ACICLOVIR 200mg TABLETS
ACICLOVIR 400mg TABLETS

PL 30306/0282-3

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Marketing Authorisations (licences) for the medicinal products ACICLOVIR 200mg and 400mg TABLETS (product licence numbers: PL 30306/0282-3). ACICLOVIR TABLETS are available by prescription only.

Aciclovir is an antiviral medicine, which acts on infected cells by stopping the virus growing.

Aciclovir tablets are used to:
- treat or prevent herpes simplex infections of the skin and mucous membranes e.g. cold sores and genital herpes
- prevent herpes simplex infections in patients whose immune system is not working properly
- treat chicken pox (varicella infection)

ACICLOVIR TABLETS raised no clinically significant safety concerns and it was, therefore, judged that the benefits of using these products outweigh the risks; hence Marketing Authorisations have been granted.
ACICLOVIR 200mg TABLETS

ACICLOVIR 400mg TABLETS

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SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Marketing Authorisations for the medicinal products ACICLOVIR 200mg and 400mg TABLETS to Actavis Group PTC ehf on 19 May 2010.

These are abridged applications submitted under Article 10(c) of EC Directive 2001/83, last paragraph. The applicant claims that these products are identical to Aciclovir Tablets BP 200mg and 400mg (PL 00142/0401-2) which were licensed for use in the UK on 26 February 1997 to Actavis UK Limited.

No new data were submitted, nor was it necessary for these simple applications, as the data are identical to those of the previously granted cross-reference products.

ACICLOVIR 200mg and 400mg TABLETS are indicated for the following:

1) Treatment of herpes simplex virus infections of the skin and mucous membranes including initial and recurrent genital herpes.
2) Suppression (prevention of recurrences) of recurrent herpes simplex infections in immunocompetent patients.
3) Prophylaxis of herpes simplex infections in immunocompromised patients.
4) Treatment of varicella (chickenpox) infection.
PHARMACEUTICAL ASSESSMENT

ACICLOVIR
The aciclovir used in these products complies with the current EDQM Certificate of Suitability and is, therefore, satisfactory.

DESCRIPTION AND COMPOSITION OF THE DRUG PRODUCT
The products contain aciclovir (Ph.Eur.). The 200mg tablets also contain lactose, magnesium stearate, polyvidone, sodium starch glycollate, Indigo Carmine Lake (E132) and microcrystalline cellulose (E460). The 400mg tablets also contain colloidal anhydrous silica, magnesium stearate, polyvidone, sodium starch glycollate, iron oxide (red) (E172) and microcrystalline cellulose (E460).

The products may be stored in either rigid injection moulded polypropylene or injection blow-moulded polyethylene containers with polyfoam wad or polyethylene ullage filler and snap-on polyethylene lids; amber glass containers with screw caps and polyfoam wad or cotton wool; or blister packs in cartons.

There appears to be no difference between the composition and packaging of the proposed product and those of the already licensed cross reference products.

The proposed shelf-life (3 years) and storage conditions (Store below 25°C in a dry place) are consistent with the details registered for the reference products.

ADDITIONAL DATA REQUIREMENTS
The manufacturing process, finished product specifications and active ingredient specification are in line with those for the reference products and are satisfactory.

Satisfactory TSE documentation has been provided for the lactose used in the 200mg tablets, no other materials of animal or human origin are used in the manufacturing process of the medicinal products.

The applicant is also the Marketing Authorisation Holder of the reference product. Letters of Access are, therefore, not required

EXPERT REPORTS
Satisfactory expert reports in the form of quality, non-clinical and clinical overall summaries are provided, with signed declarations from each expert confirming that the applicant’s product is identical to the reference products in all particulars. Expert CVs are also submitted and are acceptable.

PRODUCT LITERATURE
The proposed SPCs, PIL and labels are identical to those for the reference products and are satisfactory.

ASSESSOR’S OVERALL CONCLUSIONS
Marketing Authorisations may be granted for these products.
PRECLINICAL ASSESSMENT

No new preclinical data have been supplied with these applications and none is required for an application of this type.
CLINICAL ASSESSMENT

OVERVIEW
A statement has been provided confirming that the clinical particulars for ACICLOVIR 200mg and 400mg TABLETS are identical to those for the already licensed products; Aciclovir Tablets BP 200mg and 400mg (PL 00142/0401-2). This is satisfactory.

BIOAVAILABILITY AND BIOEQUIVALENCE
No bioequivalence study has been performed to support these applications and none is needed.

PRODUCT LITERATURE
All product literature is medically satisfactory.

ASSESSOR’S OVERALL CONCLUSIONS
It is recommended that Marketing Authorisations can be granted.
OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY
ACICLOVIR 200mg and 400mg TABLETS (PL 30306/0282-3) are identical to the already licensed reference products. These products are, therefore, pharmaceutically satisfactory.

PRECLINICAL
No new preclinical data were submitted and none are required for applications of this type.

EFFICACY
The efficacy of aciclovir is well established. The SPCs, PIL and labelling are satisfactory and consistent with those for the cross-reference products.

RISK BENEFIT ASSESSMENT
The quality of the products is acceptable, no significant preclinical or clinical safety concerns were identified, and benefit has been shown to be associated with aciclovir. The risk benefit ratio is, therefore, considered to be acceptable.
ACICLOVIR 200mg TABLETS

ACICLOVIR 400mg TABLETS

PL 30306/0282-3

STEPS TAKEN FOR ASSESSMENT

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<td>1</td>
<td>The MHRA received the Marketing Authorisation applications on 16 December 2009</td>
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<td>Following standard checks and communication with the applicant the MHRA considered the applications valid on 29 December 2009</td>
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<td>Following assessment of the applications the MHRA requested further information relating to the dossier on 31 March 2010</td>
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<td>The applications were determined on 19 May 2010</td>
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1 NAME OF THE MEDICINAL PRODUCT
ACICLOVIR 200mg TABLETS

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 200mg Aciclovir.
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Blue uncoated tablets.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications
1) Treatment of herpes simplex virus infections of the skin and mucous membranes including initial and recurrent genital herpes.
2) Suppression (prevention of recurrences) of recurrent herpes simplex infections in immunocompetent patients.
3) Prophylaxis of herpes simplex infections in immunocompromised patients.
4) Treatment of varicella (chickenpox) infection.

4.2 Posology and method of administration
Adults: Treatment of herpes simplex infections: 200mg aciclovir should be taken five times daily at approximately four hourly intervals omitting the night time dose. Treatment should continue for five days, but in severe initial infections this may have to be extended.
In severely immunocompromised patients (eg after marrow transplant) or in patients with impaired absorption from the gut the dose can be doubled to 400mg aciclovir or alternatively intravenous dosing could be considered. Dosing should begin as early as possible after the start of an infection; for recurrent episodes this should preferably be during the prodromal period or when lesions first appear.
Suppression of herpes simplex infections in immunocompetent patients: 200mg aciclovir should be taken four times daily at approximately six-hourly intervals.
Many patients may be conveniently managed on a regime of 400mg aciclovir twice daily at approximately twelve-hourly intervals.
Dosage titration down to 200mg aciclovir taken three times daily at approximately eight-hourly intervals or even twice daily at approximately twelve-hourly intervals, may prove effective.
Some patients may experience break-through infections on total daily doses of 800mg aciclovir.
Therapy should be interrupted periodically at intervals of six to twelve months, in order to observe possible changes in the natural history of the disease.
Prophylaxis of herpes simplex infections in immunocompromised patients: 200mg aciclovir should be taken four times daily at approximately six hourly intervals.
In severely immunocompromised patients (eg after marrow transplant) or in patients with impaired absorption from the gut, the dose can be doubled to 400mg aciclovir or, alternatively, intravenous dosing could be considered. The duration of prophylactic administration is determined by the duration of the period at risk.

**Dosage in children:** Treatment of herpes simplex infections, and prophylaxis of herpes simplex infections in the immunocompromised: children aged two years and over should be given the adult doses and children below the age of two years should be given half the adult dose. Treatment of varicella infection: children under 2 years should be given 200mg four times daily. Children aged 2-5 years should be given 400mg four times daily. Children aged 6 years and over should be given 800mg four times daily. Treatment should continue for 5 days. Dosing may be more accurately calculated as 20mg/kg bodyweight (not to exceed 800mg four times daily). A liquid formulation might be more suitable for small children.

No specific data are available on the suppression of herpes simplex infections or the treatment of herpes zoster infections in immunocompetent children. When treatment of herpes zoster infections is required in immunocompromised children, intravenous dosing should be considered.

**Dosage in the elderly:** In the elderly, total aciclovir body clearance declines along with creatinine clearance.

Adequate hydration of elderly patients taking high oral doses of aciclovir should be maintained. Special attention should be given to dosage reduction in elderly patients with impaired renal function.

**Dosage in renal impairment:** In the management of herpes simplex infections in patients with impaired renal function, the recommended oral doses will not lead to accumulation of aciclovir above levels that have been established by intravenous infusion. However, for patients with severe renal impairment (creatinine clearance less than 10ml/minute) an adjustment of dosage to 200mg aciclovir twice daily at approximately twelve-hourly intervals is recommended.

**Method of administration**

**Administration:** Patients who experience difficulty in swallowing the tablets may disperse them in a minimum of 50ml water which should be stirred before drinking.

For oral administration.

### 4.3 Contraindications

Known hypersensitivity to aciclovir, any other ingredients in the product or to valaciclovir.

### 4.4 Special warnings and precautions for use

The data currently available from clinical studies is not sufficient to conclude that treatment with aciclovir reduces the incidence of chickenpox-associated complications in immunocompetent patients.
Hydration status: Care should be taken to maintain adequate hydration in patients receiving higher dose oral regimens, e.g. for the treatment of herpes zoster infection (4g daily), in order to avoid the risk of possible renal toxicity.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction

- Ciclosporin: There has been a small number of transplant patients with increased serum levels of ciclosporin and signs of nephrotoxicity when aciclovir is given concurrently. Renal function should be monitored closely in patients taking both drugs.
- Cimetidine and probenecid: Cimetidine and probenecid increase the bioavailability of aciclovir by competing for active secretion by the renal tubules. Dosage adjustment is usually not necessary because of the wide therapeutic index of aciclovir.
- Mycophenolate mofetil: 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 the drugs are coadministered. However, no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.
- Theophylline: Serum levels of theophylline may be increased by concurrent administration of aciclovir and it may be necessary to reduce the dosage of theophylline if aciclovir is added to the established treatment.
- Zidovudine: Although co-administration of zidovudine and aciclovir is not usually associated with toxicity, there is a single case report of overwhelming fatigue developing in a patient when given the two drugs together. This did not occur when zidovudine and aciclovir were given alone.

4.6 Pregnancy and lactation

Pregnancy
Experience in humans is limited so the use of aciclovir should be considered only when the potential benefits outweigh the possibility of unknown risks. Herpes simplex encephalitis and varicella pneumonia constitute a significant risk for mother and foetus and primary genital herpes may retard intrauterine growth and increase the risk of premature birth and neonatal herpes infection. (See section 5.3 Preclinical Safety Data). Aciclovir readily crosses the placenta and levels in cord blood are higher than in maternal serum. Prospective studies have shown that congenital malformations do occur in infants exposed to aciclovir during pregnancy but the incidence is no higher than in the general population and they do not appear to be related to the drug. There is no experience of the effect of aciclovir on human female fertility.

Lactation
Following oral administration of 200mg aciclovir five times a day, aciclovir has been detected in breast milk at concentrations ranging from 0.6-4.1 times the corresponding plasma levels. These levels would potentially expose nursing infants to aciclovir dosages of up to 0.3mg/kg/day. Caution is therefore advised if aciclovir is to be administered to a nursing mother.
4.7 Effects on ability to drive and use machines
As aciclovir administration is occasionally associated with drowsiness and somnolence (usually in patients receiving high doses or with impaired renal function), patients should make sure that they are not affected before driving or using machinery.

4.8 Undesirable effects
An estimate of the frequency of undesirable effects has been included though this is not certain for all adverse effects. The frequencies are: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10000, <1/1000, very rare (<1/10000).

Blood and the lymphatic system disorders
Very rare: Anaemia, leucopenia and thrombocytopenia.

Immune system disorders
Rare: Dyspnoea, angioedema and anaphylaxis.

Nervous system disorders
Common: Dizziness and headache.
Rare: Reversible neurological reactions including drowsiness, confusional states, hallucinations, somnolence, convulsions, coma and malaise. These effects were usually reported in patients receiving high doses of aciclovir (usually given intravenously) or with renal impairment. Aciclovir should be used with caution in patients with underlying neurological abnormalities.

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea and abdominal pain.

Hepato-biliary disorders
Rare: Reversible rises in bilirubin and liver related enzymes.
Very rare: Hepatitis and jaundice.

Skin and sub-cutaneous tissue disorders
Common: Skin rashes, pruritus and urticaria.
Uncommon: Photosensitivity.
Rare: Erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, accelerated diffuse hair loss. This type of hair loss has been associated with a wide variety of disease processes and medicines, the relationship of the event to aciclovir therapy is uncertain.

Renal and urinary disorders
Rare: Increases in blood urea and creatinine; renal impairment, usually during intravenous therapy, which is usually reversible and responds to hydration and/or dosage reduction but may progress to acute renal failure in patients with predisposing factors.

General disorders
Common: Fatigue.
4.9 **Overdose**

Aciclovir is only partly absorbed in the gastrointestinal tract. Patients have ingested overdoses of up to 20 g aciclovir on a single occasion, usually without toxic effects. Accidental, repeated overdoses of oral aciclovir over several days have been associated with gastrointestinal effects (e.g., nausea and vomiting) and neurological effects (e.g., confusion). Patients should be observed closely for signs of toxicity. The removal of aciclovir from the blood is significantly enhanced by haemodialysis in patients with symptomatic overdose.

5 **PHARMACOLOGICAL PROPERTIES**

5.1 **Pharmacodynamic properties**

*ATC code: J05A B*

Aciclovir is an antiviral agent which is highly active *in vitro* against herpes simplex virus (HSV) types I and II and varicella zoster virus. Toxicity to mammalian host cells is low.

Aciclovir is phosphorylated after entry into herpes infected cells to the active compound aciclovir triphosphate. The first step in this process is dependent on the presence of the HSV-coded thymidine kinase. Aciclovir triphosphate acts as an inhibitor of, and substrate for, the herpes-specified DNA polymerase, preventing further viral DNA synthesis without affecting the normal cellular processes.

Herpes simplex virus develops resistance to aciclovir by selection of mutants deficient in thymidine kinase which are usually of diminished virulence with reduced infectivity and latency. Resistance is rare in immunocompetent patients on short courses of oral therapy but it is more prevalent in immunocompromised patients who have often received prolonged courses of treatment. Herpes zoster resistance develops by a similar mechanism and has been reported in immunocompromised patients undergoing prolonged therapy with aciclovir.

5.2 **Pharmacokinetic properties**

*Absorption*

Aciclovir is slowly and incompletely absorbed from the gastrointestinal tract. The peak plasma concentration occurs about 2 hours following ingestion.

*Distribution*

There is a wide distribution to various tissues, including the CSF where concentrations achieved are about 50% of those achieved in plasma. Protein binding is reported to range from 9-33%. Aciclovir crosses the placenta and is excreted in breast milk in concentrations approximately 3 times higher than those in maternal serum.

*Metabolism and Elimination*
Renal excretion is the major route of elimination by both glomerular filtration and tubular secretion. The terminal or beta-phase half-life is reported to be about 2-3 hours for adults without renal impairment. As aciclovir persists in the plasma of patients with renal insufficiency, in chronic renal failure this value is increased and may be up to 19.5 hours in anuric patients. As renal function decreases, a greater percentage of the drug is eliminated by metabolic conversion to carboxymethoxymethyl guanine. During haemodialysis the half-life is reduced to 5.7 hours, with 60% of a dose of aciclovir being removed in 6 hours. Faecal excretion may account for about 2% of a dose.

5.3 Preclinical safety data
Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rats, rabbits or mice. In a non-standard test in rats, foetal abnormalities were observed, but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain. Two generation studies in mice do not reveal any effect of aciclovir on fertility.

The results of a wide range of mutagenicity tests in vitro and in vivo indicate that aciclovir does not pose a genetic risk to man. Aciclovir was not found to be carcinogenic in long term studies in the rat and the mouse. Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of aciclovir greatly in excess of those employed therapeutically. Aciclovir has been shown to have no definite effect upon sperm count, morphology or motility in man.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Also contains: lactose, magnesium stearate, polyvidone, sodium starch glycollate, Indigo Carmine Lake (E132), Microcrystalline Cellulose (E460).

6.2 Incompatibilities
None known.

6.3 Shelf life
Shelf-life
Three years from the date of manufacture.

Shelf-life after dilution/reconstitution
Not applicable.

Shelf-life after first opening
Not applicable.

6.4 Special precautions for storage
Store below 25°C in a dry place.
6.5 **Nature and contents of container**
The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene containers with polyfoam wad or polyethylene ullage filler and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass containers with screw caps and polyfoam wad or cotton wool.

The product may also be supplied in blister packs in cartons:
- **a) Carton:** Printed carton manufactured from white folding box board.
- **b) Blister pack:** (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil with 5-7g/M² PVC and PVdC compatible heat seal lacquer on the reverse side.

The product may be contained in blister packs which enhances security of the pack increasing resistance to deliberate contamination, pilfering, etc.

Pack sizes: 25s, 28s, 30s, 35s, 56s, 60s, 100s.

Product may also be supplied in bulk packs, for reassembly purposes only, in polybags contained in tins, skillets or polybuckets filled with suitable cushioning material. Bulk packs are included for temporary storage of the finished product before final packaging into the proposed marketing containers.

Maximum size of bulk packs: 50,000.

6.6 **Special precautions for disposal**
Not applicable.

7 **MARKETING AUTHORISATION HOLDER**
Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjordur
Iceland

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 30306/0282

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
19/05/2010

10 **DATE OF REVISION OF THE TEXT**
19/05/2010
NAME OF THE MEDICINAL PRODUCT
ACICLOVIR 400mg TABLETS

QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 400mg Aciclovir.

For full list of excipients, see section 6.1.

PHARMACEUTICAL FORM
Pink uncoated tablets.

CLINICAL PARTICULARS

4.1 Therapeutic indications
1) Treatment of herpes simplex virus infections of the skin and mucous membranes including initial and recurrent genital herpes.
2) Suppression (prevention of recurrences) of recurrent herpes simplex infections in immunocompetent patients.
3) Prophylaxis of herpes simplex infections in immunocompromised patients.
4) Treatment of varicella (chickenpox) infection.

4.2 Posology and method of administration
Adults: Treatment of herpes simplex infections: 200mg aciclovir should be taken five times daily at approximately four hourly intervals omitting the night time dose. Treatment should continue for five days, but in severe initial infections this may have to be extended.
In severely immunocompromised patients (eg after marrow transplant) or in patients with impaired absorption from the gut the dose can be doubled to 400mg aciclovir or alternatively intravenous dosing could be considered.
Dosing should begin as early as possible after the start of an infection; for recurrent episodes this should preferably be during the prodromal period or when lesions first appear.
Suppression of herpes simplex infections in immunocompetent patients: 200mg aciclovir should be taken four times daily at approximately six-hourly intervals.
Many patients may be conveniently managed on a regime of 400mg aciclovir twice daily at approximately twelve-hourly intervals.
Dosage titration down to 200mg aciclovir taken three times daily at approximately eight-hourly intervals or even twice daily at approximately twelve-hourly intervals, may prove effective.
Some patients may experience break-through infections on total daily doses of 800mg aciclovir.
Therapy should be interrupted periodically at intervals of six to twelve months, in order to observe possible changes in the natural history of the disease.
Prophylaxis of herpes simplex infections in immunocompromised patients: 200mg aciclovir should be taken four times daily at approximately six hourly intervals.
In severely immunocompromised patients (eg after marrow transplant) or in patients with impaired absorption from the gut, the dose can be doubled to 400mg aciclovir or, alternatively, intravenous dosing could be considered. The duration of prophylactic administration is determined by the duration of the period at risk.

Dosage in children: Treatment of herpes simplex infections, and prophylaxis of herpes simplex infections in the immunocompromised: children aged two years and over should be given the adult doses and children below the age of two years should be given half the adult dose. Treatment of varicella infection: children under 2 years should be given 200mg four times daily. Children aged 2-5 years should be given 400mg four times daily. Children aged 6 years and over should be given 800mg four times daily. Treatment should continue for 5 days. Dosing may be more accurately calculated as 20mg/kg bodyweight (not to exceed 800mg four times daily). A liquid formulation might be more suitable for small children.

No specific data are available on the suppression of herpes simplex infections or the treatment of herpes zoster infections in immunocompetent children. When treatment of herpes zoster infections is required in immunocompromised children, intravenous dosing should be considered.

Dosage in the elderly: In the elderly, total aciclovir body clearance declines along with creatinine clearance. Adequate hydration of elderly patients taking high oral doses of aciclovir should be maintained. Special attention should be given to dosage reduction in elderly patients with impaired renal function.

Dosage in renal impairment: In the management of herpes simplex infections in patients with impaired renal function, the recommended oral doses will not lead to accumulation of aciclovir above levels that have been established by intravenous infusion. However, for patients with severe renal impairment (creatinine clearance less than 10ml/minute) an adjustment of dosage to 200mg aciclovir twice daily at approximately twelve-hourly intervals is recommended.

Method of Administration
Administration: Patients who experience difficulty in swallowing the tablets may disperse them in a minimum of 50ml water which should be stirred before drinking.

For oral administration.

4.3 Contraindications
Known hypersensitivity to aciclovir, any other ingredients in the product or to valaciclovir.

4.4 Special warnings and precautions for use
The data currently available from clinical studies is not sufficient to conclude that treatment with aciclovir reduces the incidence of chickenpox-associated complications in immunocompetent patients.

Hydration status: Care should be taken to maintain adequate hydration in patients receiving higher dose oral regimens, e.g. for the treatment of herpes zoster infection (4g daily), in order to avoid the risk of possible renal toxicity.
4.5 Interaction with other medicinal products and other forms of interaction

- Ciclosporin: There has been a small number of transplant patients with increased serum levels of ciclosporin and signs of nephrotoxicity when aciclovir is given concurrently. Renal function should be monitored closely in patients taking both drugs.
- Cimetidine and probenecid: Cimetidine and probenecid increase the bioavailability of aciclovir by competing for active secretion by the renal tubules. Dosage adjustment is usually not necessary because of the wide therapeutic index of aciclovir.
- Mycophenolate mofetil: 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 the drugs are coadministered. However, no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.
- Theophylline: Serum levels of theophylline may be increased by concurrent administration of aciclovir and it may be necessary to reduce the dosage of theophylline if aciclovir is added to the established treatment.
- Zidovudine: Although co-administration of zidovudine and aciclovir is not usually associated with toxicity, there is a single case report of overwhelming fatigue developing in a patient when given the two drugs together. This did not occur when zidovudine and aciclovir were given alone.

4.6 Pregnancy and lactation

Pregnancy
Experience in humans is limited so the use of aciclovir should be considered only when the potential benefits outweigh the possibility of unknown risks. Herpes simplex encephalitis and varicella pneumonia constitute a significant risk for mother and foetus and primary genital herpes may retard intrauterine growth and increase the risk of premature birth and neonatal herpes infection. (See section 5.3 Preclinical Safety Data). Aciclovir readily crosses the placenta and levels in cord blood are higher than in maternal serum. Prospective studies have shown that congenital malformations do occur in infants exposed to aciclovir during pregnancy but the incidence is no higher than in the general population and they do not appear to be related to the drug. There is no experience of the effect of aciclovir on human female fertility.

Lactation
Following oral administration of 200mg aciclovir five times a day, aciclovir has been detected in breast milk at concentrations ranging from 0.6-4.1 times the corresponding plasma levels. These levels would potentially expose nursing infants to aciclovir dosages of up to 0.3mg/kg/day. Caution is therefore advised if aciclovir is to be administered to a nursing mother.

4.7 Effects on ability to drive and use machines

As aciclovir administration is occasionally associated with drowsiness and somnolence (usually in patients receiving high doses or with impaired renal function), patients should make sure that they are not affected before driving or using machinery.
4.8 Undesirable effects
An estimate of the frequency of undesirable effects has been included though this is not certain for all adverse effects. The frequencies are: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10000, <1/1000, very rare (<1/10000).

Blood and the lymphatic system disorders
Very rare: Anaemia, leucopenia and thrombocytopenia.

Immune system disorders
Rare: Dyspnoea, angioedema and anaphylaxis.

Nervous system disorders
Common: Dizziness and headache.
Rare: Reversible neurological reactions including drowsiness, confusional states, hallucinations, somnolence, convulsions, coma and malaise. These effects were usually reported in patients receiving high doses of aciclovir (usually given intravenously) or with renal impairment. Aciclovir should be used with caution in patients with underlying neurological abnormalities.

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea and abdominal pain.

Hepato-biliary disorders
Rare: Reversible rises in bilirubin and liver related enzymes.
Very rare: Hepatitis and jaundice.

Skin and sub-cutaneous tissue disorders
Common: Skin rashes, pruritus and urticaria.
Uncommon: Photosensitivity.
Rare: Erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis, accelerated diffuse hair loss. This type of hair loss has been associated with a wide variety of disease processes and medicines, the relationship of the event to aciclovir therapy is uncertain.

Renal and urinary disorders
Rare: Increases in blood urea and creatinine; renal impairment, usually during intravenous therapy, which is usually reversible and responds to hydration and/or dosage reduction but may progress to acute renal failure in patients with predisposing factors.

General disorders
Common: Fatigue.
Uncommon: Fever.

4.9 Overdose
Aciclovir is only partly absorbed in the gastrointestinal tract. Patients have ingested overdoses of up to 20 g aciclovir on a single occasion, usually without toxic effects. Accidental, repeated overdoses of oral aciclovir over several days have been associated with gastrointestinal effects (eg nausea
and vomiting) and neurological effects (e.g. confusion). Patients should be observed closely for signs of toxicity. The removal of aciclovir from the blood is significantly enhanced by haemodialysis in patients with symptomatic overdose.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
ATC code: J05A B
Aciclovir is an antiviral agent which is highly active in vitro against herpes simplex virus (HSV) types I and II and varicella zoster virus. Toxicity to mammalian host cells is low.

Aciclovir is phosphorylated after entry into herpes infected cells to the active compound aciclovir triphosphate. The first step in this process is dependant on the presence of the HSV-coded thymidine kinase. Aciclovir triphosphate acts as an inhibitor of, and substrate for, the herpes-specified DNA polymerase, preventing further viral DNA synthesis without affecting the normal cellular processes.

Herpes simplex virus develops resistance to aciclovir by selection of mutants deficient in thymidine kinase which are usually of diminished virulence with reduced infectivity and latency. Resistance is rare in immunocompetent patients on short courses of oral therapy but it is more prevalent in immunocompromised patients who have often received prolonged courses of treatment. Herpes zoster resistance develops by a similar mechanism and has been reported in immunocompromised patients undergoing prolonged therapy with aciclovir.

5.2 Pharmacokinetic properties
Absorption
Aciclovir is slowly and incompletely absorbed from the gastrointestinal tract. The peak plasma concentration occurs about 2 hours following ingestion.

Distribution
There is a wide distribution to various tissues, including the CSF where concentrations achieved are about 50% of those achieved in plasma. Protein binding is reported to range from 9-33%. Aciclovir crosses the placenta and is excreted in breast milk in concentrations approximately 3 times higher than those in maternal serum.

Metabolism and Elimination
Renal excretion is the major route of elimination by both glomerular filtration and tubular secretion. The terminal or beta-phase half-life is reported to be about 2-3 hours for adults without renal impairment. As aciclovir persists in the plasma of patients with renal insufficiency, in chronic renal failure this value is increased and may be up to 19.5 hours in anuric patients. As renal function decreases, a greater percentage of the drug is eliminated by metabolic conversion to carboxymethoxymethyl guanine. During haemodialysis the
half-life is reduced to 5.7 hours, with 60% of a dose of aciclovir being removed in 6 hours. Faecal excretion may account for about 2% of a dose.

5.3 Preclinical safety data
Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rats, rabbits or mice. In a non-standard test in rats, foetal abnormalities were observed, but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain. Two generation studies in mice do not reveal any effect of aciclovir on fertility.

The results of a wide range of mutagenicity tests in vitro and in vivo indicate that aciclovir does not pose a genetic risk to man. Aciclovir was not found to be carcinogenic in long term studies in the rat and the mouse. Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of aciclovir greatly in excess of those employed therapeutically. Aciclovir has been shown to have no definite effect upon sperm count, morphology or motility in man.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Also contains: colloidal anhydrous silica, magnesium stearate, polyvidone, sodium starch glycollate, Iron Oxide (red) (E172), Microcrystalline Cellulose (E460).

6.2 Incompatibilities
None known.

6.3 Shelf life
Shelf-life
Three years from the date of manufacture.

Shelf-life after dilution/reconstitution
Not applicable.

Shelf-life after first opening
Not applicable.

6.4 Special precautions for storage
Store below 25°C in a dry place.

6.5 Nature and contents of container
The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene containers with polyfoam wad or polyethylene ullage filler and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass containers with screw caps and polyfoam wad or cotton wool.
The product may also be supplied in blister packs in cartons:

a) Carton: Printed carton manufactured from white folding box board.

b) Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil with 5-7g/M² PVC and PVdC compatible heat seal lacquer on the reverse side.

The product may be contained in blister packs which enhances security of the pack increasing resistance to deliberate contamination, pilfering, etc.

Pack sizes: 20s, 25s, 28s, 30s, 35s, 56s, 60s, 100s.

Product may also be supplied in bulk packs, for reassembly purposes only, in polybags contained in tins, skillets or polybuckets filled with suitable cushioning material. Bulk packs are included for temporary storage of the finished product before final packaging into the proposed marketing containers.

Maximum size of bulk packs: 50,000.

6.6 Special precautions for disposal
Not applicable.

7 MARKETING AUTHORISATION HOLDER
Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjordur
Iceland

8 MARKETING AUTHORISATION NUMBER(S)
PL 30306/0283

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
19/05/2010

10 DATE OF REVISION OF THE TEXT
19/05/2010
PATIENT INFORMATION LEAFLET

No leaflet mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the leaflet mock-ups has been obtained.

Approved PIL text:

Aciclovir 200mg and 400mg tablets

Read all of this leaflet carefully before you start taking this medicine.
• Keep this leaflet. You may need to read it again.
• If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

In this leaflet:
1. What Aciclovir is and what it is used for
2. Before you take Aciclovir tablets
3. How to take Aciclovir tablets
4. Possible side effects
5. How to store Aciclovir tablets
6. Further information

1. What Aciclovir is and what it is used for
Aciclovir is an antiviral medicine, which acts on infected cells by stopping the virus growing.

Aciclovir tablets are used to:
• treat or prevent herpes simplex infections of the skin and mucous membranes e.g. cold sores and genital herpes
• prevent herpes simplex infections in patients whose immune system is not working properly
• treat chicken pox (varicella infection)

2. Before you take Aciclovir tablets
Do not take Aciclovir tablets
• if you are allergic (hypersensitive) to aciclovir, any of the ingredients in Aciclovir tablets or valaciclovir (see section 6).

Take special care with Aciclovir tablets
• if you have nervous system abnormalities, please tell your doctor before you start treatment with Aciclovir tablets.
• to avoid dehydration, it is important to drink plenty of water whilst taking Aciclovir tablets, especially if you are elderly or taking doses of 4g a day or higher.

Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription. Especially:

- **cimetidine** (used to treat peptic ulcers) and **probenecid** (used to treat gout), as these increase the concentration of aciclovir.
- **mycophenolate mofetil** (medicine used in transplant patients). Care should be taken if you are taking high doses of Aciclovir, as blood levels of both drugs may increase.
- **ciclosporin** (an immunosuppressant drug). Your doctor may monitor your kidney function.
- **theophylline** (used in asthma and other breathing problems).
- **zidovudine** (used in HIV infection).

**Pregnancy and breast-feeding**
There is limited information on the use of Aciclovir tablets in pregnancy or breast-feeding. Ask your doctor or pharmacist for advice before taking this medicine.

**Driving and using machines**
Some side effects such as drowsiness and sleepiness may impair your ability to concentrate and react. Make sure you are not affected before you drive or operate machinery.

**Sugar intolerance** (200mg tablets only)
If you have been told you have an intolerance to some sugars, contact your doctor before taking this medicine, as it contains a type of sugar called lactose.

**3. How to take Aciclovir tablets**
Always take Aciclovir tablets exactly as your doctor has told you. If you are not sure, check with your doctor or pharmacist.
It is important to start treatment as soon as possible.

Swallow the tablets **with water, with or without food**. If you experience difficulty in swallowing the tablets they may be dispersed in a glass of water (at least 50ml) which should be stirred before drinking.

**Usual doses:**
- **Herpes simplex infection** (e.g. cold sores, genital herpes)
  - **Adults**
    - treatment - 200mg 5 times a day at 4 hourly intervals for 5 days
    - prevention - 200mg 4 times a day at 6 hourly intervals for 6-12 months
    - prevention in patients whose immune system is not working properly - 200mg 4 times a day at 6 hourly intervals for the period that the patient is at risk
    - patients with severely impaired kidney function - 200mg twice a day at 12 hourly intervals

If your immune system is severely impaired or you have impaired absorption from the gut, the dose may be increased or you may be given an injection (into a vein).

- **Herpes simplex infection** (e.g. cold sores, genital herpes)
  - **Children**
    - treatment –
- 2 years and over - adult dose
- under 2 years - half the adult dose
- prevention in patients whose immune system is not working properly -
  - 2 years and over - adult dose
  - under 2 years - half the adult dose

- Varicella infection (chicken pox)
  - Children
    - treatment – for 5 days
      - 6 years and over - 800mg 4 times a day
      - 2-5 years - 400mg 4 times a day
      - under 2 years - 200mg 4 times a day

A liquid formulation might be more suitable for small children.

**Elderly**
Dosage may be reduced in the elderly, especially in those whose kidneys are not working properly.

To avoid dehydration, it is important to drink plenty of water whilst taking Aciclovir tablets, especially if you are elderly or taking doses of 4g a day or higher.

**If you take more Aciclovir tablets than you should**
If you take too many Aciclovir tablets, contact your doctor immediately. Signs of an overdose include effects on the stomach and intestines such as feeling or being sick and effects on the nervous system such as confusion.

**If you forget to take Aciclovir tablets**
Do not take a double dose to make up for a forgotten dose. If you forget to take a dose, take it as soon as you remember it and then take the next dose at the right time.

4. Possible side effects
Like all medicines, Aciclovir tablets can cause side effects, although not everybody gets them.

Contact your doctor at once if you have a severe allergic reaction (anaphylaxis) such as swelling of the face, lips, tongue or throat (angioedema), difficulty breathing or swallowing.

Tell your doctor or pharmacist if you notice any of the following effects or any not listed.

**Common** (occurs in less than 1 in 10 users): dizziness, headache, feeling or being sick, diarrhoea, stomach pain, skin rashes, itching, pale or red irregular raised patches with severe itching (hives), tiredness.

**Uncommon** (occurs in less than 1 in 100 users): sensitivity to sunlight or artificial light (e.g. sunbeds), fever.

**Rare** (occurs in less than 1 in 1000 users): an increase in bilirubin and liver related enzymes, circular, irregular red patches on the skin of the hands and arms (erythema multiforme), severe form of skin rash with flushing, fever, blisters or ulcers (Stevens Johnson syndrome), severe rash involving reddening, peeling and swelling of the skin.
that resembles severe burns (toxic epidermal necrolysis), hair loss, an increase in the blood levels of urea and creatinine, impaired kidney function which may progress to kidney failure (usually during treatment by injection into a vein), nervous system reactions including drowsiness, confusion, seeing, hearing or feeling things that are not there (hallucinations), sleepiness, convulsions (fits), coma and a feeling of general discomfort and illness.

**Very rare** (occurs in less than one in 10,000 users): inflammation of the liver (hepatitis), yellowing of the skin or whites of the eyes (jaundice), changes in the numbers and types of your blood cells (anaemia, leucopenia, thrombocytopenia). If you notice increased bruising, nosebleeds, sore throats, infections, excessive tiredness, breathlessness on exertion or abnormal paleness of the skin, you should tell your doctor who may want you to have a blood test.

5. **How to store Aciclovir tablets**

Keep out of the reach and sight of children.

Store below 25°C in a dry place.

Do not use Aciclovir tablets after the expiry date stated on the label, carton or bottle. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. **Further information**

**What Aciclovir tablets contain**

- The active substance (the ingredient that makes the tablets work) is aciclovir. Each tablet contains either 200mg or 400mg of the active substance.

- The other ingredients are:
  - 200mg tablets: lactose, magnesium stearate, polyvidone, sodium starch glycollate, Indigo Carmine Lake (E132), Microcrystalline Cellulose (E460).
  - 400mg tablets: colloidal anhydrous silica, magnesium stearate, polyvidone, sodium starch glycollate, Iron oxide (red) (E172), Microcrystalline Cellulose (E460).

**What Aciclovir tablets look like and contents of the pack**

- 200mg Aciclovir tablets are blue, circular, flat bevelled-edge, uncoated tablets. Pack size is 25.
- 400mg Aciclovir tablets are pink, circular, flat bevelled-edge, uncoated tablets. Pack size is 56.

**Marketing Authorisation Holder**

Actavis Group PTC ehf, Reykjavikurvegi 76-78, 220 Hafnarfjordur, Iceland

This leaflet was last revised in April 2010.
LABELLING

No label mock-ups have been provided. In accordance with medicines legislation, the product shall not be marketed in the UK until approval of the label mock-ups has been obtained.

Approved label text for 200 mg tablets:

**Carton**

**Back**

Aciclovir 200mg Tablets
25 tablets

Place dispensing label here

Also contains: lactose. See leaflet for details.
For oral administration.
Use as directed by physician.
Keep out of the reach and sight of children.
Store below 25°C in a dry place.

MA Holder: Actavis Group PTC ehf, Reykjavikurvegi 76-78, 220 Hafnarfjordur, Iceland

PL 30306/0282

**POM**

actavis logo
Manufacturer: Actavis, Barnstaple, EX32 8NS, UK

**Side**

Aciclovir 200mg Tablets
25 tablets

**Front**

actavis logo
Aciclovir 200mg Tablets
Tablets may be swallowed whole or if necessary dispersed in water
25 tablets
For oral use

**Side**

Aciclovir 200mg Tablets
25 tablets
barcode
**Flaps**

Batch
Manufd
Exp

46x30x115

Aciclovir 200mg Tablets
25 tablets

READ ENCLOSED LEAFLET

Braille:

Aciclovir
200 mg
Tablets

**Foil**

actavis logo
Aciclovir 200mg Tablets
Approved label text for 400 mg tablets:

**Carton**

Aciclovir 400mg Tablets

56 tablets

Place dispensing label here

For oral administration.
Use as directed by physician.
Keep out of the reach and sight of children.
Store below 25°C in a dry place.

PL 30306/0283

MA Holder: Actavis Group PTC ehf, Reykjavikurvegi 76-78, 220 Hafnarfjördur, Iceland

**Side**

Aciclovir 400mg Tablets

56 tablets

**Front**

Aciclovir 400mg Tablets
Tablets may be swallowed whole or if necessary dispersed in water
56 tablets
For oral use

**Side**

Aciclovir 400mg Tablets
56 tablets
barcode

**Flaps**

Batch
Manufd
Aciclovir 400mg Tablets
56 tablets

READ ENCLOSED LEAFLET

Braille:
Aciclovir
400 mg
Tablets

Foil

Aciclovir 400mg Tablets

MON TUE WED THU FRI
AM AM AM AM AM

MON TUE WED THU FRI
PM PM PM PM PM
Module 6

Steps taken after initial procedure - Summary

The following table lists some non-safety updates to the Marketing Authorisations for these products that have been approved by the MHRA since the products were first licensed. The table includes updates that are detailed in the annex to this PAR. This is not a complete list of the post-authorisation changes that have been made to these Marketing Authorisations.

<table>
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<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
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<td>VAR Medical Type IB</td>
<td>To update section 5.2 of the SPC in line with Pharmacovigilance – 2011540 as agreed during the paediatric work sharing procedure</td>
<td>Granted 03/07/2012</td>
</tr>
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Annex 1

Assessment report for variation to update section 5.2 of the SmPCs for Aciclovir 200 mg and 400 mg Tablets as agreed during paediatric work sharing procedure.

As these variations were classified as Type IB variations, no assessment report was produced during the assessment process.

Following approval of these variations on 3rd July 2012 the following updated SmPCs have been incorporated into Marketing Authorisations for Aciclovir 200 mg Tablets (PL 30306/0282) and Aciclovir 400 mg Tablets (PL 30306/0283):
1 NAME OF THE MEDICINAL PRODUCT
ACICLOVIR 200mg TABLETS

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 200mg Aciclovir.
For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Blue uncoated tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
1) Treatment of herpes simplex virus infections of the skin and mucous membranes including initial and recurrent genital herpes (excluding severe HSV infections in immunocompromised children).
2) Suppression (prevention of recurrences) of recurrent herpes simplex infections in immunocompetent patients.
3) Prophylaxis of herpes simplex infections in immunocompromised patients.
4) Treatment of varicella (chickenpox) infection.

4.2 Posology and method of administration
Adults: Treatment of herpes simplex infections: 200mg aciclovir should be taken five times daily at approximately four hourly intervals omitting the night time dose. Treatment should continue for five days, but in severe initial infections this may have to be extended.
In severely immunocompromised patients (eg after marrow transplant) or in patients with impaired absorption from the gut the dose can be doubled to 400mg aciclovir or alternatively intravenous dosing could be considered.
Dosing should begin as early as possible after the start of an infection; for recurrent episodes this should preferably be during the prodromal period or when lesions first appear.
Suppression of herpes simplex infections in immunocompetent patients: 200mg aciclovir should be taken four times daily at approximately six-hourly intervals.
Many patients may be conveniently managed on a regime of 400mg aciclovir twice daily at approximately twelve-hourly intervals.
Dosage titration down to 200mg aciclovir taken three times daily at approximately eight-hourly intervals or even twice daily at approximately twelve-hourly intervals, may prove effective.
Some patients may experience break-through infections on total daily doses of 800mg aciclovir.
Therapy should be interrupted periodically at intervals of six to twelve months, in order to observe possible changes in the natural history of the disease.
Prophylaxis of herpes simplex infections in immunocompromised patients: 200mg aciclovir should be taken four times daily at approximately six-hourly intervals.
In severely immunocompromised patients (eg after marrow transplant) or in patients with impaired absorption from the gut, the dose can be doubled to 400mg aciclovir or, alternatively, intravenous dosing could be considered.
The duration of prophylactic administration is determined by the duration of the period at risk.
Dosage in children: Treatment of herpes simplex infections, and prophylaxis of herpes simplex infections in the immunocompromised: children aged two years and over should be given the adult doses and children below the age of two years should be given half the adult dose. Treatment of varicella infection: children under 2 years should be given 200mg four times daily. Children aged 2-5 years should be given 400mg four times daily. Children aged 6 years and over should be given 800mg four times daily. Treatment should continue for 5 days. Dosing may be more accurately calculated as 20mg/kg bodyweight (not to exceed 800mg four times daily). A liquid formulation might be more suitable for small children.
No specific data are available on the suppression of herpes simplex infections or the treatment of herpes zoster infections in immunocompetent children. When treatment of herpes zoster infections is required in immunocompromised children, intravenous dosing should be considered.
Dosage in the elderly: In the elderly, total aciclovir body clearance declines along with creatinine clearance.

Adequate hydration of elderly patients taking high oral doses of aciclovir should be maintained. Special attention should be given to dosage reduction in elderly patients with impaired renal function.

Dosage in renal impairment: In the management of herpes simplex infections in patients with impaired renal function, the recommended oral doses will not lead to accumulation of aciclovir above levels that have been established by intravenous infusion. However, for patients with severe renal impairment (creatinine clearance less than 10ml/minute) an adjustment of dosage to 200mg aciclovir twice daily at approximately twelve-hourly intervals is recommended.

Method of administration
Administration: Patients who experience difficulty in swallowing the tablets may disperse them in a minimum of 50ml water which should be stirred before drinking.

For oral administration.

4.3 Contraindications
Aciclovir tablets are contraindicated in patients known to be hypersensitive to aciclovir and valaciclovir or to any of the excipients.

4.4 Special warnings and precautions for use
Use in patients with renal impairment and in elderly patients: Aciclovir is eliminated by renal clearance, therefore the dose 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).

Prolonged or repeated courses of aciclovir in severely immune-compromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued aciclovir treatment (see section 5.1).

Hydration status: Care should be taken to maintain adequate hydration in patients receiving higher dose oral regimens, e.g. for the treatment of herpes zoster infection (4g daily), in order to avoid the risk of possible renal toxicity.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

4.5 Interaction with other medicinal products and other forms of interaction
No clinically significant interactions have been identified.

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

Ciclosporin: There has been a small number of transplant patients with increased serum levels of ciclosporin and signs of nephrotoxicity when aciclovir is given concurrently. Renal function should be monitored closely in patients taking both drugs.

Cimetidine and probenecid: Cimetidine and probenecid increase the AUC of aciclovir by competing for active secretion by the renal tubules and reduce aciclovir renal clearance. Dosage adjustment is usually not necessary because of the wide therapeutic index of aciclovir.

Mycophenolate mofetil: 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 the drugs are coadministered. However, no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.

Theophylline: Serum levels of theophylline may be increased by concurrent administration of aciclovir and it may be necessary to reduce the dosage of theophylline if aciclovir is added to the established treatment.
Zidovudine: Although co-administration of zidovudine and aciclovir is not usually associated with toxicity, there is a single case report of overwhelming fatigue developing in a patient when given the two drugs together. This did not occur when zidovudine and aciclovir were given alone.

4.6 Pregnancy and lactation

Pregnancy
Experience in humans is limited so the use of aciclovir should be considered only when the potential benefits outweigh the possibility of unknown risks. Herpes simplex encephalitis and varicella pneumonia constitute a significant risk for mother and foetus and primary genital herpes may retard intrauterine growth and increase the risk of premature birth and neonatal herpes infection. (See section 5.3 Preclinical Safety Data). Aciclovir readily crosses the placenta and levels in cord blood are higher than in maternal serum. A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of aciclovir. The registry findings 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.

Lactation
Following oral administration of 200mg aciclovir five times a day, aciclovir has been detected in breast milk at concentrations ranging from 0.6-4.1 times the corresponding plasma levels. These levels would potentially expose nursing infants to aciclovir dosages of up to 0.3mg/kg/day. Caution is therefore advised if aciclovir is to be administered to a nursing mother.

4.7 Effects on ability to drive and use machines
The clinical status of the patient and the adverse event profile of aciclovir should be borne in mind when considering the patient’s ability to drive or operate machinery. As aciclovir administration is occasionally associated with drowsiness and somnolence (usually in patients receiving high doses or with impaired renal function), patients should make sure that they are not affected before driving or using machinery. There have been no studies to investigate the effect of aciclovir 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
The frequency categories associated with the adverse events below are estimates. For most events, suitable data for estimating incidence were not available. In addition, adverse events may vary in their incidence depending on the indication.

An estimate of the frequency of undesirable effects has been included though this is not certain for all adverse effects. The following convention has been used for the classification of undesirable effects in terms of frequency: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10000, <1/1000, very rare (<1/10000).

Blood and the lymphatic system disorders
Very rare: Anaemia, leucopenia and thrombocytopenia.

Immune system disorders
Rare: Anaphylaxis.

Nervous system disorders
Common: Dizziness and headache.
Rare: Reversible neurological reactions including agitation, tremor, ataxia, dysarthria, psychotic symptoms, encephalopathy, drowsiness, confusional states, hallucinations, somnolence, convulsions, coma and malaise. These effects were usually reported in patients receiving high doses of aciclovir (usually given intravenously), with renal impairment, or with other predisposing factors (see section 4.4). Aciclovir should be used with caution in patients with underlying neurological abnormalities.
Respiratory, thoracic and mediastinal disorders
Rare: Dyspnoea

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea and abdominal pain.

Hepato-biliary disorders
Rare: Reversible rises in bilirubin and liver related enzymes. 
Very rare: Hepatitis and jaundice.

Skin and sub-cutaneous tissue disorders
Common: Skin rashes, pruritus (including photosensitivity).
Uncommon: Urticaria, accelerated diffuse hair loss.
Accelerated diffuse hair loss has been associated with a wide variety of disease processes and medicines, the relationship of the event to aciclovir therapy is uncertain.
Rare: Angioedema, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis.

Renal and urinary disorders
Rare: Increases in blood urea and creatinine; renal impairment, usually during intravenous therapy, which is usually reversible and responds to hydration and/or dosage reduction but may progress to acute renal failure in patients with predisposing factors.
Very rare: Acute renal failure, renal pain
Renal pain may be associated with renal failure.

General disorders
Common: Fatigue, fever.

4.9 Overdose

Symptoms and signs
Aciclovir is only partly absorbed in the gastrointestinal tract. Patients have ingested overdoses of up to 20 g aciclovir on a single occasion, usually without toxic effects. Accidental, repeated overdoses of oral aciclovir over several days have been associated with gastrointestinal effects (eg nausea and vomiting) and neurological effects (eg headache and confusion).

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.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties

ATC code: J05A B
Aciclovir is an antiviral agent which is highly active in vitro against herpes simplex virus (HSV) types I and II and varicella zoster virus. Toxicity to mammalian host cells is low.

Aciclovir is phosphorylated after entry into herpes infected cells to the active compound aciclovir triphosphate. The first step in this process is dependant on the presence of the HSV-coded thymidine kinase. Aciclovir triphosphate acts as an inhibitor of, and substrate for, the herpes-specified DNA polymerase, preventing further viral DNA synthesis without affecting the normal cellular processes.

Herpes simplex virus develops resistance to aciclovir by selection of mutants deficient in thymidine kinase which are usually of diminished virulence with reduced infectivity and latency. Resistance is rare in immunocompetent patients on short courses of oral therapy but it is more prevalent in immunocompromised patients who have often received prolonged
courses of treatment. Herpes zoster resistance develops by a similar mechanism and has been reported in immunocompromised patients undergoing prolonged therapy with aciclovir.

5.2 Pharmacokinetic properties
Absorption
Aciclovir is slowly and incompletely absorbed from the gastrointestinal tract. The peak plasma concentration occurs about 2 hours following ingestion.

Distribution
There is a wide distribution to various tissues, including the CSF where concentrations achieved are about 50% of those achieved in plasma. Protein binding is reported to range from 9-33%. Aciclovir crosses the placenta and is excreted in breast milk in concentrations approximately 3 times higher than those in maternal serum.

Metabolism and Elimination
Renal excretion is the major route of elimination by both glomerular filtration and tubular secretion. The terminal or beta-phase half-life is reported to be about 2-3 hours for adults without renal impairment. As aciclovir persists in the plasma of patients with renal insufficiency, in chronic renal failure this value is increased and may be up to 19.5 hours in anuric patients. As renal function decreases, a greater percentage of the drug is eliminated by metabolic conversion to carboxymethoxymethyl guanine. During haemodialysis the half-life is reduced to 5.7 hours, with 60% of a dose of aciclovir being removed in 6 hours. Faecal excretion may account for about 2% of a dose.

In neonates and young infants (0 to 3 months of age) treated with doses of 10 mg/kg administered by infusion over a one-hour period every 8 hours the Cssmax was found to be 61.2 microMol (13.8 micrograms/ml) and Cssmin to be 10.1 microMol (2.3 micrograms/ml). A separate group of neonates treated with 15 mg/kg every 8 hours showed approximate dose proportional increases, with a Cmax of 83.5 micromolar (18.8 microgram/ml) and Cmin of 14.1 micromolar (3.2 microgram/ml).

5.3 Preclinical safety data
Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rats, rabbits or mice. In a non-standard test in rats, foetal abnormalities were observed, but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain. Two generation studies in mice do not reveal any effect of aciclovir on fertility.

The results of a wide range of mutagenicity tests in vitro and in vivo indicate that aciclovir does not pose a genetic risk to man. Aciclovir was not found to be carcinogenic in long term studies in the rat and the mouse. Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of aciclovir greatly in excess of those employed therapeutically. Aciclovir has been shown to have no definite effect upon sperm count, morphology or motility in man.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Also contains: lactose, magnesium stearate, polyvidone, sodium starch glycollate, Indigo Carmine Lake (E132), Microcrystalline Cellulose (E460).

6.2 Incompatibilities
None known.

6.3 Shelf life
Shelf-life
Three years from the date of manufacture.

Shelf-life after dilution/reconstitution
Not applicable.
**Shelf-life after first opening**
Not applicable.

6.4 **Special precautions for storage**
Store below 25°C in a dry place.

6.5 **Nature and contents of container**
The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene containers with polyfoam wad or polyethylene ullage filler and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass containers with screw caps and polyfoam wad or cotton wool.

The product may also be supplied in blister packs in cartons:

a) Carton: Printed carton manufactured from white folding box board.
b) Blister pack: (i) 250µm white rigid PVC. (ii) Surface printed 20µm hard temper aluminium foil with 5-7g/M² PVC and PVdC compatible heat seal lacquer on the reverse side.

The product may be contained in blister packs which enhances security of the pack increasing resistance to deliberate contamination, pilfering, etc.

Pack sizes: 25s, 28s, 30s, 35s, 56s, 60s, 100s.

Product may also be supplied in bulk packs, for reassembly purposes only, in polybags contained in tins, skillets or polybuckets filled with suitable cushioning material. Bulk packs are included for temporary storage of the finished product before final packaging into the proposed marketing containers.

Maximum size of bulk packs: 50,000.

6.6 **Special precautions for disposal**
Not applicable.

7 **MARKETING AUTHORISATION HOLDER**
Name or style and permanent address of registered place of business of the holder of the Marketing Authorisation:

Actavis Group PTC ehf
Reykjavikurvegi 76-78
220 Hafnarfjordur
Iceland

8 **MARKETING AUTHORISATION NUMBER(S)**
PL 30306/0282

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**
19/05/2010

10 **DATE OF REVISION OF THE TEXT**
03/07/2012
1 NAME OF THE MEDICINAL PRODUCT
ACICLOVIR 400mg TABLETS

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each tablet contains 400mg Aciclovir.

For full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Pink uncoated tablets.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
1) Treatment of herpes simplex virus infections of the skin and mucous membranes including initial and recurrent genital herpes (excluding severe HSV infections in immunocompromised children).
2) Suppression (prevention of recurrences) of recurrent herpes simplex infections in immunocompetent patients.
3) Prophylaxis of herpes simplex infections in immunocompromised patients.
4) Treatment of varicella (chickenpox) infection.

4.2 Posology and method of administration
Adults: Treatment of herpes simplex infections: 200mg aciclovir should be taken five times daily at approximately four hourly intervals omitting the night time dose. Treatment should continue for five days, but in severe initial infections this may have to be extended. In severely immunocompromised patients (eg after marrow transplant) or in patients with impaired absorption from the gut the dose can be doubled to 400mg aciclovir or alternatively intravenous dosing could be considered. Dosing should begin as early as possible after the start of an infection; for recurrent episodes this should preferably be during the prodromal period or when lesions first appear.

Suppression of herpes simplex infections in immunocompetent patients: 200mg aciclovir should be taken four times daily at approximately six-hourly intervals. Many patients may be conveniently managed on a regime of 400mg aciclovir twice daily at approximately twelve-hourly intervals. Dosage titration down to 200mg aciclovir taken three times daily at approximately eight-hourly intervals or even twice daily at approximately twelve-hourly intervals, may prove effective. Some patients may experience break-through infections on total daily doses of 800mg aciclovir. Therapy should be interrupted periodically at intervals of six to twelve months, in order to observe possible changes in the natural history of the disease.

Prophylaxis of herpes simplex infections in immunocompromised patients: 200mg aciclovir should be taken four times daily at approximately six hourly intervals. In severely immunocompromised patients (eg after marrow transplant) or in patients with impaired absorption from the gut, the dose can be doubled to 400mg aciclovir or, alternatively, intravenous dosing could be considered. The duration of prophylactic administration is determined by the duration of the period at risk.

Dosage in children: Treatment of herpes simplex infections, and prophylaxis of herpes simplex infections in the immunocompromised: children aged two years and over should be given the adult doses and children below the age of two years should be given half the adult dose. Treatment of varicella infection: children under 2 years should be given 200mg four times daily. Children aged 2-5 years should be given 400mg four times daily. Children aged 6 years and over should be given 800mg four times daily. Treatment should continue for 5 days. Dosing may be more accurately calculated as 20mg/kg bodyweight (not to exceed 800mg four times daily). A liquid formulation might be more suitable for small children. No specific data are available on the suppression of herpes simplex infections or the treatment of herpes zoster infections in immunocompetent children. When treatment of herpes zoster
infections is required in immunocompromised children, intravenous dosing should be considered.

**Dosage in the elderly:** In the elderly, total aciclovir body clearance declines along with creatinine clearance. Adequate hydration of elderly patients taking high oral doses of aciclovir should be maintained. Special attention should be given to dosage reduction in elderly patients with impaired renal function.

**Dosage in renal impairment:** In the management of herpes simplex infections in patients with impaired renal function, the recommended oral doses will not lead to accumulation of aciclovir above levels that have been established by intravenous infusion. However, for patients with severe renal impairment (creatinine clearance less than 10ml/minute) an adjustment of dosage to 200mg aciclovir twice daily at approximately twelve-hourly intervals is recommended.

**Method of Administration**

**Administration:** Patients who experience difficulty in swallowing the tablets may disperse them in a minimum of 50ml water which should be stirred before drinking.

For oral administration.

### 4.3 Contraindications

Aciclovir tablets are contraindicated in patients known to be hypersensitive to aciclovir and valaciclovir or to any of the excipients.

### 4.4 Special warnings and precautions for use

**Use in patients with renal impairment and in elderly patients:**

Aciclovir is eliminated by renal clearance, therefore the dose 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).

Prolonged or repeated courses of aciclovir in severely immune-compromised individuals may result in the selection of virus strains with reduced sensitivity, which may not respond to continued aciclovir treatment (see section 5.1).

**Hydration status:** Care should be taken to maintain adequate hydration in patients receiving higher dose oral regimens, e.g. for the treatment of herpes zoster infection (4g daily), in order to avoid the risk of possible renal toxicity.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

### 4.5 Interaction with other medicinal products and other forms of interaction

No clinically significant interactions have been identified.

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

Ciclosporin: There has been a small number of transplant patients with increased serum levels of ciclosporin and signs of nephrotoxicity when aciclovir is given concurrently. Renal function should be monitored closely in patients taking both drugs.

Cimetidine and probenecid: Cimetidine and probenecid increase the AUC of aciclovir by competing for active secretion by the renal tubules and reduce aciclovir renal clearance. Dosage adjustment is usually not necessary because of the wide therapeutic index of aciclovir.

Mycophenolate mofetil: 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 the drugs are coadministered. However, no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.

Theophylline: Serum levels of theophylline may be increased by concurrent administration of aciclovir and it may be necessary to reduce the dosage of theophylline if aciclovir is added to the established treatment.
Zidovudine: Although co-administration of zidovudine and aciclovir is not usually associated with toxicity, there is a single case report of overwhelming fatigue developing in a patient when given the two drugs together. This did not occur when zidovudine and aciclovir were given alone.

4.6 Pregnancy and lactation

Pregnancy

Experience in humans is limited so the use of aciclovir should be considered only when the potential benefits outweigh the possibility of unknown risks. Herpes simplex encephalitis and varicella pneumonia constitute a significant risk for mother and foetus and primary genital herpes may retard intrauterine growth and increase the risk of premature birth and neonatal herpes infection. (See section 5.3 Preclinical Safety Data). Aciclovir readily crosses the placenta and levels in cord blood are higher than in maternal serum.

A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of aciclovir. The registry findings 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.

Lactation

Following oral administration of 200mg aciclovir five times a day, aciclovir has been detected in breast milk at concentrations ranging from 0.6-4.1 times the corresponding plasma levels. These levels would potentially expose nursing infants to aciclovir dosages of up to 0.3mg/kg/day. Caution is therefore advised if aciclovir is to be administered to a nursing mother.

4.7 Effects on ability to drive and use machines

The clinical status of the patient and the adverse event profile of aciclovir should be borne in mind when considering the patient's ability to drive or operate machinery. As aciclovir administration is occasionally associated with drowsiness and somnolence (usually in patients receiving high doses or with impaired renal function), patients should make sure that they are not affected before driving or using machinery.

There have been no studies to investigate the effect of aciclovir 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

The frequency categories associated with the adverse events below are estimates. For most events, suitable data for estimating incidence were not available. In addition, adverse events may vary in their incidence depending on the indication.

An estimate of the frequency of undesirable effects has been included though this is not certain for all adverse effects. The following convention has been used for the classification of undesirable effects in terms of frequency: very common (>1/10), common (>1/100, <1/10), uncommon (>1/1000, <1/100), rare (>1/10000, <1/1000, very rare (<1/10000).

Blood and the lymphatic system disorders

Very rare: Anaemia, leucopenia and thrombocytopenia.

Immune system disorders

Rare: Anaphylaxis.

Nervous system disorders

Common: Dizziness and headache.

Rare: Reversible neurological reactions including agitation, tremor, ataxia, dysarthria, psychotic symptoms, encephalopathy, drowsiness, confusional states, hallucinations, somnolence, convulsions, coma and malaise. These effects were usually reported in patients receiving high doses of aciclovir (usually given intravenously), with renal impairment, or with other predisposing factors (see section 4.4). Aciclovir should be used with caution in patients with underlying neurological abnormalities.
Respiratory, thoracic and mediastinal disorders
Rare: Dyspnoea

Gastrointestinal disorders
Common: Nausea, vomiting, diarrhoea and abdominal pain.

Hepato-biliary disorders
Rare: Reversible rises in bilirubin and liver related enzymes.
Very rare: Hepatitis and jaundice.

Skin and sub-cutaneous tissue disorders
Common: Skin rashes, pruritus (including photosensitivity).
Uncommon: Urticaria, accelerated diffuse hair loss.
Accelerated diffuse hair loss has been associated with a wide variety of disease processes and medicines, the relationship of the event to aciclovir therapy is uncertain.
Rare: Angioedema, erythema multiforme, Stevens Johnson syndrome, toxic epidermal necrolysis.

Renal and urinary disorders
Rare: Increases in blood urea and creatinine; renal impairment, usually during intravenous therapy, which is usually reversible and responds to hydration and/or dosage reduction but may progress to acute renal failure in patients with predisposing factors.
Very rare: Acute renal failure, renal pain
Renal pain may be associated with renal failure.

General disorders
Common: Fatigue, fever.

4.9 Overdose
Symptoms and signs
Aciclovir is only partly absorbed in the gastrointestinal tract. Patients have ingested overdoses of up to 20 g aciclovir on a single occasion, usually without toxic effects. Accidental, repeated overdoses of oral aciclovir over several days have been associated with gastrointestinal effects (eg nausea and vomiting) and neurological effects (eg headache and confusion).

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.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
ATC code: J05A B
Aciclovir is an antiviral agent which is highly active in vitro against herpes simplex virus (HSV) types I and II and varicella zoster virus. Toxicity to mammalian host cells is low.

Aciclovir is phosphorylated after entry into herpes infected cells to the active compound aciclovir triphosphate. The first step in this process is dependant on the presence of the HSV-coded thymidine kinase. Aciclovir triphosphate acts as an inhibitor of, and substrate for, the herpes-specified DNA polymerase, preventing further viral DNA synthesis without affecting the normal cellular processes.

Herpes simplex virus develops resistance to aciclovir by selection of mutants deficient in thymidine kinase which are usually of diminished virulence with reduced infectivity and latency. Resistance is rare in immunocompetent patients on short courses of oral therapy but it is more prevalent in immunocompromised patients who have often received prolonged
Herpes zoster resistance develops by a similar mechanism and has been reported in immunocompromised patients undergoing prolonged therapy with aciclovir.

5.2 Pharmacokinetic properties
Absorption
Aciclovir is slowly and incompletely absorbed from the gastrointestinal tract. The peak plasma concentration occurs about 2 hours following ingestion.

Distribution
There is a wide distribution to various tissues, including the CSF where concentrations achieved are about 50% of those achieved in plasma. Protein binding is reported to range from 9-33%. Aciclovir crosses the placenta and is excreted in breast milk in concentrations approximately 3 times higher than those in maternal serum.

Metabolism and Elimination
Renal excretion is the major route of elimination by both glomerular filtration and tubular secretion. The terminal or beta-phase half-life is reported to be about 2-3 hours for adults without renal impairment. As aciclovir persists in the plasma of patients with renal insufficiency, in chronic renal failure this value is increased and may be up to 19.5 hours in anuric patients. As renal function decreases, a greater percentage of the drug is eliminated by metabolic conversion to carboxymethoxymethyl guanine. During haemodialysis the half-life is reduced to 5.7 hours, with 60% of a dose of aciclovir being removed in 6 hours. Faecal excretion may account for about 2% of a dose.

In neonates and young infants (0 to 3 months of age) treated with doses of 10 mg/kg administered by infusion over a one-hour period every 8 hours the Cssmax was found to be 61.2 microMol (13.8 micrograms/ml) and Csmn to be 10.1 microMol (2.3 micrograms/ml). A separate group of neonates treated with 15 mg/kg every 8 hours showed approximate dose proportional increases, with a Cmax of 83.5 micromolar (18.8 microgram/ml) and Cmin of 14.1 micromolar (3.2 microgram/ml).

5.3 Preclinical safety data
Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rats, rabbits or mice. In a non-standard test in rats, foetal abnormalities were observed, but only following such high subcutaneous doses that maternal toxicity was produced. The clinical relevance of these findings is uncertain.

Two generation studies in mice do not reveal any effect of aciclovir on fertility.

The results of a wide range of mutagenicity tests in vitro and in vivo indicate that aciclovir does not pose a genetic risk to man. Aciclovir was not found to be carcinogenic in long term studies in the rat and the mouse. Largely reversible adverse effects on spermatogenesis in association with overall toxicity in rats and dogs have been reported only at doses of aciclovir greatly in excess of those employed therapeutically. Aciclovir has been shown to have no definite effect upon sperm count, morphology or motility in man.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Also contains: colloidal anhydrous silica, magnesium stearate, polyvidone, sodium starch glycollate, Iron Oxide (red) (E172), Microcrystalline Cellulose (E460).

6.2 Incompatibilities
None known.

6.3 Shelf life
Shelf-life
Three years from the date of manufacture.

Shelf-life after dilution/reconstitution
Not applicable.
6.4 **Special precautions for storage**  
Store below 25°C in a dry place.

6.5 **Nature and contents of container**  
The product containers are rigid injection moulded polypropylene or injection blow-moulded polyethylene containers with polyfoam wad or polyethylene ullage filler and snap-on polyethylene lids; in case any supply difficulties should arise the alternative is amber glass containers with screw caps and polyfoam wad or cotton wool.

The product may also be supplied in blister packs in cartons:
- **Carton:** Printed carton manufactured from white folding box board.
- **Blister pack:**  
  1. 250µm white rigid PVC.  
  2. Surface printed 20µm hard temper aluminium foil with 5-7g/M² PVC and PVdC compatible heat seal lacquer on the reverse side.

The product may be contained in blister packs which enhances security of the pack increasing resistance to deliberate contamination, pilfering, etc.

Pack sizes: 20s, 25s, 28s, 30s, 35s, 56s, 60s, 100s.

Product may also be supplied in bulk packs, for reassembly purposes only, in polybags contained in tins, skilllets or polybuckets filled with suitable cushioning material. Bulk packs are included for temporary storage of the finished product before final packaging into the proposed marketing containers. Maximum size of bulk packs: 50,000.

6.6 **Special precautions for disposal**  
Not applicable.

7 **MARKETING AUTHORISATION HOLDER**  
Name or style and permanent address of registered place of business of the holder of the Marketing Authorisation:

Actavis Group PTC ehf  
Reykjavikurvegi 76-78  
220 Hafnarfjordur  
Iceland

8 **MARKETING AUTHORISATION NUMBER(S)**  
PL 30306/0283

9 **DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**  
19/05/2010

10 **DATE OF REVISION OF THE TEXT**  
19/05/2010