1.3.1.1 Professional Information for Medicines for Human Use approved

SCHEDULING STATUS

S4

1. NAME OF THE MEDICINE

ROLIXIRD 450 MG film coated tablets.

Strength: Each Film-coated tablet contains 450 mg valganciclovir

Pharmaceutical form: Film-coated Tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

ROLIXIRD 450 MG film coated tablets :

Each film coated tablet contains 496.36 mg of Valganciclovir hydrochloride equivalent to 450 mg of valganciclovir.

Sugar-free,

For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

ROLIXIRD 450 MG 450 mg film coated Tablets:

Pink colored, oval shaped biconvex, film-coated tablets, debossed with ‘H’ on one side and ‘96’ on other side.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

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.

4.2. Posology and method of administration

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.

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

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.

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

$$CL_{CR}\ (m\ell/min) = \frac{(140 - age) \times (Wt\ [kg]) \times 0{,}85\ (if\ female)}{S_{CR}\ [\mu mol/\ell]}$$

CLCR = creatinine clearance

SCR = serum creatinine

ROLIXIRD 450 MG film-coated tablet dose for renally impaired patients

CrCl (mL/min)	**Induction dose of ROLIXIRD 450 MG film-coated tablet**	**Maintenance/Prevention dose of ROLIXIRD 450 MG film coated tablet**
≥ 60	900 mg twice daily	900 mg once daily
40 – 59	450 mg twice daily	450 mg once daily
25 – 39	450 mg once daily	450 mg every 2 days
10 – 24	450 mg every 2 days (tablets)	450 mg twice weekly
< 10	Not recommended	Not recommended

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).

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.

Paediatric patients:

Safety and efficacy have not been established in adequate and well-controlled clinical studies.

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.

4.3. Contraindications

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.

4.4. Special warnings and precautions for use

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.

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** .

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.

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 that treatment with haematopoietic growth factors and/or dose interruption be considered. (See section 4.2)

Safety and efficacy in children have not been established in adequate and well-controlled clinical studies. (See section 4.2)

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).

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.

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).

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).

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).

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).

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.

4.5. Interaction with other medicines and other forms of interaction

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** .

Imipenem-cilastatin: Convulsions have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly. These medicines should not be used concomitantly unless the potential benefit outweighs the potential risks. (See Section 4.4).

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.

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).

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 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).

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.

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.

Both **ROLIXIRD 450 MG** and zalcitabine have the potential to cause peripheral neuropathy and patients should be monitored for such events.

Stavudine: No statistically significant pharmacokinetic interactions were observed when stavudine and oral ganciclovir were given in combination.

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_{0-8h} 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.

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.

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 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).

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).

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.

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.

4.7. Effects on ability to drive and use machines

Convulsions, dizziness, and confusion have been reported with the use of **ROLIXIRD 450 MG** . If they occur, such effects may affect tasks requiring alertness, including the patient's ability to drive and operate machinery.

4.8. Undesirable effects

a. Summary of the safety profile

The most commonly reported adverse drug reactions following administration of **ROLIXIRD 450 MG** in adults are neutropenia, anaemia and diarrhoea.

Adverse reactions are listed according to MedDRA system organ class. Frequency categories are defined using the following convention: very common (≥ 1/10), common (≥ 1/100 to < 1/10), uncommon (≥ 1/1,000 to < 1/100), rare (≥ 1/10,000 to < 1/1,000) and very rare (< 1/10,000).

The overall safety profile of valganciclovir is consistent in HIV and transplant populations except that retinal detachment has only been reported in patients with CMV retinitis. However, there are some differences in the frequency of certain reactions. Valganciclovir is associated with a higher risk of diarrhoea, Pyrexia, candida infections, depression, severe neutropenia (ANC <500/µL) and skin reactions are reported more frequently in patients with HIV. Renal and hepatic dysfunction are reported more frequently in organ transplant recipients.

b. Tabulated list of adverse reactions

System Organ Class	**Frequency Category**
Infections and infestations:	
Candida infections including oral candidiasis.	Frequent
Upper respiratory tract infection	
Sepsis	

Influenza	
Urinary tract infection	
Cellulitis	
Blood and lymphatic disorders:	
Neutropenia	Frequent
Anaemia	
Thrombocytopenia	
Leukopenia	
Pancytopenia	
Bone marrow failure	Less Frequent
Aplastic anaemia	
Agranulocytosis*	
Granulocytopenia*	
Immune system disorders:	
Hypersensitivity	Frequent
Anaphylactic reaction*	Less Frequent
Metabolic and nutrition disorders:	
Decreased appetite	Frequent
Weight decreased	
Psychiatric disorders:	
Depression	Frequent
Confusional state	
Anxiety	
Agitation, Psychotic disorder,	Less Frequent
Psychotic disorder	
Thinking abnormal	
Hallucinations	

Nervous system disorders:	
Headache	Frequent
Insomnia	
Neuropathy peripheral	
Dizziness	
Paraesthesia	
Hypoaesthesia	
Seizure	
Dysgeusia (taste disturbance)	
Tremor	Less Frequent
Eye disorders:	
Visual impairment	Frequent
Retinal detachment**	
Vitreous floaters	
Eye pain	
Conjunctivitis	
Macular oedema	
Ear and labyrinth disorders:	
Ear pain	Frequent
Deafness	Less Frequent
Cardiac disorders :	
Dysrhythmias	Less Frequent
Vascular disorders :	
Hypotension	Frequent
Respiratory, thoracic and mediastinal disorders:	
Cough	Frequent
Dyspnoea	
Gastrointestinal disorders:	

Diarrhoea	Frequent
Nausea	
Vomiting	
Abdominal pain	
Dyspepsia	
Flatulence	
Abdominal pain upper	
Constipation	
Mouth ulceration	
Dysphagia	
Abdominal distention	
Pancreatitis	
Hepato-biliary disorders:	
Blood alkaline phosphatase increased	Frequent
Hepatic function abnormal	
Aspartate aminotransferase increased	
Alanine aminotransferase increased	
Skin and subcutaneous tissues disorders:	
Dermatitis	Frequent
Night sweats	Frequent
Pruritus	
Rash	
Alopecia	
Dry skin	Less Frequent
Urticaria	
Musculo-skeletal and connective tissue disorders:	
Spasms	Frequent
Myalgia	

Arthralgia	
Muscle spasms	
Renal and urinary disorders:	
Renal impairment	Frequent
Creatinine clearance renal decreased	
Blood creatinine increased	
Renal failure	Less Frequent
Haematuria	
Reproductive system and breast disorders:	
Infertility male	Less Frequent
General disorders and administration site conditions:	
Pyrexia	Frequent
Fatigue	
Pain, Chills, Malaise, Asthenia,	Frequent
Chills	
Malaise	
Asthenia	
Chest pain	Less Frequent

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).

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.

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 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.

e. Other special population

Elderly patients

Safety and efficacy have not been established.

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

4.9. Overdose

It is expected that an overdose of **ROLIXIRD 450 MG** , could also possibly result in increased renal toxicity.

Treatment

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.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

A 20.2.8 Antiviral agents

Pharmacotherapeutic group: antivirals for systemic use, nucleosides and nucleotides excl. reverse transcriptase inhibitor.

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, 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).

5.2. Pharmacokinetic properties

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 ganciclovir from valganciclovir is approximately 60 %. Systemic exposure to

valganciclovir is transient and low. Valganciclovir allows systemic exposure of ganciclovir similar to that achieved with recommended doses of IV ganciclovir.

AUC_{24} and C_{max} values for valganciclovir are approximately 1 % and 3 % of those of ganciclovir, respectively. For comparison, the bioavailability of ganciclovir after administration of 1 000 mg oral ganciclovir (as capsules) is 6 - 8 %.

Valganciclovir in HIV+, CMV+ patients:

Systemic exposure of HIV+, CMV+ patients after twice daily administration of ganciclovir and valganciclovir for one week is:

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

The efficacy of ganciclovir in increasing the time-to-progression of CMV retinitis has been shown to correlate with systemic exposure (AUC).

Valganciclovir in solid organ transplant patients:

Steady state systemic exposure of solid organ transplant patients to ganciclovir after daily oral administration of ganciclovir and valganciclovir is:

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)	28,0 ± 10,9	46,3 ± 15,2
C_{max} (µg/mL)	1,4 ± 0,5	5,3 ± 1,5

The systemic exposure of ganciclovir to heart, kidney and liver transplant recipients was similar after oral administration of valganciclovir according to the renal function dosing algorithm.

Following the administration of valganciclovir as an oral solution, equivalent systemic ganciclovir exposures were obtained compared to the tablet formulation.

Food: When valganciclovir was given with food at the recommended dose of 900 mg, increases were seen in both mean ganciclovir AUC_{24} (± 30 %) and mean ganciclovir C_{max} values (± 14 %). It is recommended that valganciclovir be administered with food.

Distribution

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

Biotransformation

Valganciclovir is rapidly and extensively metabolised to ganciclovir, no other metabolites have been detected. No metabolite of orally administered radiolabelled ganciclovir (1 000 mg single dose) accounted for more than 1 - 2 % of the radioactivity recovered in the faeces and urine.

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.

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).

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).

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_{0-24h} was comparable to that achieved by 5 mg/kg IV ganciclovir in liver transplant recipients.

5.3 Preclinical safety data

Not applicable

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 is not considered warranting any environmental concerns or requiring any special product labelling.

6. PHARMACEUTICAL PARTICULARS

6.1. List of excipients

Cellulose Microcrystalline (Avicel PH 101),

Crospovidone (Type B) (Polyplasdone XL - 10),

Povidone (Kollidone 30),

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).

6.2. Incompatibilities

Not applicable

6.3. Shelf life

Proposed shelf life: 36 months

6.4. Special precautions for storage

Store at or below 25 °C.

Keep in original packaging until required for use.

KEEP OUT OF REACH OF CHILDREN.

6.5. Nature and contents of container

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.

Pack sizes: 60's - One HDPE container contains 60 tablets.

HDPE bottle and blister packs are enclosed in an outer carton box.

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.

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

8. REGISTRATION NUMBER

49/20.2.8/0106

9. DATE OF FIRST AUTHORISATION

06 APRIL 2021