

GLAXOSMITHKLINE SOUTH AFRICA (PTY) LIMITED	Submission Date	20 Feb 2018	Type &	Clinical: Reg 9/10
KEPPRA 100 MG	Implementation Date	21 Feb 2018	Category	(11/12) notification
EACH 1,0 ML SOLUTION CONTAINS: LEVETIRACETAM 100,0 MG			Reference	v0003

CONFIDENTIAL

### 1.3.1.1 Package Insert

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3

## KEPPRA Oral Solution

### 4 SCHEDULING STATUS:

5 S3

6

### 7 PROPRIETARY NAME AND DOSAGE FORM:

8 **KEPPRA® 100 mg** oral solution

9

### 10 COMPOSITION:

11 KEPPRA 100 mg oral solution contains 100 mg levetiracetam per milliliter.

12 Preservatives: methylparahydroxybenzoate 0,027 % *m/v* and propylparahydroxybenzoate  
13 0,003 % *m/v*.

14 Contains sugar (as maltitol 300 mg/ml).

15 Contains sweetener (as acesulfame potassium 4,50 mg/ml)

16 **Excipients:** The oral solution also contains sodium citrate, citric acid monohydrate,  
17 ammonium glycyrrhizate, glycerol, grape flavour and purified water.

18

### 19 PHARMACOLOGICAL CLASSIFICATION:

20 A 2.5 Anticonvulsants, including anti-epileptics

21

### 22 PHARMACOLOGICAL ACTION:

#### 23 Pharmacodynamic properties:

24 Levetiracetam has anticonvulsant properties.

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---

25 The active substance, levetiracetam, is a pyrrolidone derivative (S-enantiomer of  $\alpha$ -ethyl-2-  
26 oxo-1-pyrrolidine acetamide), chemically unrelated to existing antiepileptic active  
27 substances.

28 The precise mechanism of action by which levetiracetam induces seizure protection is  
29 unknown. *In vitro* and *in vivo* experiments suggest that levetiracetam does not alter basic cell  
30 characteristics and normal neurotransmission.

31 The mechanism of action may relate to an interaction with a specific and stereoselective  
32 binding site that is only found within the central nervous system.

33

#### 34 **Pharmacokinetic properties:**

35 The pharmacokinetic profile is dose linear with low intra- and inter-subject variability. There  
36 is no evidence for any relevant gender, race or circadian variability. The pharmacokinetic  
37 profile is comparable in healthy volunteers and in patients with epilepsy.

38 A significant correlation between saliva and plasma concentrations has been shown in  
39 adults and children (ratio of saliva/plasma concentrations ranged from 1 to 1,7 for oral tablet  
40 and after 4 hours post-dose for oral solution formulation).

41

42 **Absorption:** Levetiracetam is rapidly absorbed after oral administration. Oral absolute  
43 bioavailability is close to 100 %. Peak plasma concentrations ( $C_{max}$ ) are achieved at 1,3  
44 hours after dosing.

45 Steady-state is achieved after two days of a twice daily administration schedule. Peak  
46 concentrations ( $C_{max}$ ) are typically 31 and 43  $\mu$ g/ml following a single 1 000 mg dose and  
47 repeated 1 000 mg twice daily dose, respectively. The extent of absorption is dose-  
48 independent and is not altered by food.

49

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---

50 **Distribution:** No tissue distribution data are available in humans. Neither levetiracetam nor  
51 its major metabolite ucb L057 are significantly bound to plasma proteins (< 10 %). The  
52 volume of distribution of levetiracetam is approximately 0,5 to 0,7 l/kg, a value close to the  
53 volume of distribution of intracellular and extracellular water.

54

55 **Metabolism:** The major metabolic pathway (24 % of the dose) is an enzymatic hydrolysis of  
56 the acetamide group. Production of this metabolite, ucb L057, is not supported by the liver  
57 cytochrome P450 isoforms. Hydrolysis of the acetamide group was measurable in a large  
58 number of tissues including whole blood but not plasma.

59 Two minor metabolites were also identified. One was obtained by hydroxylation of the  
60 pyrrolidone ring (1,6 % of the dose) and the other one by opening of the pyrrolidone ring  
61 (0,9 % of the dose). Other unidentified components accounted only for 0,6 % of the dose.  
62 No enantiomeric interconversion was evidenced *in vivo* for either levetiracetam or its major  
63 metabolite ucb L057.

64

### 65 **Elimination:**

66 The plasma half-life in adults was 7±1 hour and did not vary with dose, route of  
67 administration or repeated administration. The total body clearance was a mean of  
68 0,96 ml/min/kg.

69 The major route of excretion was via urine, accounting for a mean 95 % of the dose  
70 (approximately 93 % of the dose was excreted within 48 hours). Excretion via faeces  
71 accounted for only 0,3 % of the dose.

72 The cumulative urinary excretion of levetiracetam and its major metabolite accounted for  
73 66 % and 24 % of the dose, respectively during the first 48 hours.

74 The renal clearance of levetiracetam and ucb L057 is 0,6 and 4,2 ml/min/kg respectively  
75 indicating that levetiracetam is excreted by glomerular filtration with subsequent tubular re-

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---

76 absorption and that ucb L057 is also excreted by active tubular secretion in addition to  
77 glomerular filtration.

78

79 **Elderly:** In the elderly, the half-life is increased by about 40 % (10 to 11 hours). This is  
80 related to the decrease in renal function in this population.

81

82 **Children (4 to 12 years):** Following single dose administration (20 mg/kg) to epileptic  
83 children, the half-life of levetiracetam was 6,0 hours. The apparent clearance was  
84 1,43 ml/min/kg.

85 Following repeated oral dose administration (20 to 60 mg/kg/day) to epileptic children (4 to  
86 12 years), levetiracetam was rapidly absorbed. Peak plasma concentration was observed  
87 0,5 to 1,0 hour after dosing. Linear and dose proportional increases were observed for peak  
88 plasma concentrations and area under the curve. The elimination half-life was approximately  
89 5 hours. The apparent body clearance was 1,1 ml/min/kg.

90

91 **Infants and children (1 month to 4 years):** Following single dose administration (20 mg/kg)  
92 of a 10 % oral solution to epileptic children (1 month to 4 years), levetiracetam was rapidly  
93 absorbed and peak plasma concentrations were observed approximately 1 hour after  
94 dosing. The pharmacokinetic results indicated that half-life was shorter (5,3 hours) than for  
95 adults (7,2 hours) and apparent clearance was faster (1,5 ml/min/kg) than for adults  
96 (0,96 ml/min/kg). Based on this study, elimination in infants less than 6 months may be  
97 reduced by 30 %.

98 The exposure to the major metabolite, was lower in children than in adults.

99

100 **Renal impairment:** The apparent body clearance of both levetiracetam and of its metabolite  
101 ucb L057 is correlated to the creatinine clearance. It is therefore recommended to adjust the

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---

102 maintenance daily dose of levetiracetam, based on creatinine clearance in patients with  
103 moderate and severe renal impairment (see DOSAGE AND DIRECTIONS FOR USE).  
104 In anuric end-stage renal disease adult subjects, the half-life was approximately 25 and  
105 3,1 hours during interdialytic and intradialytic periods respectively. The fractional removal of  
106 levetiracetam was 51 % during a typical 4-hour dialysis session.

107

108 **Hepatic Impairment:** In subjects with mild and moderate hepatic impairment, there was no  
109 relevant modification of the clearance of levetiracetam. In most subjects with severe hepatic  
110 impairment, the clearance of levetiracetam was reduced by more than 50 % due to a  
111 concomitant renal impairment (see DOSAGE AND DIRECTIONS FOR USE).

112

#### 113 **INDICATIONS:**

114 KEPPRA is indicated as adjunctive therapy in the treatment of partial onset seizures with or  
115 without secondary generalization in adults and children from 4 years of age with epilepsy.

116

#### 117 **CONTRA-INDICATIONS:**

118 Hypersensitivity to levetiracetam or other pyrrolidone derivatives or any of the excipients.  
119 Patients with rare hereditary problems of fructose intolerance should not take KEPPRA oral  
120 solution.

121 The use of KEPPRA is contra-indicated in pregnancy and lactation (see PREGNANCY AND  
122 LACTATION).

123

#### 124 **WARNINGS AND SPECIAL PRECAUTIONS:**

125 Due to its complete and linear absorption, plasma levels can be predicted from the oral dose  
126 of levetiracetam expressed as mg/kg bodyweight. Therefore, there is no need for plasma  
127 level monitoring of levetiracetam.

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---

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129 **Discontinuation:** If KEPPRA has to be discontinued, it is recommended to withdraw it  
130 gradually (e.g. 500 mg twice daily decrements every two to four weeks in adults: 10 mg/kg  
131 twice daily decrements every two weeks in children).

132

133 **Seizure frequency:** An increase in seizure frequency of more than 25 % was reported in  
134 14 % of KEPPRA treated adult and paediatric patients, whereas it was reported in 26 % and  
135 21 % of placebo treated adult and paediatric patients, respectively.

136

137 **Renal insufficiency:** The administration of KEPPRA to patients with renal impairment may  
138 require dose adaptation. In patients with severely impaired hepatic function, assessment of  
139 renal function is recommended before dose selection (see DOSAGE AND DIRECTIONS  
140 FOR USE).

141

142 **Suicide:** Suicide, suicide attempt and suicidal ideation have been reported in patients  
143 treated with KEPPRA. Patients should be advised to immediately report any symptoms of  
144 depression and/or suicidal ideation to their prescribing physician.

145

146 **Effects on ability to drive and use machines:** No studies on the effect on the ability to  
147 drive and use machines have been performed. Patients might experience somnolence or  
148 other CNS related symptoms. Therefore, caution is recommended in those patients when  
149 performing skilled tasks, e.g. driving vehicles or operating machinery.

150

151 **Excipients:** Among its excipients, KEPPRA oral solution includes glycerol which can cause  
152 headache, stomach upset and diarrhoea and maltitol which has a mild laxative effect.

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CONFIDENTIAL

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153 Patients with rare hereditary condition of sorbitol/maltitol/lactitol intolerance should not take  
 154 KEPPRA oral solution.

155

**156 INTERACTIONS:**

**157 Antiepileptic medicines:**

158 Data indicate that KEPPRA did not influence the serum concentration of existing  
 159 antiepileptic medicines (phenytoin, carbamazepine, valproic acid, phenobarbital, lamotrigine,  
 160 gabapentin and primidone) and that these antiepileptic medicines did not influence the  
 161 pharmacokinetics of KEPPRA.

162 As in adults, there is no clear evidence of clinically significant medicinal product interactions  
 163 in paediatric patients receiving up to 60 mg/kg/day KEPPRA.

164 A retrospective assessment of pharmacokinetic interactions in children and adolescents with  
 165 epilepsy (4 to 17 years) showed that adjunctive therapy with KEPPRA did not significantly  
 166 influence the steady state serum concentrations of concomitantly administered  
 167 carbamazepine and valproate. A similar finding was observed for topiramate and  
 168 lamotrigine. However, data suggested a 22 % higher levetiracetam clearance in children  
 169 taking enzyme-inducing antiepileptic medicinal products. Dosage adjustment is not required.

170

**171 Probenecid:**

172 Probenecid (500 mg four times daily), a renal tubular secretion blocking agent, has been  
 173 shown to inhibit the renal clearance of the primary metabolite but not of levetiracetam.

174 Nevertheless, the concentration of this metabolite remains low.

175 It is expected that medicines excreted by active tubular secretion could reduce the renal  
 176 clearance of the metabolite. The effect of KEPPRA on probenecid and other actively  
 177 secreted medicine like NSAIDs, sulphonamides and methotrexate, is unknown.

178

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CONFIDENTIAL

### 1.3.1.1 Package Insert

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#### 179 **Oral contraceptives and other pharmacokinetic interactions:**

180 KEPPRA 1 000 mg daily did not influence the pharmacokinetics of oral contraceptives  
181 (ethinyl oestradiol and levonorgestrel); endocrine parameters (luteinising hormone and  
182 progesterone) were not modified. KEPPRA 2 000 mg daily did not influence the  
183 pharmacokinetics of digoxin and warfarin; prothrombin times were not modified. Co-  
184 administration with digoxin, oral contraceptives and warfarin did not influence the  
185 pharmacokinetics of levetiracetam.

186

#### 187 **Antacids:**

188 No data on the influence of antacids on the absorption of KEPPRA are available.

189

#### 190 **Food and alcohol:**

191 The extent of absorption of KEPPRA was not altered by food, but the rate of absorption was  
192 slightly reduced. No data on the interaction of KEPPRA with alcohol are available.

193

#### 194 **PREGNANCY AND LACTATION:**

195 There is no adequate information on the use of KEPPRA during pregnancy. Studies in  
196 animals have shown reproductive toxicity. The potential risk for humans is unknown (see  
197 CONTRA-INDICATIONS).

198 Physiological changes during pregnancy may affect levetiracetam concentration. There have  
199 been reports of decreased levetiracetam concentration during pregnancy.

200 Safety in breastfeeding has not been established. Levetiracetam is excreted in human breast  
201 milk. Patients using KEPPRA should not breastfeed their babies (see CONTRA-  
202 INDICATIONS).

203

#### 204 **DOSAGE AND DIRECTIONS FOR USE:**

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CONFIDENTIAL

### 1.3.1.1 Package Insert

205 The oral solution may be diluted in a glass of water and may be taken with or without food. A  
 206 graduated oral syringe and instructions for use in the patient information leaflet are provided  
 207 with the oral solution. The daily dose is administered in two equal divided doses.  
 208

#### 209 **Adults (> 18 years) and adolescents (12 to 17 years):**

210 As adjunctive therapy, the initial therapeutic dose is 500 mg twice daily. This dose can be  
 211 started on the first day of treatment. Depending upon the clinical response and tolerance,  
 212 the daily dose can be increased up to 1 500 mg twice daily. Dose changes can be made in  
 213 500 mg twice daily increments or decrements every two to four weeks. The maximum daily  
 214 dose is 3 000 mg.  
 215

#### 216 **Elderly (65 years and older):**

217 Adjustment of the dose is recommended in elderly patients with compromised renal function  
 218 (see 'Patients with renal impairment' below).  
 219

#### 220 **Children aged 4 to 11 years:**

221 The initial dose is 10 mg/kg twice daily. This dose can be started on the first day of  
 222 treatment.

223 Depending upon the clinical response and tolerance, the daily dose can be increased up to  
 224 30 mg/kg twice daily. Dose changes can be made in 10 mg/kg twice daily increments or  
 225 decrements every two weeks. Dosage in children 50 kg or greater is the same as in adults.

#### **Recommended dosage for children and adolescents with normal renal function.**

<b>Weight</b>	<b>Starting dose 10 mg/kg twice daily</b>	<b>Maximum dose 30 mg/kg twice daily</b>
15 kg <sup>(1)</sup>	150 mg twice daily	450 mg twice daily
20 kg <sup>(1)</sup>	200 mg twice daily	600 mg twice daily
25 kg	250 mg twice daily	750 mg twice daily
From 50 kg <sup>(2)</sup>	500 mg twice daily	1 500 mg twice daily

<sup>(1)</sup> Children 20 kg or less should preferably start treatment with a levetiracetam 100 mg/ml oral solution.

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CONFIDENTIAL

**1.3.1.1 Package Insert**

<sup>(2)</sup> Dosage in children and adolescents 50 kg or more is the same as in adults. The graduated syringe contains up to 1 000 mg levetiracetam (corresponding to 10 ml) with a graduation every 25 mg (corresponding to 0,25 ml).

226

**227 Infants and children less than 4 years:**

228 There is insufficient data to recommend the use of KEPPRA in children under 4 years of  
229 age.

230

**231 Patients with renal impairment:**

232 The KEPPRA daily dose must be individualised according to renal function.

233 For adult patients refer to the following table and adjust the dose as indicated. To use this  
234 dosing table, an estimate of the patient's creatinine clearance (Clcr) in ml/min is needed. The

235 Clcr may be estimated from serum creatinine (mg/dl) determination using the following  
236 formula:

237

238 Then Clcr for children is adjusted for body surface area (BSA) as follows:

239 
$$\text{Clcr} = \frac{[140 - \text{age (years)} \times \text{weight (kg)}]}{\text{serum creatinine } (\mu\text{mol/l})} \times 0,85 \text{ (for women)}$$

240  
241  
242

243 
$$\text{Clcr (ml/min/1,73m}^2) = \frac{\text{Clcr (ml/min)}}{\text{BSA subject (m}^2)} \times 1,73$$

244  
245

246

**247 Dosing adjustment for adult patients with impaired renal function.**

Group	Creatinine clearance (ml/min)	Dosage and frequency
Normal	> 80	500 to 1 500 mg twice daily
Mild	50-79	500 to 1 000 mg twice daily
Moderate	30-49	250 to 750 mg twice daily
Severe	< 30	250 to 500 mg twice daily
End-stage renal disease patients undergoing dialysis <sup>(1)</sup>	-	500 to 1 000 mg once daily <sup>(2)</sup>

248 (1) A 750 mg loading dose is recommended on the first day of treatment with levetiracetam.

249 (2) Following dialysis, a 250 mg to 500 mg supplemental dose is recommended.

250

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CONFIDENTIAL

**1.3.1.1 Package Insert**

**251 Patients with hepatic impairment:**

252 No dose adjustment is needed in patients with mild to moderate hepatic impairment. In  
 253 patients with severe hepatic impairment, the creatinine clearance may underestimate the  
 254 renal insufficiency. Therefore a 50 % reduction of the daily maintenance dose is  
 255 recommended when the creatinine clearance is < 70 ml/min.

256

**257 SIDE EFFECTS:**

258 The most commonly reported side effects are somnolence, asthenia and dizziness.  
 259 The most commonly reported undesirable effects were somnolence, hostility, nervousness,  
 260 emotional lability, agitation, anorexia, asthenia and headache in the paediatric population.  
 261 Safety results in paediatric patients were consistent with the safety profile of KEPPRA in  
 262 adults.

263

**264 Clinical trial data:**

265 Undesirable effects reported in clinical studies (adults and children), the frequency is defined  
 266 as follows:

267 Very common ( $\geq 1/10$ )

268 Common ( $\geq 1/100$  to  $< 1/10$ )

269 Uncommon ( $\geq 1/1\ 000$  to  $< 1/100$ )

270 Rare ( $\geq 1/10\ 000$  to  $< 1/1\ 000$ )

271 Very rare ( $< 1/10\ 000$ ), including isolated reports, not known (cannot be estimated on  
 272 available data).

System Organ Class	Frequency	Side-effect
Infections and infestations	Common	infection, nasopharyngitis
Blood and lymphatic system disorders	Common	thrombocytopenia

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CONFIDENTIAL

**1.3.1.1 Package Insert**

Metabolism and nutrition disorders	Common	anorexia, weight increase The risk of anorexia is higher when topiramate is co-administered with KEPPRA
Psychiatric disorders	Common	aggression, agitation, depression, emotional lability/mood swings, hostility, insomnia, irritability, nervousness, personality disorders, abnormal thinking
Nervous system disorders	Very common Common	somnolence/fatigue amnesia, ataxia, convulsion, dizziness, headache, hyperkinesia, tremour, balance disorder, disturbance in attention, memory impairment
Eye disorders	Common	diplopia, blurred vision
Ear and labyrinth disorders	Common	vertigo
Respiratory, thoracic and mediastinal disorders	Common	cough increased
Gastrointestinal disorders	Common	abdominal pain, diarrhoea, dyspepsia, nausea, vomiting
Skin and subcutaneous tissue disorders	Common	eczema, pruritus, rash
Musculoskeletal, connective tissue and bone disorders	Common	myalgia
General disorders and administrative site conditions	Very common	asthenia
Injury and poisoning	Common	accidental injury

273

**274 Post marketing data:**

275 In addition to adverse events reported during clinical studies, and listed above, the following  
276 adverse events have been reported in post-marketing experience. Data are insufficient to  
277 support an estimate of their incidence in the population to be treated.

**278 Nervous system disorders: paraesthesia**

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CONFIDENTIAL

### 1.3.1.1 Package Insert

279 **Psychiatric disorders:** abnormal behaviour, anger, anxiety, confusion, hallucination,  
280 psychotic disorder, suicide, suicide attempt and suicide ideation

281 **Gastrointestinal disorders:** pancreatitis

282 **Hepatobiliary disorders:** hepatic failure, hepatitis, liver function test abnormal

283 **Metabolism and nutritional disorders:** weight loss

284 **Skin and subcutaneous tissue disorders:** toxic epidermal necrolysis, Stevens-Johnson  
285 syndrome, erythema multiforme and alopecia

286 **Blood and lymphatic system disorders:** leucopenia, neutropenia, pancytopenia (with bone  
287 marrow suppression identified in some of the cases).

288

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

290 There is no experience with doses greater than 5 000 mg/day orally. No serious adverse  
291 events were reported by healthy volunteers at single doses up to and including 5 000 mg  
292 orally. Symptoms of overdose: somnolence, agitation, depressed level of consciousness,  
293 respiratory depression and coma. In acute, significant overdose, the stomach may be  
294 emptied by gastric lavage or by induction of emesis. There is no specific antidote for  
295 levetiracetam. Treatment for an overdose will be symptomatic and may include  
296 haemodialysis. The dialyser extraction efficiency is 60 % for levetiracetam and 74 % for the  
297 metabolite ucb L057.

298

### 299 **IDENTIFICATION:**

300 Clear, colourless solution with grape flavour.

301

### 302 **PRESENTATION:**

303 KEPPRA 100 mg oral solution is supplied in a 300 ml amber glass bottle with a white  
304 polypropylene, child-resistant closure. It is packed in a cardboard box and may or may not

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CONFIDENTIAL

**1.3.1.1 Package Insert**

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305 contain a 10 ml graduated syringe made of polyethylene with a polystyrene piston and an  
306 adaptor for the syringe.

307

**308 STORAGE INSTRUCTIONS:**

309 Store at or below 30 °C.

310 Due to sensitivity to light, store in the original container.

311 KEEP OUT OF REACH OF CHILDREN.

312

**313 REGISTRATION NUMBER:**

314 A40/2.5/0587

315

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

**317 REGISTRATION:**

318 GlaxoSmithKline South Africa (Pty) Ltd

319 39 Hawkins Avenue

320 Epping Industria 1, 7460

321

**322 DATE OF PUBLICATION OF THIS PACKAGE INSERT:**

323 Registration date: 09 October 2009

324 Revision approval date: 11 October 2013

325 Date of implementation of Regulation 11: 21 February 2018

326

PDS-04

Namibia Reg No. 07/2.5/0086 NS2

Botswana Reg No. BOT1402618 S2

327

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**328 Manufacturer:**

329 NextPharma SAS

330 17, Route de Meulan

331 78520 Limay, France

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**333 HISTORY:**

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334 Approved October 2009

335 Amended: 19/04/2010 (Transfer of applicancy to GSK). Approved 11 November 2010

336 Amended: 12 April 2011: in-line with PDS04

337 Amended: 16 January 2013 (in line with CCC recommendations dated 17/08/2012) – annotated

338 Amended: 06 June 2013 (in line with CCC recommendations dated 08/04/2013) – clean

339 Amended: 06 August 2013 (in response to CCC recommendations dated 30/07/2013). **Approved 11 October 2013**

340 Amended: 19 January 2012 (CMC - D2011-3869 – inclusion of adaptor). **Approved 10 Jun 2014**

341 Amended: 18 July 2016 (CMC – Type: B4a; D2014-8015.v0002 – CTD rebaseline dossier). Implemented 16-08-2016

342

343 **Amended: 20 Feb 2018 (to bring in line with Regulation 11 and 12 of Act 101/1965 as amended). Implemented 21-**

344 **Feb-2018**

345