NEW ZEALAND DATA SHEET

VACLOVIR

1. Product Name

Vaclovir 500 mg & 1000 mg, film coated tablet.

2. Qualitative and Quantitative Composition

Each film coated tablet contains 500 mg or 1000 mg of valaciclovir (as hydrochloride).

For the full list of excipients, see section 6.1.

3. Pharmaceutical Form

VACLOVIR 500 mg tablets are presented as white coloured, oval shaped, biconvex film coated tablets with a break line on one side and plain on the other side. Each tablet contains valaciclovir hydrochloride equivalent to 500 mg valaciclovir.

VACLOVIR 1000 mg tablets are presented as white coloured, oval shaped, biconvex film coated tablets with a break line on one side and plain on the other side. Each tablet contains valaciclovir hydrochloride equivalent to 1000 mg valaciclovir.

VACLOVIR 500 mg and VACLOVIR 1000 mg tablets can be divided into equal doses.

4. Clinical Particulars

4.1 Therapeutic indications

VACLOVIR is indicated for the treatment of herpes zoster (shingles) and the reduction of zoster – associated pain, which includes acute and post herpetic neuralgia, when given to immunocompetent patients in infection of less than 72 hours duration.

VACLOVIR is indicated for the treatment of herpes simplex infections of the skin and mucous membranes including initial and recurrent genital herpes in immunocompetent patients.

VACLOVIR can prevent lesion development when taken at the first signs and symptoms of a herpes simplex virus (HSV) recurrence.

VACLOVIR is indicated for the prevention (suppression) of recurrent herpes simplex infections of the skin and mucous membranes, including genital herpes in immunocompetent and immunocompromised patients.

VACLOVIR is indicated for the prophylaxis of cytomegalovirus (CMV) infection and disease, following organ transplantation. CMV prophylaxis with VACLOVIR reduces acute graft rejection (renal transplant patients), opportunistic infections and other herpes virus infections (herpes simplex virus (HSV), varicella zoster virus (VZV)).

4.2 Dose and method of administration

Dose

Treatment of varicella zoster virus infections

Herpes zoster (shingles) including ophthalmic zoster

The dosage in adults is 1000 mg of VACLOVIR to be taken 3 times daily for 7 days.

Treatment of herpes simplex infections

The dosage in adults is 500 mg of VACLOVIR to be taken twice daily.

For recurrent episodes, treatment should be for 5 days. For initial episodes, which can be more severe, treatment may have to be extended to 10 days. Dosing should begin as early as possible. For recurrent episodes of herpes simplex, this should ideally be during the prodromal period or immediately the first signs or symptoms appear.

Prevention (suppression) of recurrences of herpes simplex infections

In immunocompetent adult patients, 500 mg of VACLOVIR to be taken once daily.

Some patients with very frequent recurrences (e.g. 10 or more per year) may gain additional benefit from the daily dose of 500 mg being taken as a divided dose (250 mg twice daily).

For immunocompromised adult patients the dose is 500 mg twice daily.

Prophylaxis of cytomegalovirus infection (CMV) and disease

Dosage in adults and adolescents (from 12 years of age)

The dosage of VACLOVIR is 2 g four times a day, to be initiated as early as possible post-transplant. This dose should be reduced according to creatinine clearance.

The duration of treatment will usually be 90 days, but may need to be extended in high risk patients.

Special populations

Elderly

Dosage modification is not required unless renal function is significantly impaired. Adequate hydration should be maintained.

Renal impairment

Herpes zoster treatment and herpes simplex treatment and prevention (suppression)

Caution is advised when administering VACLOVIR to patients with impaired renal function. Adequate hydration should be maintained.

The dosage of VACLOVIR should be reduced in patients with significantly impaired renal function as shown in the table below.

There is no experience with valaciclovir use in paediatric patients with a creatinine clearance of <50 mL/min/1.73m^2.

Indication	**Creatinine clearance mL/min**	**VACLOVIR dosage**
Herpes zoster (treatment) in immunocompetent patients	at least 50 30 to 49 10-29 less than 10	1 g three times a day 1 g twice a day 1 g once a day 500 mg once a day

Herpes simplex (treatment) in immunocompetent patients	at least 30 less than 30	500 mg twice a day 500 mg once a day
Herpes simplex prevention (suppression): - immunocompetent patients - immunocompromised patients	 at least 30 less than 30 at least 30 less than 30	 500 mg once a day 250 mg once a day 500 mg twice a day 500 mg once a day

In patients on intermittent haemodialysis, the VACLOVIR dosage should be administered after the haemodialysis has been performed.

CMV prophylaxis

Caution is advised when administering VACLOVIR to patients with impaired renal function. Adequate hydration should be maintained.

The dosage of VACLOVIR should be adjusted in patients with impaired renal function as shown in the table below:

Creatinine clearance mL/min	**VACLOVIR dosage**
75 or greater	2 g four times daily
50 to less than 75	1.5 g four times a day
25 to less than 50	1.5 g three times a day
10 to less than 25	1.5 g twice a day
less than 10 or dialysis[◊]	1.5 g once a day

[◊]In patients on haemodialysis, the VACLOVIR dosage should be administered after the haemodialysis has been performed.

The creatinine clearance should be monitored frequently, especially during periods when renal function is changing rapidly e.g. immediately after transplantation or engraftment. The VACLOVIR dosage should be adjusted accordingly.

Hepatic impairment

Studies with a 1 g unit dose of valaciclovir show that dose modification is not required in patients with mild or moderate cirrhosis (hepatic synthetic function maintained). Pharmacokinetic data in patients with advanced cirrhosis (impaired hepatic synthetic function and evidence of portal-systemic shunting) do not indicate the need for dosage adjustment; however, clinical experience is limited. For higher doses recommended for CMV prophylaxis (see section 4.4).

Paediatric

There are no data available on the use of valaciclovir in children.

4.3 Contraindications

VACLOVIR is contra-indicated in patients known to be hypersensitive to valaciclovir, aciclovir or any components of the formulations of VACLOVIR.

4.4 Special warnings and precautions for use

Thrombotic thrombocytopenic purpura or haemolytic uraemic syndrome (TTP/HUS), in some cases resulting in death, has occurred in patients with advanced HIV disease who were treated with valaciclovir for prolonged periods and also in allogenic bone marrow transplant and renal transplant recipients who were treated with valaciclovir while participating in clinical trials at doses of 8 grams per day. Treatment with valaciclovir should be stopped immediately if clinical signs, symptoms, and laboratory abnormalities consistent with TTP/HUS occur.

Similar signs have been observed in patients with the same underlying or concurrent conditions who were not treated with valaciclovir.

Use of valaciclovir at doses of 1000 mg/day in immunocompromised patients with $CD4^+$ counts > $100x10^6$L has not been associated with occurrences of thrombotic microangiopathy (TMA). However use in severely immunocompromised patients ($CD4^+$ counts < $100x10^6$ L) has not been examined at this low dosage.

Hydration status

Care should be taken to ensure adequate fluid intake in patients who are at risk of dehydration, particularly the elderly.

Patients without adequate hydration: Precipitation of aciclovir in renal tubules may occur when the solubility (2.5 mg/mL) is exceeded in the intratubular fluid. Adequate hydration should be maintained for all patients.

Use in genital herpes

Suppressive therapy with valaciclovir reduces the risk of transmitting genital herpes. It does not cure genital herpes or completely eliminate the risk of transmission. In addition to therapy with valaciclovir, it is recommended that patients use safer sex practices.

Central nervous system effect

Reversible neurological reactions including dizziness, confusion, hallucinations, rarely decreased consciousness and very rarely tremor, ataxia, dysarthria, convulsions, encephalopathy and coma have been reported. These events are usually seen in patients with renal impairment or with other predisposing factors. In organ transplant patients receiving high doses (8 g daily) of valaciclovir for CMV prophylaxis, neurological reactions occurred more frequently compared with lower doses. Valaciclovir should be discontinued if central nervous system adverse reactions occur.

Use in renal impairment and in elderly patients

Aciclovir is eliminated by renal clearance, therefore the dose of valaciclovir must be reduced in patients with renal impairment (see section 4.2). Elderly patients are likely to have reduced renal function and therefore the need for dose reduction must be considered in this group of patients. Both elderly patients and patients with renal impairment are at increased risk of developing neurological side effects and should be closely monitored for evidence of these effects. In the reported cases, these reactions were generally reversible on discontinuation of treatment (see section 4.8).

Use of high dose valaciclovir in hepatic impairment and liver transplantation

There are no data available on the use of high doses of valaciclovir (8 g/day) in patients with liver disease. Caution should therefore be exercised when administering high doses of valaciclovir to these patients. Specific studies of valaciclovir have not been conducted in liver transplantation; however high dose aciclovir prophylaxis has been shown to reduce CMV infection and disease

4.5 Interaction with other medicines and other forms of interaction

The combination of valaciclovir with nephrotoxic medicinal products should be made with caution, especially in subjects with impaired renal function, and warrants regular monitoring of renal function.

This applies to concomitant administration with aminoglycosides, organoplatinum compounds, iodinated contrast media, methotrexate, pentamidine, foscarnet, ciclosporin, and tacrolimus.

Aciclovir is eliminated primarily unchanged in the urine via active renal tubular secretion. Any medicines administered concurrently that compete with this mechanism may increase aciclovir plasma concentrations following valaciclovir administration.

Following 1 g valaciclovir, cimetidine and probenecid increase the AUC of aciclovir by this mechanism, and reduce aciclovir renal clearance. However, no dosage adjustment is necessary at this dose because of the wide therapeutic index of aciclovir.

In patients receiving high-dose valaciclovir (8 g/day) for CMV prophylaxis, caution is required during concurrent administration with medicines which compete with aciclovir for elimination, because of the potential for increased plasma levels of one or both medicines or their metabolites. Increases in plasma AUCs of aciclovir and of the inactive metabolite of mycophenolate mofetil, an immunosuppressant agent used in transplant patients, have been shown when oral aciclovir and mycophenolate mofetil are co-administered.

Care is also required (with monitoring for changes in renal function) if administering high-dose valaciclovir with medicines which affect other aspects of renal physiology (e.g. ciclosporin, tacrolimus).

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data on the use of valaciclovir in pregnancy. VACLOVIR should only be used in pregnancy if the potential benefits of treatment outweigh the potential risk.

Pregnancy registries have documented the pregnancy outcomes in women exposed to valaciclovir or to any formulation of aciclovir (the active metabolite of valaciclovir); 111 and 1246 outcomes (29 and 756 exposed during the first trimester of pregnancy), respectively, were obtained from women prospectively registered. The findings of the aciclovir pregnancy registry have not shown an increase in the number of birth defects amongst aciclovir-exposed subjects compared with the general population, and any birth defects showed no uniqueness or consistent pattern to suggest a common cause. Given the small number of women enrolled into the valaciclovir pregnancy registry, reliable and definitive conclusions could not be reached regarding the safety of valaciclovir in pregnancy.

Breast-feeding

Aciclovir, the principal metabolite of valaciclovir, is excreted in breast milk. Following oral administration of a 500 mg dose of valaciclovir, peak aciclovir concentrations (C_{max}) in breast milk ranged from 0.5 to 2.3 (median 1.4) times the corresponding maternal aciclovir serum concentrations. The aciclovir breast milk to maternal serum AUC ratios ranged from 1.4 to 2.6 (median 2.2). The median aciclovir concentration in breast milk was 2.24 micrograms/mL (9.95 micromoles/L). With a maternal valaciclovir dosage of 500 mg twice daily, this level would expose a nursing infant to a daily oral aciclovir dosage of about 0.61 mg/kg/day. The elimination half-life of aciclovir from breast milk was similar to that for serum.

Unchanged valaciclovir was not detected in maternal serum, breast milk or infant urine.

Caution is therefore advised if VACLOVIR is to be administered to a nursing woman. However aciclovir is used to treat neonatal herpes simplex at intravenous doses of 30 mg/kg/day.

Fertility

No human fertility studies were performed with valaciclovir, but no changes in sperm count, motility or morphology were reported in 20 patients after 6 months of daily treatment with 400 mg to 1 g aciclovir.

4.7 Effects on ability to drive and use machines

The clinical status of the patient and the adverse event profile of valaciclovir should be borne in mind when considering the patient's ability to drive or operate machinery. There have been no studies to investigate the effect of valaciclovir on driving performance or the ability to operate machinery. Further a detrimental effect on such activities cannot be predicted from the pharmacology of the active substance.

4.8 Undesirable effects

Adverse reactions are listed below by MedDRA body system organ class and by frequency.

The frequency categories used are:

very common	≥ 1 in 10,
common	≥ 1 in 100 and < 1 in 10,
uncommon	≥ 1 in 1,000 and < 1 in 100,
rare	≥ 1 in 10,000 and < 1 in 1,000,
very rare	< 1 in 10,000.

Clinical trial data have been used to assign frequency categories to adverse reactions if, in the trials, there was evidence of an association with valaciclovir (i.e. there was a statistically significant difference between the incidence in patients taking valaciclovir and placebo). For all other adverse events, spontaneous post-marketing data has been used as a basis for allocating frequency.

Clinical trial data

Nervous system disorders

Common: Headache

Gastrointestinal disorders

Common: Nausea

Post-marketing data

Blood and lymphatic system disorders

Very rare: Leukopenia, thrombocytopenia

Leukopenia is mainly reported in immunocompromised patients

Immune system disorders

Very rare: Anaphylaxis

Psychiatric and nervous system disorders

Rare: Dizziness, confusion, hallucinations, decreased consciousness

Very rare: Agitation, tremor, ataxia, dysarthria, psychotic symptoms, convulsions, encephalopathy, coma

The above events are generally reversible and usually seen in patients with renal impairment or with other predisposing factors (see section 4.4). In organ transplant patients receiving high doses (8 g daily) of valaciclovir for CMV prophylaxis, neurological reactions occurred more frequently compared with lower doses.

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnoea

Gastrointestinal disorders

Rare: Abdominal discomfort, vomiting, diarrhoea

Hepato-biliary disorders

Very rare: Reversible increases in liver function tests

These are occasionally described as hepatitis.

Skin and subcutaneous tissue disorders

Uncommon: Rashes including photosensitivity

Rare: Pruritus

Very rare: Urticaria, angioedema

Renal and urinary disorders

Rare: Renal impairment

Very rare: Acute renal failure, renal pain

Renal pain may be associated with renal failure.

Other:

There have been reports of renal insufficiency, microangiopathic haemolytic anaemia and thrombocytopenia (sometimes in combination) in severely immunocompromised patients, particularly those with advanced HIV disease, receiving high doses (8 g daily) of valaciclovir for prolonged periods in clinical trials. These findings have been observed in patients not treated with valaciclovir who have the same underlying or concurrent conditions.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicine is important. It allows continued monitoring of the benefit/risk balance of the medicine. Healthcare professionals are asked to report any suspected adverse reactions https://nzphvc.otago.ac.nz/reporting/

4.9 Overdose

Symptoms and signs

Acute renal failure and neurological symptoms, including confusion, hallucinations, agitation, decreased consciousness and coma, have been reported in patients receiving overdoses of valaciclovir. Nausea and vomiting may also occur. Caution is required to prevent inadvertent overdosing. Many of the reported cases involved renally impaired and elderly patients receiving repeated overdoses, due to lack of appropriate dosage reduction.

Treatment

Patients should be observed closely for signs of toxicity. Haemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered a management option in the event of symptomatic overdose.

For further advice on management of overdose please contact the National Poisons Information Centre (0800 POISON or 0800 764 766).

5. Pharmacological Properties

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Direct acting antivirals, ATC code: J05AB11

Mechanism of action

Valaciclovir, an antiviral, is the L-valine ester of acyclovir. Aciclovir is a purine (guanine) nucleoside analogue.

Valaciclovir is rapidly and almost completely converted in man to aciclovir and valine, probably by the enzyme referred to as valaciclovir hydrolase.

Aciclovir is a specific inhibitor of the herpes viruses with *in vitro* activity against HSV type 1 and type 2, VZV, CMV, Epstein-Barr Virus (EBV), and human herpes virus 6 (HHV-6). Aciclovir inhibits herpes virus DNA synthesis once it has been phosphorylated to the active triphosphate form.

The first stage of phosphorylation requires the activity of a virus-specific enzyme. In the case of HSV, VZV and EBV this enzyme is the viral thymidine kinase (TK), which is only present in virus infected cells. Selectivity is maintained in CMV with phosphorylation, at least in part, being mediated through the phosphotransferase gene product of UL97. This requirement for activation of aciclovir by a virus specific enzyme largely explains its selectivity.

The phosphorylation process is completed (conversion from mono- to triphosphate) by cellular kinases. Aciclovir triphosphate competitively inhibits the virus DNA polymerase and incorporation of this nucleoside analogue results in obligate chain termination, halting virus DNA synthesis and thus blocking virus replication.

Pharmacodynamic effects

Resistance is normally due to a thymidine kinase deficient phenotype which results in a virus which is profoundly disadvantaged in the natural host. Infrequently, reduced sensitivity to aciclovir has been described as a result of subtle alterations in either the virus thymidine kinase or DNA polymerase. The virulence of these variants resembles that of the wild-type virus.

Extensive monitoring of clinical HSV and VZV isolates from patients receiving aciclovir therapy or prophylaxis has revealed that virus with reduced sensitivity to aciclovir is extremely rare in the immunocompetent and is only found infrequently in severely immunocompromised individuals e.g. organ or bone marrow transplant recipients, patients receiving chemotherapy for malignant disease and people infected with the human immunodeficiency virus (HIV).

5.2 Pharmacokinetic properties

Absorption

After oral administration valaciclovir is well absorbed and rapidly and almost completely converted to aciclovir and valine. This conversion is probably mediated by an enzyme isolated from human liver referred to as valaciclovir hydrolase.

The bioavailability of aciclovir from 1000 mg valaciclovir is 54%, and is not reduced by food. Valaciclovir pharmacokinetics are not dose-proportional. The rate and extent of absorption decreases with increasing dose, resulting in a less than proportional increase in C_{max} over the therapeutic dose range and a reduced bioavailability at doses above 500 mg. Mean peak aciclovir concentrations are 10-37 micromoles/L (2.2-8.3 micrograms/mL) following single doses of 250-2000 mg valaciclovir to healthy subjects with normal renal function, and occur at a median time of 1.00-2.00 hours post dose.

Peak plasma concentrations of valaciclovir are only 4% of aciclovir levels, occur at a median time of 30 to 100 minutes post dose, and are at or below the limit of quantification 3 hours after dosing. The valaciclovir and aciclovir pharmacokinetic profiles are similar after single and repeat dosing.

Herpes zoster and herpes simplex do not significantly alter the pharmacokinetics of valaciclovir and aciclovir after oral administration of valaciclovir.

Distribution

Binding of valaciclovir to plasma proteins is very low (15%). CSF penetration, determined by CSF/plasma AUC ratio, is about 25% for aciclovir and the metabolite 8-hydroxy-aciclovir (8-OH-ACV), and about 2.5% for the metabolite 9-(carboxymethoxy) methylguanine (CMMG) (see section 5.2).

Biotransformation

After oral administration, valaciclovir is converted to aciclovir and L-valine by first-pass intestinal and/or hepatic metabolism. Aciclovir is converted to a small extent to the metabolites 9-(carboxymethoxy) methylguanine (CMMG) by alcohol and aldehyde dehydrogenase and to 8-hydroxy-aciclovir (8-OH-ACV) by aldehyde oxidase. Approximately 88% of the total combined plasma exposure is attributable to aciclovir, 11% to CMMG and 1% to 8-OH-ACV. Neither valaciclovir nor aciclovir is metabolised by cytochrome P450 enzymes.

Elimination

In patients with normal renal function the plasma elimination half-life of aciclovir after both single and multiple dosing with valaciclovir is approximately 3 hours. Less than 1% of the administered dose of valaciclovir is recovered in the urine as unchanged drug. Valaciclovir is eliminated in the urine principally as aciclovir (greater than 80% of the recovered dose) and the known aciclovir metabolite, 9-(carboxymethoxy) methylguanine (CMMG).

Special patient populations:

Renal impairment

The elimination of aciclovir is correlated to renal function, and exposure to aciclovir will increase with increased renal impairment. In patients with end-stage renal disease, the average elimination half-life of aciclovir after valaciclovir administration is approximately 14 hours, compared with about 3 hours for normal renal function (see section 4.2).

Exposure to aciclovir and its metabolites CMMG and 8-OH-ACV in plasma and cerebrospinal fluid (CSF) was evaluated at steady-state after multiple-dose valaciclovir administration in 6 subjects with normal renal function (mean creatinine clearance 111 mL/min, range 91-144 mL/min) receiving 2000 mg every 6 hours and 3 subjects with severe renal impairment (mean CLcr 26 mL/min, range 17-31 mL/min) receiving 1500 mg every 12 hours. In plasma as well as CSF, concentrations of aciclovir, CMMG and 8-OH-ACV were on average 2, 4 and 5-6 times higher, respectively, in severe renal impairment compared with normal renal function. There was no difference in extent of CSF penetration (as determined by CSF/plasma AUC ratio) for aciclovir, CMMG or 8-OH-aciclovir between the two populations (see section 5.2).

Hepatic impairment

Administration of valaciclovir to patients with moderate (biopsy-proven cirrhosis) or severe (with and without ascites and biopsy-proven cirrhosis) liver disease indicated that the rate but not the extent of conversion of valaciclovir to aciclovir is reduced, and the aciclovir half-life is not affected. Dosage modification is not recommended for patients with cirrhosis.

HIV infection

In patients with HIV infection, the disposition and pharmacokinetic characteristics of aciclovir after oral administration of single or multiple doses of 1000 mg or 2000 mg valaciclovir are unaltered compared with healthy subjects.

Organ transplantation

In transplant recipients receiving valaciclovir 2000 mg four times daily, aciclovir peak concentrations are similar to or greater than those in healthy volunteers receiving the same dose. The estimated daily AUCs are appreciably greater.

Elderly

After single-dose administration of 1 gram of valaciclovir in healthy geriatric volunteers, the half-life of aciclovir was 3.11 ± 0.51 hours, compared with 2.91 ± 0.63 hours in healthy younger adult volunteers. The pharmacokinetics of aciclovir following single- and multiple-dose oral administration of valaciclovir in geriatric volunteers varied with renal function. Dose reduction may be required in geriatric patients, depending on the underlying renal status of the patient (see section 4.2).

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, and carcinogenic potential.

Fertility

In animal studies, valaciclovir did not affect fertility. However, high parenteral doses of aciclovir caused testicular effects in rats and dogs.

Teratogenicity

Valaciclovir was not teratogenic in rats or rabbits. Valaciclovir is almost completely metabolised to aciclovir. Subcutaneous administration of aciclovir in internationally accepted tests did not produce teratogenic effects in rats or rabbits. In additional studies in rats, foetal abnormalities were observed at subcutaneous doses that produced plasma levels of 100 microgram/mL and maternal toxicity.

Mutagenicity

The results of mutagenicity tests *in vitro* and *in vivo* indicate that valaciclovir is unlikely to pose a genetic risk to humans.

Carcinogenicity

Valaciclovir was not carcinogenic in bio-assays performed in mice and rats.

6. Pharmaceutical Particulars

6.1 List of excipients

VACLOVIR tablets contain the following excipients:

- Cellulose microcrystalline
- Magnesium stearate
- Hypromellose
- Titanium dioxide
- Polyethylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

Store at or below 25°C.

6.5 Nature and contents of container

VACLOVIR 500 mg tablets are available in OPA / AL / PVC / AL cold form blister packs of 2, 4, 6, 10, 20, 30, 42, 60, 80, 90, 100, 240 & 480 tablets and HDPEB bottles of 30, 100, 240, 480 & 500 tablets.

VACLOVIR 1000 mg tablets are available in OPA / AL / PVC / AL cold form blister packs of 3, 21 & 30 tablets and HDPE bottles of 100 & 250 tablets.

Not all strengths, pack types or sizes may be marketed.

6.6 Special precautions for disposal

N/A

7. Medicines Schedule

Prescription Medicine

8. Sponsor Details

Mylan New Zealand Ltd
PO Box 11183
Ellerslie
AUCKLAND
Telephone 0800 579 811

9. Date of First Approval

16 September 2010

10. Date of Revision of the Text

27 January 2021

Section	Summary of changes
1, 2, 3, 4.2, 6.5	Removed all information related to Vaclovir 250 mg.
8	Updated sponsor contact number.