy and tolerability is recommended.

214 REQUIP XL tablets should be taken as a single daily dose and should be taken at a  
 215 similar time each day. The tablet(s) must be swallowed whole and must not be chewed,  
 216 crushed or divided. REQUIP XL tablets may be taken with or without food.

217

**218 Treatment initiation:**

219 The dose should be titrated according to the individual clinical response.

220 The recommended initial dose is 2 mg once daily for one week. A guide for the titration  
 221 regimen for the first four weeks of treatment is given in the table below:

Week			
1	2	3	4

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Total daily dosage (mg)	2	4	6	8
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222

223 **Therapeutic regimen:**

224 If sufficient symptomatic control is not achieved or maintained after the initial titration  
 225 period, as described above, the daily dose may then be increased by increments of up  
 226 to 4 mg once every one to two weeks, as necessary. The dose may be adjusted  
 227 depending on the therapeutic response. The dose may be increased up to a maximum  
 228 of 24 mg once daily.

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

230 When REQUIP XL tablets are given as adjunct therapy to L-dopa, it may be possible to  
 231 reduce gradually the L-dopa dose, depending on the clinical response. In clinical trials,  
 232 the L-dopa dose was reduced gradually by approximately 30 % in patients receiving  
 233 REQUIP XL tablets concurrently.

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

236 In clinical trials it was shown that a reduction of the L-dopa dose may ameliorate  
 237 dyskinesia (see WARNINGS AND SPECIAL PRECAUTIONS).

238 REQUIP XL should be discontinued gradually by reducing the daily dose over the period  
 239 of one week.

240 If treatment is interrupted for one day or more, re-initiation by dose titration should be  
 241 considered (see above).

242

243 **Switching from REQUIP tablets to REQUIP XL tablets:**

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

247 The table below shows the recommended dose of REQUIP XL tablets for patients  
 248 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

249  
 250 After switching to REQUIP XL tablets, the dose may be adjusted depending on the  
 251 therapeutic response (see 'Treatment initiation' and 'Therapeutic regimen' above).

252

**253 *Switching from other dopamine agonists to REQUIP:***

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

257

**258 *When stopping REQUIP XL:***

259 REQUIP XL should be discontinued gradually by reducing the number of daily doses  
 260 over the period of one week.

261

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262 **Children and Adolescents:** The safety and efficacy of REQUIP XL has not been  
263 established in patients under 18 years of age. Therefore REQUIP XL is not  
264 recommended for use in patients within this age group.

265

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

268

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

271 A study into the use of REQUIP XL in patients with end stage renal disease (patients on  
272 haemodialysis) has shown that a dose adjustment in these patients is required as  
273 follows:

- 274 - The recommended initial dose of REQUIP XL is 2 mg once daily. Further dose  
275 escalations should be based on tolerability and efficacy. The recommended  
276 maximum dose is 18 mg/day in patients receiving regular dialysis. Supplemental  
277 doses after dialysis are not required.

278 The use of REQUIP XL in patients with severe renal impairment (creatinine clearance  
279 less than 30 ml/min) without regular dialysis has not been studied (see CONTRA-  
280 INDICATIONS).

281

**282 Hepatic Impairment:**

283 The use of REQUIP XL in patients with hepatic impairment has not been studied,  
284 administration of REQUIP XL to such patients is not recommended.

285

**286 SIDE EFFECTS:**

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287 During the pre-marketing development of REQUIP, patients received REQUIP either  
 288 without L-dopa (early Parkinson’s disease studies) or as concomitant therapy with L-  
 289 dopa (advanced Parkinson’s disease studies). Because these two populations may have  
 290 differential risks for various adverse events, the adverse events for the two populations  
 291 have been separated.

292 Adverse events are listed below by system organ class and frequency. Frequencies are  
 293 defined as: very common ( $\geq 1/10$ ), common ( $\geq 1/100$ ,  $< 1/10$ ), uncommon ( $\geq 1/1\ 000$ ,  
 294  $< 1/100$ ), rare ( $\geq 1/10\ 000$ ,  $< 1/1\ 000$ ) very rare ( $< 1/10\ 000$ ), including isolated reports.

295 Unless otherwise indicated, the data in the following table was observed with both  
 296 REQUIP and REQUIP XL formulations.

297

298 **Clinical trial data:**

	Use in Monotherapy Studies	Use in Adjunct Therapy Studies
<b>Psychiatric disorders</b> common	hallucinations	confusion, hallucinations <sup>1</sup>
<b>Nervous system disorders</b> very common common	somnolence, syncope <sup>1</sup> dizziness, including vertigo <sup>2</sup>	dyskinesia <sup>3</sup> somnolence <sup>2</sup> , dizziness (including vertigo)
<b>Vascular disorders</b> common uncommon	postural hypotension <sup>2</sup> , hypotension <sup>2</sup>	postural hypotension <sup>2</sup> , hypotension <sup>2</sup>
<b>Gastrointestinal disorders</b> very common common	nausea abdominal pain <sup>1</sup> , vomiting <sup>1</sup> , dyspepsia <sup>1</sup> , constipation <sup>2</sup>	nausea, constipation <sup>2</sup>

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	Use in Monotherapy Studies	Use in Adjunct Therapy Studies
<p><b>General disorders and administrative site conditions</b></p> <p>common</p>	oedema peripheral (including leg oedema)	oedema peripheral <sup>2</sup>

- 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).

299

300 **Post-marketing data:**

301 **Immune system disorders:** hypersensitivity reactions (including urticaria, angioedema,  
302 rash, pruritus)

303 **Psychiatric disorders:** psychotic reactions (other than hallucinations) including  
304 delusion, paranoia, delirium. Impulse control symptoms, increased libido including  
305 hypersexuality, pathological gambling (see WARNINGS AND SPECIAL  
306 PRECAUTIONS)

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

308 \* Extreme somnolence and/or sudden onset of sleep may occur (see WARNINGS AND  
309 SPECIAL PRECAUTIONS). Patients experiencing this phenomenon cannot resist the  
310 urge to sleep and on waking may be unaware of any tiredness prior to the sleep.  
311 Where data are available, all such cases recovered after down-titration or withdrawal  
312 of REQUIP XL

313 **Vascular disorders:** hypotension, postural hypotension

314 Dopamine agonists such as REQUIP XL appear to impair the systemic regulation of  
315 blood pressure, with resulting postural hypotension, especially during dose escalation.

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316 Parkinson's disease patients, in addition, appear to have an impaired capacity to  
 317 respond to a postural challenge. Parkinson's patients being treated with REQUIP XL  
 318 therefore require careful monitoring for signs and symptoms of postural hypotension,  
 319 especially during dose escalation and should be informed of this risk (see WARNINGS  
 320 AND SPECIAL PRECAUTIONS).

321

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

323 The frequencies of the following adverse events listed in the following table are

324 unknown.

	Adverse events occurring in $\geq 1$ % 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)	
<b><i>Infections and infestations</i></b>	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
<b><i>Neoplasms benign, malignant and unspecified (including cysts and polyps)</i></b>	basal cell carcinoma	-	malignant breast neoplasm, bladder carcinoma, benign brain neoplasm, esophageal carcinoma, lipoma, rectal carcinoma, uterine neoplasm, uraemia, (malignant) laryngeal neoplasm
<b><i>Blood and lymphatic system disorders</i></b>	-	-	thrombocytopenia, hypochromic anaemia, eosinophilia, leukocytosis, leukopenia, lymphocytosis, lymphopenia
<b><i>Endocrine disorders</i></b>	-	-	hypothyroidism, hyperthyroidism, goiter, SIADH
<b><i>Metabolism and nutrition disorders</i></b>	hyperglycaemia, gout	-	hypoglycaemia, hyperphosphataemia, hyperuricaemia, diabetes mellitus, hypokalaemia, hypercholesterolaemia, hyperkalaemia, acidosis, hyponatraemia, dehydration, vitamin B12 deficiency, hypochloroemia
<b><i>Psychiatric disorders</i></b>	confusion, hallucinations,	insomnia, hallucinations,	dysphoria, increased libido, agitation, apathy, depersonalization, paranoid

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	<b>Adverse events occurring in ≥1 % Parkinson's disease patients in REQUIP clinical trials</b>		<b>Adverse events occurring in &lt;1 % patients in all clinical trials</b>
	<b>Early Parkinson's Disease (without L-dopa)</b>	<b>Advanced Parkinson's Disease (with L-dopa)</b>	
	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
<b><i>Nervous system disorders</i></b>	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
<b><i>Eye disorders</i></b>	abnormal vision	-	abnormal lacrimation, conjunctivitis, blepharitis, glaucoma, abnormal accommodation, blepharospasm, eye pain, photophobia, scotoma
<b><i>Ear and labyrinth disorders</i></b>	-	vertigo, tinnitus	tinnitus, earache, decreased hearing
<b><i>Cardiac disorders</i></b>	bradycardia	myocardial infarction	cardiac failure, bradycardia, tachycardia, supraventricular tachycardia, angina pectoris, bundle branch block, cardiac arrest, cardiomegaly, mitral insufficiency, ventricular tachycardia
<b><i>Vascular disorders</i></b>	hot flushes, orthostatic symptoms	orthostatic symptoms, hot flushes	aneurysm, varicose veins, phlebitis, peripheral gangrene, haematoma, limb embolism, gangrene, deep thrombophlebitis, leg thrombophlebitis, thrombosis, lymphoedema
<b><i>Respiratory, thoracic and mediastinal</i></b>	cough	-	hiccups, asthma, epistaxis, pleurisy, pulmonary oedema, pulmonary embolism
<b><i>Gastrointestinal disorders</i></b>	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, peridontitis, 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,

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	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)	
<b>Hepatobiliary disorders</b>	-	-	bilirubinaemia, cholecystitis, cholelithiasis, biliary pain
<b>Skin and subcutaneous tissue disorders</b>	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
<b>Musculoskeletal and connective tissue disorders</b>	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)
<b>Renal and urinary disorders</b>	haematuria	haematuria	glycosuria, dysuria, micturition frequency, albuminuria, nocturia, polyuria, renal calculus, acute renal failure
<b>Reproductive system and breast disorders</b>	-	-	gynaecomastia, amenorrhoea, vaginal haemorrhage, penile (penis) disorder, prostatic disorder, balanoposthitis, epididymitis, perineal pain, breast enlargement, uterine haemorrhage, ejaculation disorder, Peyronie's disease
<b>General disorders and administrative site conditions</b>	fatigue, pain, asthaenia, leg oedema, rigors	pain, asthenia, fatigue, chest pain, leg oedema, abnormal gait	peripheral oedema, fever, influenza-like symptoms, generalized oedema, thirst
<b>Investigations</b>	weight loss	increased drug level	increased hepatic enzymes, increased BUN, increased alkaline phosphatase, increased LDH, weight increased, increased CPK
<b>Injury, poisoning and procedural complications</b>	falls	injury, falls	-

325

**326 KNOWN SYMPTOMS OF OVERDOSAGE AND PARTICULARS OF ITS TREATMENT:**

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

330

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331 **IDENTIFICATION:**

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

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

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

338

339 **PRESENTATION:**

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

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

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

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

354

355 **STORAGE INSTRUCTIONS:**

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356 Store at or below 25 °C. Store in original package.

357 Keep out of reach of children.

358

**359 REGISTRATION NUMBER:**

360 REQUIP XL 2 mg: 41/5.4.1/0604

361 REQUIP XL 4 mg: 41/5.4.1/0606

362 REQUIP XL 8 mg: 41/5.4.1/0607

363

**364 NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF**

**365 REGISTRATION:**

366 GlaxoSmithKline South Africa (Pty) Ltd

367 39 Hawkins Avenue

368 Epping Industria 1, 7460

369

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

371 Last approval: 01 March 2013

372 Date compliant with Regulation 11: 02 February 2016

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**374 History:**

375

376 Proposed: 15 March 2006 (Inclusion of Prolonged-release tablets for Parkinson's disease)

377 Amended: 10 August 2007 (in-line with CCC recommendations dated 26/04/2007)

378 Amended: 24 January 2008 (in line with CCC recommendations dated 14/12/2007)

379 Amended: 25 March 2008 (new proprietary name proposed for prolonged release tablets – REQUIP XL)

380 Amended: 31 March 2008 (response to CCC recommendations dated 22/02/2008) – compliant pi

381 Amended: 21 April 2009 (In line with GCT versions 17, 19 - 21)

382 Amended: 2 February 2010 (Correction of spelling errors as highlighted in CCC recommendation 13 August 2009 for RLS) – Included as Attachment 1

383 Amended: 05 October 2010 (in response to CCC recommendations dated 27/07/2010 – Response D2010-4334)

384 Amended: 28-07-2010 Cape town address details reflected

385 Amended: 04 October 2012 (compliant response to CCC recommendations dated 05/09/2012) Approved: 01 March 2013

386 Amended: 30 April 2013 (applicant address to CT, amendment to blister material)

387 Amended: 02 February 2016 (Implementation of Regulation 9 and 10)

388

389

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

392