Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Valganciclovir Rowex 450 mg film coated tablet

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 496.3 mg of valganciclovir hydrochloride equivalent to 450 mg of valganciclovir (as free base).
For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet

Pink, oval, biconvex, film coated tablets (16.7 x 7.8 mm), debossed with “J” on one side and “156” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Valganciclovir Rowex is indicated for the induction and maintenance treatment of cytomegalovirus (CMV) retinitis in adult patients with acquired immunodeficiency syndrome (AIDS).
Valganciclovir Rowex is indicated for the prevention of CMV disease in CMV-negative adults and children (aged from birth to 18 years) who have received a solid organ transplant from a CMV-positive donor.

4.2 Posology and method of administration

Caution – Strict adherence to dosage recommendations is essential to avoid overdose; see sections 4.4 and 4.9.
Valganciclovir is rapidly and extensively metabolised to ganciclovir after oral dosing. Oral valganciclovir 900 mg b.i.d. is therapeutically equivalent to intravenous ganciclovir 5 mg/kg b.i.d.

Treatment of cytomegalovirus (CMV) retinitis
Adult patients

Induction treatment of CMV retinitis:
For patients with active CMV retinitis, the recommended dose is 900 mg valganciclovir (two Valganciclovir Rowex 450 mg tablets) twice a day for 21 days and, whenever possible, taken with food. Prolonged induction treatment may increase the risk of bone marrow toxicity (see section 4.4).

Maintenance treatment of CMV retinitis:
Following induction treatment, or in patients with inactive CMV retinitis, the recommended dose is 900mg valganciclovir (two Valganciclovir Rowex 450 mg tablets) once daily and, whenever possible, taken with food. Patients whose retinitis worsens may repeat induction treatment; however, consideration should be given to the possibility of viral drug resistance.

Paediatric population
The safety and efficacy of valganciclovir in the treatment of CMV retinitis have not been established in adequate and well-controlled clinical studies in paediatric patients.

Prevention of CMV disease in solid organ transplantation:
Adult patients
For kidney transplant patients, the recommended dose is 900 mg (two Valganciclovir Rowex 450 mg tablets) once daily, starting within 10 days post-transplantation and continuing until 100 days post-transplantation. Prophylaxis may

be continued until 200 days post- transplantation (see sections 4.4, 4.8 and 5.1).

For patients who have received a solid organ transplant other than kidney, the recommended dose is 900 mg (two Valganciclovir Rowex 450 mg tablets) once daily, starting within 10 days post-transplantation and continuing until 100 days post-transplantation.

Whenever possible, the tablets should be taken with food.

Paediatric population
In paediatric solid organ transplant patients, aged from birth, who are at risk of developing CMV disease, the recommended once daily dose of Valganciclovir Rowex is based on body surface area (BSA) and creatinine clearance (CrCl) derived from Schwartz formula (CrCLS), and is calculated using the equation below:
Paediatric Dose (mg) = 7 x BSA x CrCLS (see Mosteller BSA formula and Schwartz Creatinine Clearance formula below).
If the calculated Schwartz creatinine clearance exceeds 150 mL/min/1.73m^2, then a maximum value of 150 mL/min/1.73m^2 should be used in the equation:

$$Mosteller\ BSA\ (m^2) = \sqrt{\frac{Height\ (cm)\ x\ Weight\ (kg)}{3600}}$$

$$Schwartz\ Creatinine\ Clearance\ (ml/min/1.73m^2) = \frac{k\ x\ Height\ (cm)}{Serum\ Creatinine\ (mg/dl)}$$

where k = 0.45* for patients aged < 2 years, 0.55 for boys aged 2 to < 13 years and girls aged 2 to 16 years, and 0.7 for boys aged 13 to 16 years. Refer to adult dosing for patients older than 16 years of age.
The k values provided are based on the Jaffe method of measuring serum creatinine and may require correction when enzymatic methods are used.

*For appropriate sub-populations a lowering of k value may also be necessary (e.g. in paediatric patients with low birth weight).
For paediatric kidney transplant patients, the recommended once daily mg dose (7 x BSA x CrCLS) should start within 10 days post-transplantation and continue until 200 days post-transplantation.
For paediatric patients who have received a solid organ transplant other than kidney, the recommended once daily mg dose (7x BSA x CrCLS) should start within 10 days post-transplantation and continue until 100 days post-transplantation.
All calculated doses should be rounded to the nearest 25 mg increment for the actual deliverable dose. If the calculated dose exceeds 900 mg, a maximum dose of 900 mg should be administered. The oral solution is the preferred formulation since it provides the ability to administer a dose calculated according to the formula above; however, valganciclovir film-coated tablets may be used if the calculated doses are within 10% of available tablet doses, and the patient is able to swallow tablets. For example, if the calculated dose is between 405 mg and 495 mg, one 450 mg tablet may be taken.
It is recommended to monitor serum creatinine levels regularly and consider changes in height and body weight and adapt the dose as appropriate during the prophylaxis period.

Special dosage instructions

Patients with renal impairment:
Serum creatinine levels or creatinine clearance should be monitored carefully. Dosage adjustment is required according to creatinine clearance, as shown in the table below (see sections 4.4 and 5.2).
An estimated creatinine clearance (ml/min) can be related to serum creatinine by the following formulae:

$$\text{For males} = \frac{(140 - \text{age [years]}) \times (\text{body weight [kg]})}{(72) \times (0.011 \times \text{serum creatinine [micromol/l]})}$$

For females = 0.85 x male value

CrCl (ml/min)	Induction dose of valganciclovir	Maintenance/Prevention dose of valganciclovir
≥ 60	900 mg (2 tablets) twice daily	900 mg (2 tablets) once daily
40 – 59	450 mg (1 tablet) twice daily	450 mg (1 tablet) once daily
25 – 39	450 mg (1 tablet) once daily	450 mg (1 tablet) every 2 days
10 – 24	450 mg (1 tablet) every 2 days	450 mg (1 tablet) 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 Valganciclovir Rowex film coated tablets should not be used in these patients (see sections 4.4 and 5.2).

Patients with hepatic impairment:
Safety and efficacy of valganciclovir tablets have not been studied in patients with hepatic impairment (see section 5.2).

Paediatric population:
Dosing of paediatric SOT patients is individualised based on a patient's renal function, together with body length and weight.

Elderly patients:
Safety and efficacy have not been established in this patient population.

Patients with severe leucopenia, neutropenia, anaemia, thrombocytopenia and pancytopenia; See section 4.4 before initiation of therapy.

If there is a significant deterioration of blood cell counts during therapy with Valganciclovir Rowex, treatment with haematopoietic growth factors and/or dose interruption should be considered (see section 4.4).

Method of administration
Valganciclovir Rowex is administered orally, and whenever possible, should be taken with food (see section 5.2).

Precautions to be taken before handling or administering the medicinal product
The tablets should not be broken or crushed. Since Valganciclovir Rowex 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.

For paediatric patients who are unable to swallow, another pharmaceutical form can be used, e.g. powder for oral solution.

4.3 Contraindications

Valganciclovir Rowex is contra-indicated in patients with hypersensitivity to valganciclovir, ganciclovir or to any of the excipients listed in section 6.1.

Due to the similarity of the chemical structure of valganciclovir and that of aciclovir and valaciclovir, a cross-hypersensitivity reaction between these drugs is possible. Therefore, Valganciclovir Rowex is contra-indicated in patients with hypersensitivity to aciclovir and valaciclovir.
Valganciclovir Rowex is contra-indicated during breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Prior to the initiation of valganciclovir treatment, patients should be advised of the potential risks to the foetus. In animal studies, ganciclovir was found to be mutagenic, teratogenic, aspermatogenic and carcinogenic, and a suppressor of female fertility. Valganciclovir Rowex should, therefore, be considered a potential teratogen and carcinogen in humans with the potential to cause birth defects and cancers (see section 5.3). It is also considered likely that Valganciclovir Rowex causes temporary or permanent inhibition of spermatogenesis. Women of child bearing potential must be advised to use effective contraception during treatment. Men must be advised to practise barrier contraception during treatment, and for at least 90 days thereafter, unless it is certain that the female partner is not at risk of pregnancy (see sections 4.6, 4.8 and 5.3).

Valganciclovir has the potential to cause carcinogenicity and reproductive toxicity in the long term.

Severe leucopenia, neutropenia, anaemia, thrombocytopenia, pancytopenia, bone marrow depression and aplastic anaemia have been observed in patients treated with valganciclovir (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 25000/µl, or the haemoglobin level is less than 8 g/dl (see sections 4.2 and 4.8).

When extending prophylaxis beyond 100 days the possible risk of developing leucopenia and neutropenia should be taken into account (see sections 4.2, 4.8 and 5.1).
Valganciclovir Rowex should be used with caution in patients with pre-existing haematological cytopenia or a history of drug-related haematological cytopenia and in patients receiving radiotherapy.

It is recommended that complete blood counts and platelet counts should be monitored regularly during therapy. Increased haematological monitoring may be warranted in patients with renal impairment and paediatrics, at a minimum each time the patient attends the transplant clinic. In patients developing severe leucopenia, neutropenia, anaemia and/or thrombocytopenia, it is recommended that treatment with haematopoietic growth factors and/or dose interruption be considered (see sections 4.2).

The bioavailability of ganciclovir after a single dose of 900 mg valganciclovir is approximately 60 %, compared with approximately 6 % after administration of 1000 mg oral ganciclovir (as capsules). Excessive exposure to ganciclovir may be associated with life-threatening adverse reactions. Therefore, careful adherence to the dose recommendations is advised when instituting therapy, when switching from induction to maintenance therapy and in patients who may switch from oral ganciclovir to valganciclovir as Valganciclovir Rowex cannot be substituted for ganciclovir capsules on a one-to-one basis. Patients switching from ganciclovir capsules should be advised of the risk of overdosage if they take more than the prescribed number of Valganciclovir Rowex tablets
(see sections 4.2 and 4.9).

In patients with impaired renal function, dosage adjustments based on creatinine clearance are required (see sections 4.2 and 5.2).

Valganciclovir Rowex film coated tablets should not be used in patients on haemodialysis (see sections 4.2 and 5.2).

Convulsions have been reported in patients taking imipenem-cilastatin and ganciclovir. valganciclovir should not be used concomitantly with imipenem-cilastatin unless the potential benefits outweigh the potential risks (see section 4.5).

Patients treated with valganciclovir and (a) didanosine, (b) drugs that are known to be myelosuppressive (e.g. zidovudine), or (c) substances affecting renal function, should be closely monitored for signs of added toxicity (see section 4.5).
The controlled clinical study using valganciclovir for the prophylactic treatment of CMV disease in transplantation, as detailed in section 5.1 did not include lung and intestinal transplant patients. Therefore, experience in these transplant patients is limited.

4.5 Interaction with other medicinal products and other forms of interaction

Drug interactions with valganciclovir
In-vivo drug interaction studies with Valganciclovir Rowex have not been performed. Since valganciclovir is extensively and rapidly metabolised to ganciclovir; drug interactions associated with ganciclovir will be expected for valganciclovir.

Drug interactions with ganciclovir
Imipenem-cilastatin
Convulsions have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly. These drugs should not be used concomitantly unless the potential benefits outweigh the potential risks (see section 4.4).

Probenecid
Probenecid given with oral ganciclovir resulted in statistically significantly 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 secretion. Therefore, patients taking probenecid and Valganciclovir Rowex should be closely monitored for ganciclovir toxicity.

Trimethoprim
No clinically significant pharmacokinetic interaction was observed when trimethoprim and oral ganciclovir were given in combination. However, there is a potential for toxicity to be enhanced since both drugs are known to be myelosuppressive and therefore both drugs should be used concomitantly only if the potential benefits outweigh the risks.

Mycophenolate Mofetil
Since both mycophenolate mofetil (MMF) and ganciclovir have the potential to cause neutropenia and leucopenia, patients should be monitored for additive toxicity.

Stavudine
No clinically significant interactions were observed when stavudine and oral ganciclovir were given in combination.

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. There was no clinically significant effect on ganciclovir concentrations. Patients should be closely monitored for didanosine toxicity (see section 4.4).

Other antiretrovirals (including therapy for HIV, HBV/HCV)
At clinically relevant plasma concentrations of ganciclovir and other antivirals for the inhibition of human immunodeficiency virus (HIV) or HBV/HCV, there is unlikely to be a synergistic or antagonistic effect on the activity of either ganciclovir or the other antivirals.
The metabolic interaction potential of valganciclovir or ganciclovir is low due to the lack of cytochrome P450 involvement in the metabolism of either valganciclovir or ganciclovir. In addition, ganciclovir is not a substrate to P-glycoprotein, nor does it affect the UDP-glucuronosyltransferase (UGT enzyme). Therefore metabolic and drug transport interactions of valganciclovir or ganciclovir with the following classes of antivirals are considered unlikely:

- Non-nucleoside reverse transcriptase inhibitors (NNRTIs), e.g. rilpivirine, etravirine, efavirenz
- Protease inhibitors (PIs), e.g. darunavir, boceprevir and telaprevir
- Entry inhibitors (fusion inhibitor and CCR5 co-receptor antagonist), e.g. enfuvirtide and maraviroc

• HIV integrase strand transfer inhibitor (INSTI), e.g. raltegravir

Since ganciclovir is excreted through the kidney via glomerular filtration and active tubular secretion (section 5.2), coadministration of valganciclovir with antiviral drugs that share the tubular secretion pathway may change the plasma concentrations of valganciclovir and/or the coadministered drug. Some examples include nucleos(t)ide analog reverse-transcriptase inhibitors (NRTIs) (including those used for HBV therapy), e.g. lamivudine, emtricitabine, tenofovir, adefovir and entecavir. The renal clearance of ganciclovir may also be inhibited due to nephrotoxicity caused by drugs such as cidofovir, foscarnet, NRTIs (e.g. tenofovir, adefovir). Concomitant use of valganciclovir with any of these drugs should be considered only if the potential benefits outweigh the potential risks (see section 4.4).

Other potential drug interactions

Toxicity may be enhanced when valganciclovir is co-administered with, or is given immediately before or after, other drugs that inhibit replication of rapidly dividing cell populations such as occur in the bone marrow, testes and germinal layers of the skin and gastrointestinal mucosa. Examples of these types of drugs are dapsone, pentamidine, flucytosine, vincristine, vinblastine, adriamycin, amphotericin B, trimethoprim/sulpha combinations, nucleoside analogues and hydroxyurea and pegylated interferons/ribavirin (with or without boceprevir or telaprevir).

Concomitant use of valganciclovir with all of these drugs should be considered only if the potential benefits outweigh the potential risks (see section 4.4).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are no data from the use of Valganciclovir Rowex in pregnant women. Its active metabolite, ganciclovir, readily diffuses across the human placenta. Based on its pharmacological mechanism of action and reproductive toxicity observed in animal studies with ganciclovir (see section 5.3) there is a theoretical risk of teratogenicity in humans. Valganciclovir Rowex should not be used in pregnancy unless the therapeutic benefit for the mother outweighs the potential risk of teratogenic damage to the child.

Breast-feeding

It is unknown if ganciclovir is excreted in breast milk, but the possibility of ganciclovir being excreted in the breast milk and causing serious adverse reactions in the nursing infant cannot be discounted. Therefore, breast-feeding must be discontinued (see section 4.3).

Fertility

Women of child-bearing potential must be advised to use effective contraception during treatment. Male patients must be advised to practise barrier contraception during, and for at least 90 days following treatment with Valganciclovir Rowex unless it is certain that the female partner is not at risk of pregnancy (see section 5.3).

4.7 Effects on ability to drive and use machines

No studies on the effects on ability to drive and use machines have been performed.

Convulsions, sedation, dizziness, ataxia, and/or confusion have been reported with the use of valganciclovir and/or ganciclovir. 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

Valganciclovir is a prodrug of ganciclovir, which is rapidly and extensively metabolised to ganciclovir after oral administration. The undesirable effects known to be associated with ganciclovir use can be expected to occur with valganciclovir. All of the undesirable effects observed with valganciclovir clinical studies have been previously observed with ganciclovir. The most commonly reported adverse drug reactions following administration of valganciclovir in adults are neutropenia, anaemia and diarrhoea.

Valganciclovir is associated with a higher risk of diarrhoea compared to intravenous ganciclovir. In addition,

valganciclovir is associated with a higher risk of neutropenia and leucopenia compared to oral ganciclovir.

Severe neutropenia (ANC < 500 cells/μl) is seen more frequently in AIDS patients with CMV retinitis undergoing treatment with valganciclovir than in solid organ transplant patients receiving valganciclovir (see section 4.4).

The frequency of adverse reactions reported in clinical trials with either valganciclovir, oral ganciclovir, or intravenous ganciclovir is presented in the table below. The adverse reactions listed were reported in clinical trials in patients with AIDS for the induction or maintenance treatment of CMV retinitis, or in liver, kidney or heart transplant patients for the prophylaxis of CMV disease. The term (severe) in parenthesis in the table indicates that the adverse reaction has been reported in patients at both mild/moderate intensity and severe/life-threatening intensity at that specific frequency.
The overall safety profile of valganciclovir did not change with the extension of prophylaxis up to 200 days in adult kidney transplant patients at high risk of CMV disease (D+/R-). Leucopenia 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.

b) Tabulated list of adverse reactions
Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Body System	**Very Common (≥1/10)**	**Common (≥1/100 to <1/10)**	**Uncommon (≥1/1000 to < 1/100)**	**Rare (≥1/10,000 to < 1/1000)**
Infections and infestations		Oral candidiasis, sepsis (bacteraemia, viraemia), cellulitis, urinary tract infection		
Blood and lymphatic system disorders	(Severe) neutropenia, anaemia	Severe anaemia, (severe) thrombocytopenia, (severe) leucopenia, (severe) pancytopenia	Bone marrow failure	Aplastic anaemia
Immune system disorders			Anaphylactic reaction	
Metabolism and nutrition disorders		Decreased appetite, anorexia		
Psychiatric disorders		Depression, anxiety, confusion, abnormal thinking	Agitation, psychotic disorder, hallucination	
Nervous system disorders		Headache, insomnia, dysgeusia, (taste disturbance), hypoaesthesia, paraesthesia, peripheral neuropathy, dizziness, convulsion	Tremor	
Eye disorders		Macular oedema, retinal detachment,	Visual disturbance, conjunctivitis	

		vitreous floaters, eye pain		
Ear and labyrinth disorders		Ear pain	Deafness	
Cardiac disorders			Arrhythmia	
Vascular disorders			Hypotension	
Respiratory, thoracic and mediastinal disorders	Dyspnoea	Cough		
Gastrointestinal disorders	Diarrhoea	Nausea, vomiting, abdominal pain, upper abdominal pain, dyspepsia, constipation, flatulence, dysphagia	Abdominal distension, mouth ulceration, pancreatitis	
Hepatobiliary disorders		(Severe) hepatic function abnormal, blood alkaline phosphatase increased, aspartate aminotransferase increased	Alanine aminotransferase increased	
Skin and subcutaneous tissue disorders		Dermatitis, night sweats, pruritus	Alopecia, urticaria, dry skin	
Musculoskeletal and connective tissue disorders		Back pain, myalgia, arthralgia, muscle spasms		
Renal and urinary disorders		Creatinine clearance renal decreased, renal impairment	Haematuria, renal failure	
Reproductive system and breast disorders			Male infertility	
General disorders and administration site conditions		Fatigue, pyrexia, chills, pain, chest pain, malaise, asthenia		
Investigations		Weight decreased, blood creatinine increased		

Severe thrombocytopenia may be associated with potentially life-threatening bleeding. Retinal detachment has only been reported in AIDS patients treated with valganciclovir for CMV retinitis.

c) Paediatric population
Valganciclovir has been studied in 179 paediatric solid organ transplant patients who were at risk of developing CMV disease (aged 3 weeks to 16 years) and in 133 neonates with symptomatic congenital CMV disease (aged 2 to 31 days), with duration of ganciclovir exposure ranging from 2 to 200 days.
The most frequently reported adverse reactions on treatment in paediatric clinical trials were diarrhoea, nausea, neutropenia, leucopenia and anaemia.
In solid organ transplant patients, the overall safety profile was similar in paediatric patients as compared to adults. However, the rates of certain adverse events, such as upper respiratory tract infection, pyrexia, abdominal pain and dysuria, which may be characteristic of the paediatric population, were reported in higher incidence in paediatrics than in adults. Neutropenia was also reported with slightly higher incidence in the two studies conducted in paediatric solid organ transplant patients as compared to adults, but there was no correlation between neutropenia and infectious adverse events in the paediatric population.
In kidney transplant paediatric patients, prolongation of valganciclovir exposure up to 200 days was not associated with an overall increase in the incidence of adverse events. The incidence of severe neutropenia (ANC < 500/µL) was higher in paediatric kidney patients treated until Day 200 as compared to paediatric patients treated until Day 100 and as compared to adult kidney transplant patients treated until Day 100 or Day 200 (see section 4.4).
Only limited data are available in neonates or infants with symptomatic congenital CMV infection treated with valganciclovir, however the safety appears to be consistent with the known safety profile of valganciclovir/ganciclovir.

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 via HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

Overdose experience with Valganciclovir
One adult developed fatal bone marrow depression (medullary aplasia) after several days of dosing that was at least 10-fold greater than recommended for the patient's degree of renal impairment (decreased creatinine clearance).
It is expected that an overdose of valganciclovir could also possibly result in increased renal toxicity (see sections 4.2 and 4.4).
Haemodialysis and hydration may be of benefit in reducing blood plasma levels in patients who receive an overdose of valganciclovir (see section 5.2).

Overdose experience with intravenous ganciclovir
Reports of overdoses with intravenous ganciclovir have been received from clinical trials and during post-marketing experience. In some of these cases no adverse events were reported. 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, elevated creatinine.
- Gastrointestinal toxicity: abdominal pain, diarrhoea, vomiting.
- Neurotoxicity: generalised tremor, convulsion.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: antivirals for systemic use, nucleosides and nucleotides excl. reverse transcriptase inhibitors. ATC code: J05A B14.

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 virustatic 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).
The clinical antiviral effect of valganciclovir has been demonstrated in the treatment of AIDS patients with newly diagnosed CMV retinitis (Clinical trial WV15376). CMV shedding was decreased in urine from 46 % (32/69) of patients at study entry to 7 % (4/55) of patients following four weeks of valganciclovir treatment.

Clinical efficacy and safety
Adult patients
Treatment of CMV retinitis:
Patients with newly diagnosed CMV retinitis were randomised in one study to induction therapy with either valganciclovir 900mg b.i.d or intravenous ganciclovir 5 mg/kg b.i.d. The proportion of patients with photographic progression of CMV retinitis at week 4 was comparable in both treatment groups, 7/70 and 7/71 patients progressing in the intravenous ganciclovir and valganciclovir arms respectively.

Following induction treatment dosing, all patients in this study received maintenance treatment with valganciclovir given at the dose of 900 mg once daily. The mean (median) time from randomisation to progression of CMV retinitis in the group receiving induction and maintenance treatment with valganciclovir was 226 (160) days and in the group receiving induction treatment with intravenous ganciclovir and maintenance treatment with valganciclovir was 219 (125) days.

Prevention of CMV disease in transplantation:
A double-blind, double-dummy clinical active comparator study has been conducted in heart, liver and kidney transplant patients (lung and gastro-intestinal transplant patients were not included in the study) at high-risk of CMV disease (D+/R-) who received either valganciclovir (900 mg od) or oral ganciclovir (1000 mg tid) starting within 10 days of transplantation until Day 100 post- transplant. The incidence of CMV disease (CMV syndrome + tissue invasive disease) during the first 6 months post-transplant was 12.1 % in the valganciclovir arm (n=239) compared with 15.2 % in the oral ganciclovir arm (n=125). The large majority of cases occurred following cessation of prophylaxis (post-Day 100) with cases in the valganciclovir arm occurring on average later than those in the oral ganciclovir arm. The incidence of acute rejection in the first 6 months was 29.7 % in patients randomised to valganciclovir compared with 36.0 % in the oral ganciclovir arm, with the incidence of graft loss being equivalent, occurring in 0.8 % of patients, in each arm.

A double-blind, placebo controlled study has been conducted in 326 kidney transplant patients at high risk of CMV disease (D+/R -) to assess the efficacy and safety of extending valganciclovir CMV prophylaxis from 100 to 200 days post-transplant. Patients were randomized (1:1) to receive valganciclovir tablets (900 mg od) within 10 days of transplantation either until Day 200 post-transplant or until Day 100 post-transplant followed by 100 days of placebo.

The proportion of patients who developed CMV disease during the first 12 months post-transplant is shown in the table below.

Percentage of Kidney Transplant Patients with CMV Disease †, 12 Month ITT Population[#]

	Valganciclovir 900 mg od 100 Days (N = 163)	Valganciclovir 900 mg od 200 Days (N = 155)	Between Treatment Group Difference
Patients with confirmed or assumed CMV disease[‡]	71 (43.6%) [35.8% ; 51.5%]	36 (23.2%) [16.8% ; 30.7%]	20.3% [9.9% ; 30.8%]
Patients with confirmed CMV disease	60 (36.8%) [29.4% ; 44.7%]	25 (16.1%) [10.7% ; 22.9%]	20.7% [10.9% ; 30.4%]

† CMV Disease is defined as either CMV syndrome or tissue invasive CMV.

‡ Confirmed CMV is a clinically confirmed case of CMV disease. Patients were assumed to have CMV disease if there was no week 52 assessment and no confirmation of CMV disease before this time point.

The results found up to 24 months were in line with the up to 12 month results: Confirmed or assumed CMV disease was 48.5% in the 100 days treatment arm versus 34.2% in the 200 days treatment arm; difference between the treatment groups was 14.3% [3.2 %; 25.3%].

Significantly less high risk kidney transplant patients developed CMV disease following CMV prophylaxis with valganciclovir until Day 200 post-transplant compared to patients who received CMV prophylaxis with valganciclovir until Day 100 post-transplant.

The graft survival rate as well as the incidence of biopsy proven acute rejection was similar in both treatment groups. The graft survival rate at 12 months post-transplant was 98.2 % (160/163) for the 100 day dosing regimen and 98.1 % (152/155) for the 200 day dosing regimen. Up to 24 month post-transplant, four additional cases of graft loss were reported, all in the 100 days dosing group. The incidence of biopsy proven acute rejection at 12 months post-transplant was 17.2% (28/163) for the 100 day dosing regimen and 11.0% (17/155) for the 200 day dosing regimen. Up to 24 month post-transplant, one additional case has been reported in the 200 days dosing group.

Viral Resistance

Virus resistant to ganciclovir can arise after chronic dosing with valganciclovir by selection of mutations in the viral kinase gene (UL97) responsible for ganciclovir monophosphorylation and/or the viral polymerase gene (UL54). Viruses containing mutations in the UL97 gene are resistant to ganciclovir alone, whereas viruses with mutations in the UL54 gene are resistant to ganciclovir but may show cross-resistance to other antivirals that also target the viral polymerase.

Treatment of CMV retinitis:

Genotypic analysis of CMV in polymorphonuclear leucocytes (PMNL) isolates from 148 patients with CMV retinitis enrolled in one clinical study has shown that 2.2 %, 6.5 %, 12.8 %, and 15.3 % contain UL97 mutations after 3, 6, 12 and 18 months, respectively, of valganciclovir treatment.

Prevention of CMV disease in transplantation:

Active comparator study

Resistance was studied by genotypic analysis of CMV in PMNL samples collected i) on Day 100 (end of study drug prophylaxis) and ii) in cases of suspected CMV disease up to 6 months after transplantation. From the 245 patients randomised to receive valganciclovir, 198 Day 100 samples were available for testing and no ganciclovir resistance mutations were observed. This compares with 2 ganciclovir resistance mutations detected in the 103 samples tested (1.9 %) for patients in the oral ganciclovir comparator arm.

Of the 245 patients randomised to receive valganciclovir, samples from 50 patients with suspected CMV disease were tested and no resistance mutations were observed. Of the 127 patients randomised on the ganciclovir comparator arm, samples from 29 patients with suspected CMV disease were tested, from which two resistance mutations were observed, giving an incidence of resistance of 6.9 %.

Extending prophylaxis study from 100 to 200 days post-transplant
Genotypic analysis was performed on the UL54 and UL97 genes derived from virus extracted from 72 patients who met the resistance analysis criteria: patients who experienced a positive viral load (>600 copies/ml) at the end of prophylaxis and/or patients who had confirmed CMV disease up to 12 months (52 weeks) post-transplant. Three patients in each treatment group had a known ganciclovir resistance mutation.

Paediatric population
Treatment of CMV retinitis:
The European Medicines Agency has waived the obligation to perform studies with valganciclovir in all subsets of the paediatric population in the treatment of infection due to CMV in immuno-compromised patients (see section 4.2 for information on paediatric use).

Prevention of CMV disease in transplantation
A phase II pharmacokinetic and safety study in paediatric solid organ transplant recipients (aged 4 months to 16 years, n = 63) receiving valganciclovir once daily for up to 100 days according to the paediatric dosing algorithm (see section 4.2) produced exposures similar to that in adults (see section 5.2). Follow up after treatment was 12 weeks. CMV D/R serology status at baseline was D+/R- in 40%, D+/R+ in 38%, D-/R+ in 19% and D-/R- in 3% of the cases. Presence of CMV virus was reported in 7 patients. The observed adverse drug reactions were of similar nature as those in adults (see section 4.8).
A phase IV tolerability study in paediatric kidney transplant recipients (aged 1 to 16 years, n=57) receiving valganciclovir once daily for up to 200 days according to the dosing algorithm (see section 4.2) resulted in a low incidence of CMV. Follow up after treatment was 24 weeks. CMV D/R serology status at baseline was D+/R+ in 45%, D+/R- in 39%, D-/R+ in 7%, D-/R- in 7% and ND/R+ in 2% of the cases. CMV viremia was reported in 3 patients and a case of CMV syndrome was suspected in one patient but not confirmed by CMV PCR by the central laboratory. The observed adverse drug reactions were of similar nature to those in adults (see section 4.8).
These data support the extrapolation of efficacy data from adults to children and provide posology recommendations for paediatric patients.
A phase I pharmacokinetic and safety study in heart transplant patients (aged 3 weeks to 125 days, n=14) who received a single daily dose of valganciclovir according to the paediatric dosing algorithm (see section 4.2) on 2 consecutive days produced exposures similar to those in adults (see section 5.2). Follow up after treatment was 7 days. The safety profile was consistent with other paediatric and adult studies, although patient numbers and valganciclovir exposure were limited in this study.
Congenital CMV
The efficacy and safety of ganciclovir and/or valganciclovir was studied in neonates and infants with congenital symptomatic CMV infection in two studies.
In the first study, pharmacokinetics and safety of a single dose of valganciclovir (dose range 14-16-20 mg/kg/dose) was studied in 24 neonates (aged 8 to 34 days) with symptomatic congenital CMV disease (see section 5.2). The neonates received 6 weeks of antiviral treatment, whereas 19 of the 24 patients received up to 4 weeks of treatment with oral valganciclovir, in the remaining 2 weeks they received i.v. ganciclovir. The 5 remaining patients received i.v. ganciclovir for the most time of the study period. In the second study the efficacy and safety of six weeks versus six months of valganciclovir treatment was studied in 109 infants aged 2 to 30 days with symptomatic congenital CMV disease. All infants received oral valganciclovir at a dose of 16 mg/kg b.i.d. for 6 weeks. After 6 weeks of treatment the infants were randomized 1:1 to continue treatment with valganciclovir at the same dose or receive a matched placebo to complete 6 months of treatment.
This treatment indication is not currently recommended for valganciclovir. The design of the studies and results obtained are too limited to allow appropriate efficacy and safety conclusions on valganciclovir.

5.2 Pharmacokinetic properties

The pharmacokinetic properties of valganciclovir have been evaluated in HIV- and CMV-seropositive patients, patients with AIDS and CMV retinitis and in solid organ transplant patients.

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. Systemic exposure to valganciclovir is transient and low. The absolute bioavailability of ganciclovir from valganciclovir is approximately 60 % across all the patient populations

studied and the resultant exposure to ganciclovir is similar to that after its intravenous administration (please see below). For comparison, the bioavailability of ganciclovir after administration of 1000 mg oral ganciclovir (as capsules) is 6 - 8 %.

Valganciclovir in HIV positive, CMV positive patients:
Systemic exposure of HIV positive, CMV positive 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, p.o.) 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 (1000 mg t.i.d.) n = 82	Valganciclovir (900 mg, od) 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.

Food effect:
Dose proportionality with respect to ganciclovir AUC following administration of valganciclovir in the dose range 450 to 2625 mg was demonstrated only under fed conditions. When valganciclovir was given with food at the recommended dose of 900 mg, higher values were seen in both mean ganciclovir AUC (approximately 30 %) and mean ganciclovir C_{max} values (approximately 14 %) than in the fasting state. Also, the inter-individual variation in exposure of ganciclovir decreases when taking valganciclovir with food. valganciclovir has only been administered with food in clinical studies. Therefore, it is recommended that valganciclovir be administered with food (see section 4.2).

Distribution
Because of rapid conversion of valganciclovir to ganciclovir, protein binding of valganciclovir was not determined. Plasma protein binding of ganciclovir was 1 – 2 % over concentrations of 0.5 and 51 µg/ml. The steady state volume of distribution (V_d) of ganciclovir after intravenous administration was 0.680 ± 0.161 l/kg (n=114).

Biotransformation
Valganciclovir is rapidly and extensively metabolised to ganciclovir; no other metabolites have been detected. No metabolite of orally administered radiolabelled ganciclovir (1000 mg single dose) accounted for more than 1 – 2 % of the radioactivity recovered in the faeces or urine.

Elimination
Following dosing with valganciclovir, renal excretion, as ganciclovir, by glomerular filtration and active tubular secretion is the major route of elimination of valganciclovir. Renal clearance accounts for 81.5 % ± 22 % (n=70) of the systemic clearance of ganciclovir. Post-hoc Bayesian estimates for population mean apparent clearance of ganciclovir

in patients with CrCl > 60 ml/min is 14.05 ± 4.13 l/h. In patients with renal impairment, the mean apparent clearance of ganciclovir is 8.46 ± 1.67 l/h (CrCl between 40 and 60 ml/min) and 7.00 ± 1.08 l/h (CrCl between 25 and 40 ml/min). The half-life of ganciclovir from valganciclovir is 4.1 ± 0.9 hours in HIV- and CMV-seropositive patients.

Pharmacokinetics in special clinical situations

Patients with renal impairment

Decreasing renal function resulted in decreased clearance of ganciclovir from valganciclovir with a corresponding increase in terminal half-life. Therefore, dosage adjustment is required for renally impaired patients (see sections 4.2 and 4.4).

Patients undergoing haemodialysis

For patients receiving haemodialysis dose recommendations for valganciclovir 450 mg film-coated tablets cannot be given. This is because an individual dose of valganciclovir required for these patients is less than the 450 mg tablet strength. Thus, valganciclovir film-coated tablets should not be used in these patients (see sections 4.2 and 4.4).

Patients with hepatic impairment

The safety and efficacy of Valganciclovir Rowex film-coated tablets have not been studied in patients with hepatic impairment. Hepatic impairment should not affect the pharmacokinetics of ganciclovir since it is excreted renally and, therefore, no specific dose recommendation is made.

Patients with cystic fibrosis

In a phase I pharmacokinetic study in lung transplant recipients with or without cystic fibrosis (CF), 31 patients (16 CF/15 non-CF) received post-transplant prophylaxis with 900 mg/day valganciclovir. The study indicated that cystic fibrosis had no statistically significant influence on the overall average systemic exposure to ganciclovir in lung transplant recipients. Ganciclovir exposure in lung transplant recipients was comparable to that shown to be efficacious in the prevention of CMV disease in other solid organ transplant recipients.

Paediatric population

In a phase II pharmacokinetic and safety study in paediatric solid organ transplant recipients (aged 4 months to 16 years, n = 63) valganciclovir was given once daily for up to 100 days. Pharmacokinetic parameters were similar across organ type and age range and comparable with adults. Population pharmacokinetic modeling suggested that bioavailability was approximately 60%. Clearance was positively influenced by both body surface area and renal function.

In a phase I pharmacokinetic and safety study in paediatric heart transplant recipients (aged 3 weeks to 125 days, n = 14), valganciclovir was given once daily for two study days. Population pharmacokinetics estimated that mean bioavailability was 64%.

A comparison of the results from these two studies and the pharmacokinetic results from the adult population shows that ranges of $AUC_{0\text{-}24h}$ were very similar across all age groups, including adults. Mean values for $AUC_{0\text{-}24h}$ and C_{max} were also similar across the paediatric age groups < 12 years old, although there was a trend of decreasing mean values for $AUC_{0\text{-}24h}$ and C_{max} across the entire pediatric age range, which appeared to correlate with increasing age. This trend was more apparent for mean values of clearance and half-life ($t_{1/2}$); however this is to be expected as clearance is influenced by changes in weight, height and renal function associated with patient growth, as indicated by population pharmacokinetic modelling.

The following table summarizes the model-estimated $AUC_{0\text{-}24h}$ ranges for ganciclovir from these two studies, as well as mean and standard deviation values for $AUC_{0\text{-}24h,}$ C_{max}, CL and t ½ for the relevant paediatric age groups compared to adult data:

PK Parameter	**Adults***	**Paediatrics**			
	≥ 18 years (n=160)	**< 4 months (n = 14)**	**4 months - ≤ 2 years (n=17)**	**> 2 - < 12 years (n=21)**	**≥ 12 years – 16 years (n=25)**
$AUC_{0\text{-}24h}$ (µg·h/ml)	46.3 ± 15.2	68.1 ± 19.8	64.3 ± 29.2	59.2 ± 15.1	50.3 ± 15.0
Range of $AUC_{0\text{-}24h}$	15.4 – 116.1	34 - 124	34 - 152	36 - 108	22 - 93
C_{max} (µg/ml)	5.3 ± 1.5	10.5 ± 3.36	10.3 ± 3.3	9.4 ± 2.7	8.0 ± 2.4

Clearance (l/h)	12.7 ± 4.5	1.25 ± 0.473	2.5 ± 2.4	4.5 ± 2.9	6.4 ± 2.9
$t_{1/2}$ (h)	6.5 ± 1.4	1.97 ± 0.185	3.1 ±1.4	4.1 ± 1.3	5.5 ± 1.1

* Extracted from study report PV 16000

The once daily dose of valganciclovir in both of the studies described above was based on body surface area (BSA) and creatinine clearance (CrCl) derived from a modified Schwartz formula, and was calculated using dosing algorithm presented in section 4.2.

Ganciclovir pharmacokinetics following valganciclovir administration were also evaluated in two studies in neonates and infants with symptomatic congenital CMV disease. In the first study 24 neonates aged 8 to 34 days received 6 mg/kg intravenous ganciclovir twice daily. Patients were then treated with oral valganciclovir, where the dose of valganciclovir powder for oral solution ranged from 14 mg/kg to 20 mg/kg twice daily; total treatment duration was 6 weeks. A dose of 16 mg/kg twice daily of valganciclovir powder for oral solution provided comparable ganciclovir exposure as 6 mg/kg intravenous ganciclovir twice daily in neonates, and also achieved ganciclovir exposure similar to the effective adult 5 mg/kg intravenous dose.
In the second study, 109 neonates aged 2 to 30 days received 16 mg/kg valganciclovir powder for oral solution twice daily for 6 weeks and subsequently 96 out of 109 enrolled patients were randomized to continue receiving valganciclovir or placebo for 6 months. However, the mean $AUC_{0\text{-}12h}$ was lower compared to the mean $AUC_{0\text{-}12h}$ values from the first study. The following table shows the mean values of AUC, C_{max}, and $t_{½}$ including standard deviations compared with adult data:

PK Parameter	Adults	Paediatrics (neonates and infants)		
	5 mg/kg GAN Single dose (n=8)	**6 mg/kg GAN Twice daily (n=19)**	**16 mg/kg VAL Twice daily (n=19)**	**16 mg/kg VAL Twice daily (n = 100)**
$AUC_{0\text{-}\infty}$ (µg·h/mL)	25.4 ± 4.32	-	-	-
$AUC_{0\text{-}12h}$ (µg·h/mL)	-	38.2 ± 42.7	30.1 ± 15.1	20.85 ± 5.40
C_{max} (µg/ml)	9.03 ± 1.26	12.9 ± 21.5	5.44 ± 4. 04	-
$t_{1/2}$ (h)	3.32 ± 0.47	2.52 ± 0. 55	2.98 ± 1. 26	2.98 ± 1.12

GAN = Ganciclovir, i.v. VAL = Valganciclovir, oral

These data are too limited to allow conclusions regarding efficacy or posology recommendations for paediatric patients with congenital CMV infection.

5.3 Preclinical safety data

Valganciclovir is a pro-drug of ganciclovir and therefore effects observed with ganciclovir apply equally to valganciclovir. Toxicity of valganciclovir in pre-clinical safety studies was the same as that seen with ganciclovir and was induced at ganciclovir exposure levels comparable to, or lower than, those in humans given the induction dose. These findings were gonadotoxicity (testicular cell loss) and nephrotoxicity (uraemia, cell degeneration), which were irreversible; myelotoxicity (anaemia, neutropenia, lymphocytopenia) and gastrointestinal toxicity (mucosal cell necrosis), which were reversible.

Further studies have shown ganciclovir to be mutagenic, carcinogenic, teratogenic, embryotoxic, aspermatogenic (i.e. impairs male fertility) and to suppress female fertility.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Core:
Cellulose microcrystalline (PH101)
Crospovidone (Type A)
Povidone (K-30)
Stearic acid 50

Film-coating:
Opadry Pink 15B24005:
Hypromellose (3 cP)
Hypromellose (6 cP)
Titanium dioxide (E171)
Macrogol 400
Iron oxide red (E172)
Polysorbate 80

6.2 Incompatibilities

Not applicable

6.3 Shelf life

3 years

Bottles:
After first opening: 2 months

6.4 Special precautions for storage

This medicine does not require any special storage condition

6.5 Nature and contents of container

Aluminium/PVC/Aluminium/OPA blister: 10, 30, 60, 90, 120 film-coated tablets.

HDPE container with [child resistant] polypropylene screw caps with aluminium pulp liners and cotton enclosed: 60 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Rowex Ltd
Bantry
Co. Cork
Ireland

8 MARKETING AUTHORISATION NUMBER

PA0711/233/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 9th January 2015

10 DATE OF REVISION OF THE TEXT