1.3.1.1 Professional Information for Medicines for Human Use approved

LINE NO		REFERENCE
1.	**SCHEDULING STATUS**	
2.	**S4**	
3.		
4.	**1. NAME OF THE MEDICINE**	**As requested**
5.	ROLIXIRD 450 MG 450 mg film coated tablets.	**by SAHPRA**
6.	Strength: Each Film-coated tablet contains 450 mg valganciclovir	
7.	Pharmaceutical form: Film-coated Tablets	
8.		
9.	**2. QUALITATIVE AND QUANTITATIVE COMPOSITION**	
10.	ROLIXIRD 450 MG 450 mg film coated tablets :	
11.	Each film coated tablet contains 496.36 mg of Valganciclovir	
12.	hydrochloride equivalent to 450 mg of valganciclovir.	
13.	Sugar-free,	
14.	For full list of excipients, see section 6.1.	
15.		
16.	**3. PHARMACEUTICAL FORM**	
17.	ROLIXIRD 450 MG 450 mg film coated Tablets:	
18.	Pink colored, oval shaped biconvex, film-coated tablets, debossed with	
19.	‘H’ on one side and ‘96’ on other side.	
20.		
21	**4. CLINICAL PARTICULARS**	
22.	**4.1. Therapeutic indications**	

23. 24. 25. 26. 27. 28.	ROLIXIRD 450 MG is indicated for the treatment of cytomegalovirus (CMV) retinitis in acquired immunodeficiency syndrome (AIDS) patients. The prevention of CMV disease in solid organ transplant patients at risk i.e. donor seropositive and recipient seronegative.	**As requested by SAHPRA**
29.	**4.2. Posology and method of administration**	
30. 31. 32 33. 34. 35.	**Posology - Strict adherence to dosage recommendations is essential to avoid overdose.** The bioavailability of ganciclovir from ROLIXIRD 450 MG is up to 10-fold higher than from ganciclovir capsules, therefore the dosage and administration of ROLIXIRD 450 MG should be closely followed.	**As requested by SAHPRA**
36. 37. 38. 39. 40. 41. 42. 43. 44. 45. 46. 47. 48. 49.	**Treatment of cytomegalovirus (CMV) retinitis** **Standard dosage in adult patients** **Induction treatment of CMV retinitis** For patients with active CMV retinitis, the recommended dose is 900 mg ROLIXIRD 450 MG twice a day for 21 days. Prolonged induction treatment may increase the risk of bone marrow toxicity. Maintenance treatment of CMV retinitis Following induction treatment, or in patients with inactive CMV retinitis, the recommended dose is 900 mg ROLIXIRD 450 MG once daily. Patients whose retinitis worsens may repeat induction treatment; however, consideration should be given to the possibility of viral drug resistance. **Prevention of CMV disease in solid organ transplantation**	

50. 51. 52. 53. 54. 55. 56.	For kidney transplant patients, the recommended dose is 900 mg once daily depending on creatinine clearance, starting within 10 days of transplantation until 200 days post-transplantation. For patients who have received a solid organ transplant other than the kidney, the recommended dose is 900 mg once daily, starting within 10 days of transplantation until 100 days post transplantation.	
58. 59. 60. 61. 62. 63. 64. 65. 66 67. 68. 69 70. 71. 72. 73. 74. 75. 76. 77.	**Special Dosage instructions** **Patients with renal impairment** Serum creatinine levels or creatinine clearance should be monitored carefully. Dosage adjustment is required for adult patients based on creatinine clearance, as shown in tables 2 and 3 below. Creatinine clearance (mℓ/min) is calculated from serum creatinine by the following formulae: CL_{CR} (mL/min) = $\frac{(140 - age) \times (Wt\ [kg]) \times constant^*}{S_{CR}\ [\mu mol/\ell]}$ * Constant = 1,23 for males and 1,04 for females (0,85 x 1,23 = 1,04) The South African Renal Society recommends simplifying the above formula by omitting the constant of 1,23 for males CL_{CR} (mℓ/min) = $\frac{(140 - age) \times (Wt\ [kg]) \times 0{,}85\ (if\ female)}{S_{CR}\ [\mu mol/\ell]}$ CLCR = creatinine clearance SCR = serum creatinine **ROLIXIRD 450 MG 450 film-coated tablet dose for renally impaired patients**	**As requested by SAHPRA**

CrCl (mL/min)	**Induction dose of ROLIXIRD 450 MG**	**Maintenance/Prevention dose of ROLIXIRD 450**

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<table>
<tr><th></th><th>450 film-coated tablet</th><th>MG 450 film coated tablet</th></tr>
<tr><td>≥ 60</td><td>900 mg twice daily</td><td>900 mg once daily</td></tr>
<tr><td>40 – 59</td><td>450 mg twice daily</td><td>450 mg once daily</td></tr>
<tr><td>25 – 39</td><td>450 mg once daily</td><td>450 mg every 2 days</td></tr>
<tr><td>10 – 24</td><td>450 mg every 2 days (tablets)</td><td>450 mg twice weekly</td></tr>
<tr><td>< 10</td><td>Not recommended</td><td>Not recommended</td></tr>
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<td>89.
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<td>Patients undergoing haemodialysis
For patients on haemodialysis (CrCl < 10 mL/min) a dose recommendation cannot be given. Thus ROLIXIRD 450 MG film coated tablets should not be used in these patients (See sections 4.4 and 5.2).</td>
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<td>Patients with severe leucopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia Patients with severe leucopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with ROLIXIRD 450 MG and ganciclovir. Therapy should not be initiated if the absolute neutrophil count is less than 500
Cells /µℓ or the platelet count is less than 25 000/µℓ or the haemoglobin is less than 8 g/dℓ. (See section 4.4).
Elderly: Safety and efficacy have not been established.</td>
<td>As requested by SAHPRA</td>
</tr>
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105. 106. 107. 108.	**Paediatric patients:** Safety and efficacy have not been established in adequate and well- controlled clinical studies.	
109. 110. 111. 112. 113. 114. 115. 116. 117. 118. 119. 121. 122. 123. 124.	**Method of administration** ROLIXIRD 450 MG is administered orally, and should be taken with food. ROLIXIRD 450 MG is administered orally, and should be taken with food. Precautions to be taken before handling or administering the medicine The tablets should not be broken or crushed. Since Valganciclovir Teva is considered a potential teratogen and carcinogen in humans, caution should be observed in handling broken tablets (see section 4.4). Avoid direct contact of broken or crushed tablets with skin or mucous membranes. If such contact occurs, wash thoroughly with soap and water, rinse eyes thoroughly with sterile water, or plain water if sterile water is unavailable.	**As requested by SAHPRA**
125.	**4.3. Contraindications**	
126. 127. 128. 129. 130. 131.	ROLIXIRD 450 MG is contraindicated in patients with known hypersensitivity to valganciclovir, ganciclovir or to any excipient of the product. Due to the similarity of the chemical structure of ROLIXIRD 450 MG and that of aciclovir and valaciclovir, a cross-hypersensitivity reaction between these medicines is possible.	**As requested by SAHPRA**
132.	**4.4. Special warnings and precautions for use**	

133. 134. 135. 136. 137.	Porphyria. The Drug Database for Acute Porphyria, compiled by the Norwegian Porphyria Centre (NAP O S) and the Porphyria Centre Sweden, classifies valganciclovir as not porphyrinogenic; it may be used as a drug of first choice and no precautions are needed.	
138. 139. 140. 141. 142.	Women of child-bearing potential must be advised to use effective contraception during treatment. Male patients should be advised to practice barrier contraception during, and for at least 90 days following treatment with ROLIXIRD 450 MG.	**As requested by SAHPRA**
143. 144. 145. 146. 147. 148. 149. 150. 151. 152. 153. 154. 155.	Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with ROLIXIRD 450 MG and ganciclovir. Therapy should not be initiated if the absolute neutrophil count is less than 500 cells/μℓ, or the platelet count is less than 25 000/μℓ, or the haemoglobin level is less than 8 g/dℓ. When extending prophylaxis beyond 100 days the possible risk of developing leukopenia and neutropenia should be taken into account (see sections 4.2, 4.8 and 5.1). Valganciclovir should be used with caution in patients with pre-existing haematological cytopenias or a history of drug-related haematological cytopenia and in patients receiving radiotherapy.	
156. 157. 158. 159.	It is recommended that complete blood counts and platelet counts be monitored during therapy. In patients with severe leucopenia, neutropenia, anaemia and/or thrombocytopenia, it is recommended	**As requested by SAHPRA**

160. 161.	that treatment with haematopoietic growth factors and/or dose interruption be considered. (See section 4.2)	
162. 163. 164.	Safety and efficacy in children have not been established in adequate and well-controlled clinical studies. (See section 4.2)	**As requested by SAHPRA**
165. 166. 167. 168. 169. 170. 171.	The bioavailability of ganciclovir from ROLIXIRD 450 MG is up to 10- fold higher than from ganciclovir capsules. ROLIXIRD 450 MG cannot be substituted for ganciclovir capsules on a one-to-one basis. Patients switching from ganciclovir capsules should be advised of the risk of over dosage if they take more than the prescribed number of ROLIXIRD 450 MG tablets. (See section 4.2).	**As requested by SAHPRA**
172. 173. 174. 175.	In patients with impaired renal function, dosage adjustments based on creatinine clearance are required. (See section 4.2) For patients on haemodialysis (CrCl < 10 mL/min) a tablet dose recommendation cannot be given.	**As requested by SAHPRA**
176. 177. 178. 179. 180.	Convulsions have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly. ROLIXIRD 450 MG should not be used concomitantly with imipenem-cilastatin unless the potential benefit outweighs the potential risks. (See section 4.5).	**As requested by SAHPRA**
181. 182. 183. 184.	Zidovudine and ROLIXIRD 450 MG each have the potential to cause neutropenia and anaemia. Some patients may not tolerate concomitant therapy at full dosage. (See section 4.5).	**As requested by SAHPRA**

185. 186. 187. 188.	Didanosine plasma concentrations may increase during concomitant use with ROLIXIRD 450 MG, therefore patients should be closely monitored for didanosine toxicity. (See section 4.5).	**As requested by SAHPRA**
189. 190. 191. 192.	Concomitant use of other medicines that are known to be myelosuppressive or associated with renal impairment with ROLIXIRD 450 MG may result in added toxicity. (See section 4.5).	**As requested by SAHPRA**
193. 194. 195. 196. 197. 198.	Since ROLIXIRD 450 MG is considered a potential teratogen and carcinogen in humans. If a broken tablet makes direct contact with skin, the area should be washed thoroughly with soap and water. If the solution gets into the eye, the eye should immediately be thoroughly washed with water.	
199. 200.	**4.5. Interaction with other medicines and other forms of interaction**	
201. 202. 203. 204. 205. 206. 207. 208.	The following medicines, valaciclovir, didanosine, nelfinavir, ciclosporin, omeprazole and mycophenolate mofetil did not affect the permeability of valganciclovir (rat in-situ model). ROLIXIRD 450 MG is metabolised to ganciclovir. Therefore, interactions associated with ganciclovir will be expected for ROLIXIRD 450 MG.	
209. 210. 211.	**Imipenem-cilastatin:** Convulsions have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly. These	**As requested by SAHPRA**

212. 213.	medicines should not be used concomitantly unless the potential benefit outweighs the potential risks. (See Section 4.4).	
214. 215. 216. 217. 218. 219. 220. 221.	**Probenecid:** Probenecid given with oral ganciclovir resulted in statistically significant decreased renal clearance of ganciclovir (20 %) leading to statistically significantly increased exposure (40 %). These changes were consistent with a mechanism of interaction involving competition for renal tubular excretion. Therefore, patients taking probenecid and ROLIXIRD 450 MG should be closely monitored for Ganciclovir toxicity.	
223. 224. 225. 226. 227. 228. 229. 230. 231.	**Zidovudine:** When zidovudine was given in the presence of oral ganciclovir there was a small (17 %), but statistically significant increase in the AUC of zidovudine. There was also a trend towards lower ganciclovir concentrations when administered with zidovudine, although this was not statistically significant. However, since both zidovudine and ganciclovir have the potential to cause neutropenia and anaemia, some patients may not tolerate concomitant therapy at full dosage. (See: Section 4.4).	**As requested by SAHPRA**
232. 233. 234. 235. 236. 237. 238. 239.	**Didanosine:** Didanosine plasma concentrations were found to be consistently raised when given with ganciclovir (both intravenous and oral). At ganciclovir oral doses of 3 and 6 g/day, an increase in the AUC of didanosine ranging from 84 to 124 % has been observed, and likewise at intravenous doses of 5 and 10 mg/kg/day, an increase in the AUC of didanosine ranging from 38 to 67 % has been observed. This increase cannot be explained by competition for renal tubular secretion, as there was an increase in the percentage of didanosine	**As requested by SAHPRA**

240. 241. 242. 243. 244. 245. 246.	dose excreted. This increase could arise from either increased bioavailability or decreased metabolism. There was no clinically significant effect on ganciclovir concentrations. However, given the increase in didanosine plasma concentrations in the presence of ganciclovir, patients should be closely monitored for didanosine toxicity. (See: Section 4.4).	
247. 248. 249. 250. 251. 252. 253. 254. 255. 256. 257. 258. 259.	**Mycophenolate Mofetil:** Based on the results of a single dose administration study of recommended doses of oral mycophenolate mofetil (MMF) and intravenous ganciclovir and the known effects of renal impairment on the pharmacokinetics of MMF and ganciclovir, it is anticipated that co- administration of these agents (which have the potential to compete for renal tubular secretion) will result in increases in phenolic glucuronide of mycophenolic acid (MPAG) and ganciclovir concentration. No substantial alteration of mycophenolic acid (MPA) pharmacokinetics is anticipated and MMF dose adjustment is not required. In patients with renal impairment in which MMF and ganciclovir are co-administered, the dose recommendation of ganciclovir should be observed and patients monitored carefully.	
260. 261. 262. 263. 264. 265. 266.	**Zalcitabine** increased the AUC_{0-8h} of oral ganciclovir by 13 %. There were no statistically significant changes in any of the other pharmacokinetic parameters assessed. Additionally there were no clinical relevant changes in zalcitabine pharmacokinetics in the presence of oral ganciclovir although a small increase in the elimination rate constant was observed.	

267. 268. 269.	Both ROLIXIRD 450 MG and zalcitabine have the potential to cause peripheral neuropathy and patients should be monitored for such events.	
270. 271. 272. 273.	**Stavudine:** No statistically significant pharmacokinetic interactions were observed when stavudine and oral ganciclovir were given in combination.	
274. 275. 276. 277. 278. 279. 282. 283. 284. 285.	**Trimethoprim:** Trimethoprim statistically significantly decreased the renal clearance of oral ganciclovir by 16,3 % and this was associated with a statistically significant decrease in the terminal elimination rate and the corresponding increase in half-life by 15 %. However, these changes are unlikely to be clinically significant, as $AUC_{0\text{-}8h}$ and C_{max} were unaffected. The only statistically significant change in trimethoprim pharmacokinetic parameters when co-administered with ganciclovir was a 12 % increase in $C_{min.}$ However, this is unlikely to be of clinical significance and no dose adjustment is recommended.	
286. 287. 288. 289. 290. 291.	**Ciclosporin**: There was no evidence that introduction of ganciclovir affects the pharmacokinetics of ciclosporin based on the comparison of ciclosporin trough concentrations. However, there was some evidence of increases in the maximum serum creatinine value observed following initiation of ganciclovir therapy.	
292. 293. 294. 295.	**Other potential interactions**: Toxicity may be enhanced when ganciclovir is co-administered with, or is given immediately before or after, other medicines that inhibit replication of rapidly dividing cell populations such as occur in the bone marrow, tested and germinal	**As requested by SAHPRA**

296. 297. 298. 299. 300. 301. 302. 303.	layers of the skin and gastrointestinal mucosa, or that are associated with renal impairment (such as dapsone, pentamidine, flucytosine, vincristine, vinblastine, adriamycin, amphotericin B, trimethoprim/sulfa combinations, nucleoside analogues and hydroxyurea). Therefore, these medicines should be considered for concomitant use with ROLIXIRD 450 MG only if the potential benefits outweigh the potential risks. (See: Section 4.4).	
304. 305. 306. 307. 308 309. 310. 311.	**4.6. Fertility, pregnancy and lactation** Effects on fertility: No human data on the effect of valganciclovir on fertility are available. Fertility studies have not been repeated with valganciclovir because of the rapid and extensive conversion of valganciclovir to ganciclovir in the body. Ganciclovir is associated with impaired fertility in animal studies (see section 5.3).	**As requested by SAHPRA**
312. 313. 314. 315. 316.	**Pregnancy** **ROLIXIRD 450 MG** active metabolite ganciclovir readily diffuses across the human placenta. The safety of **ROLIXIRD 450 MG** for use in pregnant women has not been established.	**As requested by SAHPRA**
317. 318. 319. 321. 322. 323.	**Breastfeeding** Pre-and postnatal development has not been studied with ROLIXIRD 450 MG, but the possibility of ganciclovir being excreted in breast milk and causing serious adverse reactions in the breast- fed infant. Women using ROLIXIRD 450 MG should not breastfeed their infants.	**As requested by SAHPRA**

324.	**4.7. Effects on ability to drive and use machines**	**As requested by SAHPRA**
325.	Convulsions, dizziness, and confusion have been reported with the use	
326.	of ROLIXIRD 450 MG. If they occur, such effects may affect tasks	
327.	requiring alertness, including the patient's ability to drive and operate	
328.	machinery.	
329.		
330.	**4.8. Undesirable effects**	**As requested by SAHPRA**
330.	**a. Summary of the safety profile**	
331.	The most commonly reported adverse drug reactions following	
332.	administration of ROLIXIRD 450 MG in adults are neutropenia,	
333.	anaemia and diarrhoea.	
334.		
335.	Adverse reactions are listed according to MedDRA system organ class.	
336.	Frequency categories are defined using the following convention: very	
337.	common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000	
338.	to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).	
339.		
340.	The overall safety profile of valganciclovir is consistent in HIV and	
341.	transplant populations except that retinal detachment has only been	
342.	reported in patients with CMV retinitis. However, there are some	
343.	differences in the frequency of certain reactions. Valganciclovir is	
344.	associated with a higher risk of diarrhoea, Pyrexia, candida infections,	
345.	depression, severe neutropenia (ANC <500/µL) and skin reactions are	
346.	reported more frequently in patients with HIV. Renal and hepatic	
347.	dysfunction are reported more frequently in organ transplant recipients.	
348.		
349.	**b. Tabulated list of adverse reactions**	

350.	**System Organ Class**	**Frequency Category**	**As requested by SAHPRA**
351.	**Infections and infestations:**		
352.	Candida infections including oral candidiasis.	Frequent	
353.	Upper respiratory tract infection		
354.	Sepsis		
355.	Influenza		
356.	Urinary tract infection		
357.	Cellulitis		
358.	**Blood and lymphatic disorders:**		
359.	Neutropenia	Frequent	
360.	Anaemia		
361.	Thrombocytopenia		
362.	Leukopenia		
363.	Pancytopenia		
364.	Bone marrow failure	Less Frequent	
365.	Aplastic anaemia		
366.	Agranulocytosis*		
367.	Granulocytopenia*		
368.	**Immune system disorders:**		
369.	Hypersensitivity	Frequent	
370.	Anaphylactic reaction*	Less Frequent	
371.	**Metabolic and nutrition disorders:**		
372.	Decreased appetite	Frequent	
374.	Weight decreased		
375.	**Psychiatric disorders:**		
376.	Depression	Frequent	
377.	Confusional state		

378.	Anxiety		
379.	Agitation, Psychotic disorder,	Less Frequent	
380.	Psychotic disorder		
380.	Thinking abnormal		
381.	Hallucinations		
382.	**Nervous system disorders:**		
383.	Headache	Frequent	
384.	Insomnia		
385.	Neuropathy peripheral		
386.	Dizziness		
387.	Paraesthesia		
388.	Hypoaesthesia		
389.	Seizure		
390.	Dysgeusia (taste disturbance)		
389.	Tremor	Less Frequent	
390.	**Eye disorders:**		
391.	Visual impairment	Frequent	
392.	Retinal detachment**		
393.	Vitreous floaters		
394.	Eye pain		
395.	Conjunctivitis		
396.	Macular oedema		
397.	**Ear and labyrinth disorders:**		
398.	Ear pain	Frequent	
399.	Deafness	Less Frequent	
400.	**Cardiac disorders** :		
401.	Dysrhythmias	Less Frequent	
	Vascular disorders :		

402.	Hypotension	Frequent	
401.	**Respiratory, thoracic and mediastinal disorders:**		
402.	Cough	Frequent	
403.	Dyspnoea		
404.	**Gastrointestinal disorders:**		
405.	Diarrhoea	Frequent	
406.	Nausea		
407.	Vomiting		
408.	Abdominal pain		
409.	Dyspepsia		
410.	Flatulence		
411.	Abdominal pain upper		
412.	Constipation		
413.	Mouth ulceration		
414.	Dysphagia		
415.	Abdominal distention		
416.	Pancreatitis		
417.	**Hepato-biliary disorders:**		
418.	Blood alkaline phosphatase increased	Frequent	
419.	Hepatic function abnormal		
420.	Aspartate aminotransferase increased		
421.	Alanine aminotransferase increased		
422.	**Skin and subcutaneous tissues disorders:**		
423.	Dermatitis	Frequent	
424.	Night sweats	Frequent	
425.	Pruritus		
426.	Rash		

Line	Adverse reaction	Frequency
427.	Alopecia	
428.	Dry skin	Less Frequent
429.	Urticaria	
430.	**Musculo-skeletal and connective tissue disorders:**	
431.	Spasms	Frequent
432.	Myalgia	
433.	Arthralgia	
434.	Muscle spasms	
435.	**Renal and urinary disorders:**	
436.	Renal impairment	Frequent
437.	Creatinine clearance renal decreased	
438.	Blood creatinine increased	
439.	Renal failure	Less Frequent
440.	Haematuria	
441.	**Reproductive system and breast disorders:**	
442.	Infertility male	Less Frequent
443.	**General disorders and administration site conditions:**	
444.	Pyrexia	Frequent
445.	Fatigue	
446.	Pain, Chills, Malaise, Asthenia,	Frequent
447.	Chills	
448.	Malaise	
449.	Asthenia	
450.	Chest pain	Less Frequent
451.		
452.		
453.		

454. 456. 457. 458. 459. 460.	**c. Description of selected adverse reactions** The risk of neutropenia is not predictable on the basis of the number of neutrophils before treatment. Neutropenia usually occurs during the first or second week of induction therapy. The cell count usually normalises within 2 to 5 days after discontinuation of the drug or dose reduction (see section 4.4).	
461. 462. 463. 464. 465. 466. 467. 468.	**d. Thrombocytopenia** Patients with low baseline platelet counts (< 100,000 /µL) have an increased risk of developing thrombocytopenia. Patients with iatrogenic immunosuppression due to treatment with immunosuppressive drugs are at greater risk of thrombocytopenia than patients with AIDS (see section 4.4). Severe thrombocytopenia may be associated with potentially life-threatening bleeding.	
469. 470. 471. 472. 473. 474. 475. 476. 477. 478. 479. 480. 481.	Influence of treatment duration or indication on adverse reactions Severe neutropenia (ANC <500/µL) is seen more frequently in CMV retinitis patients (14%) undergoing treatment with valganciclovir, intravenous or oral ganciclovir than in solid organ transplant patients receiving valganciclovir or oral ganciclovir. In patients receiving valganciclovir or oral ganciclovir until Day 100 post-transplant, the incidence of severe neutropenia was 5% and 3% respectively, whilst in patients receiving valganciclovir until Day 200 post-transplant the incidence of severe neutropenia was 10%. There was a greater increase in serum creatinine seen in solid organ transplant patients treated until Day 100 or Day 200 post-transplant with both valganciclovir and oral ganciclovir when compared to CMV	

482. 483. 484. 485. 486. 487. 488. 489.	retinitis patients. However, impaired renal function is a feature common in solid organ transplantation patients. The overall safety profile of **ROLIXIRD 450 MG** did not change with the extension of prophylaxis up to 200 days in high risk kidney transplant patients. Leukopenia was reported with a slightly higher incidence in the 200 days arm while the incidence of neutropenia, anaemia and thrombocytopenia were similar in both arms.	
491. 492. 493. 494.	**e. Other special population** **Elderly patients** Safety and efficacy have not been established.	
495. 496. 497. 498. 499. 500. 501. 502. 503.	**f. Reporting of suspected adverse reactions** Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions to SAHPRA via The '6.04 Adverse Drug Reactions Reporting Form'. Found under SAHPRA's publications: https://www/sahpra.org.za/Publications/Index/8	
504.	**4.9. Overdose**	
505. 506. 507.	It is expected that an overdose of **ROLIXIRD 450 MG**, could also possibly result in increased renal toxicity.	
508. 509.	**Treatment**	**As requested by SAHPRA**

510. 512. 513. 514. 515. 516. 517. 518. 519. 520. 521. 523. 524.	Haemodialysis and hydration may be of benefit in reducing blood plasma levels in patients who receive an overdose of **ROLIXIRD 450 MG**. **Overdose experience with IV ganciclovir:** The majority of patients experienced one or more of the following adverse events: Haematological toxicity: pancytopenia, bone marrow depression, medullary aplasia, leucopenia, neutropenia, granulocytopenia. Hepatotoxicity: hepatitis, liver function disorder. Renal toxicity: worsening of haematuria in a patient with pre-existing renal impairment, acute renal failure, and elevated creatinine. Gastrointestinal toxicity: abdominal pain, diarrhoea, vomiting. Neurotoxicity: generalised tremor, convulsion.	
525.	**5. PHARMACOLOGICAL PROPERTIES**	
526.	**5.1. Pharmacodynamic properties**	
527. 528. 529. 530.	A 20.2.8 Antiviral agents Pharmacotherapeutic group: antivirals for systemic use, nucleosides and nucleotides excl. reverse transcriptase inhibitor.	**As requested by SAHPRA**
531. 532. 533. 534. 535. 536. 537. 538.	**Mechanism of Action:** Valganciclovir is an L-valyl ester (prodrug) of ganciclovir. After oral administration, valganciclovir is rapidly and extensively metabolised to ganciclovir by intestinal and hepatic esterases. Ganciclovir is a synthetic analogue of 2'-deoxyguanosine and inhibits replication of herpes viruses *in vitro* and *in vivo*. Sensitive human viruses include human cytomegalovirus (HCMV), herpes simplex virus-1 and -2 (HSV-1 and HSV-2), human herpes virus -6, -7 and -8 (HHV-6, HHV-7,	**As requested by SAHPRA**

539. 540. 541. 542. 543. 544. 545. 546. 547. 548. 549. 550. 551. 552. 553. 554. 555. 556. 557. 558. 559. 560.	HHV8), Epstein-Barr virus (EBV), varicella-zoster virus (VZV) and hepatitis B virus (HBV). In CMV-infected cells, ganciclovir is initially phosphorylated to ganciclovir monophosphate by the viral protein kinase, pUL97. Further phosphorylation occurs by cellular kinases to produce ganciclovir triphosphate, which is then slowly metabolised intracellularly. Triphosphate metabolism has been shown to occur in HSV- and HCMV- infected cells with half-lives of 18 and between 6 and 24 hours respectively, after the removal of extracellular ganciclovir. As the phosphorylation is largely dependent on the viral kinase, phosphorylation of ganciclovir occurs preferentially in virus-infected cells. The virus static activity of ganciclovir is due to inhibition of viral DNA synthesis by: (a) competitive inhibition of incorporation of deoxyguanosine-triphosphate into DNA by viral DNA polymerase, and (b) incorporation of ganciclovir triphosphate into viral DNA causing termination of, or very limited, further viral DNA elongation. Antiviral activity The *in-vitro* anti-viral activity, measured as IC_{50} of ganciclovir against CMV, is in the range of 0.08 µM (0.02 µg/mL) to 14 µM (3.5 µg/mL).	
561.	**5.2. Pharmacokinetic properties**	
562. 563. 564. 565.	**Absorption** Valganciclovir is a prodrug of ganciclovir. It is well absorbed from the gastrointestinal tract and rapidly and extensively metabolised in the intestinal wall and liver to ganciclovir. The absolute bioavailability of	

566. ganciclovir from valganciclovir is approximately 60 %. Systemic
567. exposure to valganciclovir is transient and low. Valganciclovir allows
568. systemic exposure of ganciclovir similar to that achieved with
569. recommended doses of IV ganciclovir.
570. AUC_{24} and C_{max} values for valganciclovir are approximately 1 % and 3
571. % of those of ganciclovir, respectively. For comparison, the
572. bioavailability of ganciclovir after administration of 1 000 mg oral
578. ganciclovir (as capsules) is 6 - 8 %.
579. Valganciclovir in HIV+, CMV+ patients:
580. Systemic exposure of HIV+, CMV+ patients after twice daily
581. administration of ganciclovir and valganciclovir for one week is:
592.–598.

Parameter	**Ganciclovir (5 mg/kg, i.v.) n = 18**	**Valganciclovir (900 mg, once daily) n = 25**	
		Ganciclovir	**Valganciclovir**
AUC (0-12 h) (µg·h/mℓ)	28,6 ± 9,0	32,8 ± 10,1	0,37 ± 0,22
C_{max} (µg/mℓ)	10,4 ± 4,9	6,7 ± 2,1	0,18 ± 0,06

599. The efficacy of ganciclovir in increasing the time-to-progression of
600. CMV retinitis has been shown to correlate with systemic exposure
601. (AUC).
602. Valganciclovir in solid organ transplant patients:
603. Steady state systemic exposure of solid organ transplant patients to
604. ganciclovir after daily oral administration of ganciclovir and
605. valganciclovir is:
606.
607.

608.–613.

Parameter	Ganciclovir (1 000 mg three times daily) n = 82	Valganciclovir (900 mg, once daily) n = 161 Ganciclovir
AUC (0-24 h) (µg·h/mL) C_{max} (µg/mL)	28,0 ± 10,9 1,4 ± 0,5	46,3 ± 15,2 5,3 ± 1,5

614. The systemic exposure of ganciclovir to heart, kidney and liver
615. transplant recipients was similar after oral administration of
616. valganciclovir according to the renal function dosing algorithm.
617. Following the administration of valganciclovir as an oral solution,
618. equivalent systemic ganciclovir exposures were obtained compared to
619. the tablet formulation.
620. Food: When valganciclovir was given with food at the recommended
621. dose of 900 mg, increases were seen in both mean ganciclovir AUC_{24}
622. (± 30 %) and mean ganciclovir C_{max} values (± 14 %). It is
623. recommended that valganciclovir be administered with food.
624.
625.

626. **Distribution**
627. Plasma protein binding of ganciclovir was 1 - 2 % over concentrations
628. of 0,5 and 51 µg/mL. The steady state volume of distribution of
629. ganciclovir after IV administration was 0,680 ± 0,161 ℓ/kg.
630.

631. **Biotransformation**
632. Valganciclovir is rapidly and extensively metabolised to ganciclovir, no
633. other metabolites have been detected. No metabolite of orally
634. administered radiolabelled ganciclovir (1 000 mg single dose)

635. 636. 637.	accounted for more than 1 - 2 % of the radioactivity recovered in the faeces and urine.	
638. 639. 640. 641. 642. 643. 644.	**Elimination** The major route of elimination of valganciclovir as ganciclovir is renal excretion, by glomerular filtration and active tubular secretion. Renal clearance accounts for 81,5 % ± 22 % of the systemic clearance of valganciclovir. The half-life of ganciclovir from valganciclovir is 4,1 ± 0,9 hours in HIV- and CMV-seropositive patients.	
645. 646. 647. 648. 649. 650. 651.	**Special Populations** **Patients with renal impairment** Decreasing renal function resulted in decreased clearance of ganciclovir from valganciclovir with an increase in terminal half-life. Therefore, dosage adjustment is required for renally impaired patients. (See section 4.2).	**As requested by SAHPRA**
652. 653. 654. 655. 656. 657. 658. 659. 660. 661.	Haemodialysis: For patients receiving haemodialysis (CrCl < 10 mL/min); it is recommended that IV ganciclovir is used. The individual dose of ROLIXIRD 450 MG required for these patients is less than the 450 mg tablet strength. Approximately half of the ganciclovir present at the start of dialysis is removed during dialysis. The mean intra- dialysis half-life and mean interdialysis half-life is estimated to be 3,47 h and 51,0 h respectively. However, for patients receiving haemodialysis (CrCl < 10 mL/min) 50 mg/mL powder for oral solution is recommended to provide an individualised dose. (See section 4.2).	**As requested by SAHPRA**

662.		
663. 664. 665. 666. 667. 668. 669. 670. 671.	**Patients with hepatic impairment** The pharmacokinetics of valganciclovir in stable liver transplant recipients were investigated in one open-label 4-crossover study. The absolute bioavailability of ganciclovir from valganciclovir, following a single dose of 900 mg valganciclovir under fed conditions was approximately 60 %, in agreement with estimates obtained in other patient populations. Ganciclovir $AUC_{0\text{-}24h}$ was comparable to that achieved by 5 mg/kg IV ganciclovir in liver transplant recipients.	
672. 673. 674.	**5.3 Preclinical safety data** **Not applicable**	
675. 676. 677. 678. 679. 680. 681. 682. 683.	**Environmental Risk Assessment** **ROLIXIRD 450 MG** is a well-established active ingredient used in pharmaceutical preparations for human use. Given the anticipated pattern of use and disposal of the product, the environmental exposure of the active substance and metabolites are expected to be very limited. The use of **ROLIXIRD 450 MG** Tablets 450 mg is not considered warranting any environmental concerns or requiring any special product labelling.	
684.	**6. PHARMACEUTICAL PARTICULARS**	
685. 686. 687. 688.	**6.1. List of excipients** Cellulose Microcrystalline (Avicel PH 101), Crospovidone (Type B) (Polyplasdone XL - 10), Povidone (Kollidone 30),	

689. 690. 691. 692. 693. 694.	Cellulose Microcrystalline (Avicel PH 102), Magnesium stearate (Ligamed MF-2-V), Opadry pink YS-1-14519A (contains HPMC 2910/Hypromellose 3cP, HPMC 2910/Hypromellose 6cP, Titanium Dioxide, Macrogol/PEG 400, Iron oxide red, Polysorbate 80, Purified water).	
695. 696. 697.	**6.2. Incompatibilities** Not applicable	
698. 699. 700.	**6.3. Shelf life** Proposed shelf life: 36 months	
701.	**6.4. Special precautions for storage**	
702. 703. 704. 705.	Store at or below 25 °C. Keep in original packaging until required for use. **KEEP OUT OF REACH OF CHILDREN.**	
706.	**6.5. Nature and contents of container**	
707. 708. 709. 710. 711. 712. 713. 714. 715.	**Blister strips:** 60 tablets are packed in a Blister strips of 25 µ Polyamide/ 45 µ Aluminium foil/ 60 µ PVC film. Pack sizes: 10 film coated tablets per blister. One box contains 10 x 6 blisters. **HDPE bottles:** 60 tablets are packed in white opaque round HDPE container closed with a white opaque polypropylene continuous thread closures with wad having induction sealing liner.	

716. 717. 718.	Pack sizes: 60's - One HDPE container contains 60 tablets. HDPE bottle and blister packs are enclosed in an outer carton box.	
719. 720. 721. 722. 723.	**6.6. Special precautions for disposal of a used medicine or waste materials derived from such medicine and other handling of the product** No special requirements.	
724. 725. 726. 727. 728. 729. 730. 731. 732.	**7. NAME AND BUSINESS ADDRESS OF THE HOLDER OF THE CERTIFICATE OF REGISTRATION** AUROGEN SA (Pty) Ltd Woodhill Office Park, Building 1, First Floor 53 Phillip Engelbrecht Avenue Meyersdal, Ext. 12, 1448 Johannesburg South Africa	
733. 734.	**8. REGISTRATION NUMBER** **49/20.2.8/0106**	
735. 736.	**9. DATE OF FIRST AUTHORISATION** **06 APRIL 2021**	
737. 738.	**10. DATE OF REVISION OF TEXT**	

REFERENCES

Ref. no.	**Reference name**	**Pages**
Ref 1	South African Innovator, Valcyte 450 mg. Roche Products (Pty) Ltd., 24 Frickerweg Road, Illovo, Gauteng, South Africa. Dated: 23 November 2017	**p.2 – 23**
Ref 2	Summary of Product Characteristics, Valganciclovir Aurobindo 450 mg Film-Coated Tablets, Aurobindo Pharma (Portugal), Unipessoal, Lda. Av. do Forte, no 3 - Parque Suecia, Edificio. IV, 2°, 2794-038 Carnaxide.	**p.24– 44**
Ref 3	Goodman & Gilman's The Pharmacological Basis of Therapeutics, 12th Edition	**p.45 –46**
Ref 4	Martindale: The Complete Drug Reference, 38th Edition	**p.47– 48**
Ref 5	Annex to the European commission guideline on 'Excipients in the labelling and package leaflet of medicinal products for human use'	**p.49– 69**