

**ACICLOVIR 250MG POWDER FOR SOLUTION FOR INFUSION
(ACICLOVIR)**

PL 20851/0005

UKPAR

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**ACICLOVIR 250MG POWDER FOR SOLUTION FOR INFUSION
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PL 20851/0005

LAY SUMMARY

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Wockhardt UK Holdings Limited a Marketing Authorisation (licence) for the medicinal product Aciclovir 250mg Powder for Solution for Infusion (PL 20851/0005) on 4th December 2007. This is a prescription-only medicine (POM) used to stop viruses spreading in the body.

Aciclovir 250mg Powder for Solution for Infusion contains the active ingredient aciclovir, which belongs to a group of medicines called anti-virals. Aciclovir is used to treat herpes infections in babies and patients with a low resistance to disease, encephalitis (inflammation of the brain) caused by herpes virus, and severe infections of the genitals caused by herpes virus. It is also used to prevent repeated herpes infections in people who have a low resistance to disease. Aciclovir for infusion is also used to treat chickenpox and 'shingles'.

The proposed product was considered to be a generic version of the reference product Zovirax IV 250mg (PL 00003/0159, The Wellcome Foundation Ltd).

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of using Aciclovir 250mg Powder for Solution for Infusion outweigh the risk, hence a Marketing Authorisation has been granted.

**ACICLOVIR 250MG POWDER FOR SOLUTION FOR INFUSION
(ACICLOVIR)**

PL 20851/0005

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted Wockhardt UK Holdings Limited a Marketing Authorisation for the medicinal product Aciclovir 250mg Powder for Solution for Infusion (PL 20851/0005) on 4th December 2007. The product is a prescription-only medicine (POM).

The application was submitted as a national, abridged, standard application, according to Article 10.1 (a) (iii) first paragraph (now article 10(1)) of Directive 2001/83/EC, as amended. The application refers to the innovator product, Zovirax IV 250mg (PL 00003/0159). This product was authorised to The Wellcome Foundation Ltd on 6th April 1982.

The product is presented as a lyophilised powder for solution for infusion containing 250mg aciclovir. It is a powder to which sterile water or a sterile salt solution has to be added before it can be used. Once made up, the solution can be given by a controlled-rate infusion pump. Alternatively, the solution can have more liquid added to make it weaker so that it can be given to you as a drip (an infusion).

Aciclovir 250mg Powder for Solution for Infusion is indicated for the prophylaxis and treatment of a variety of viral infections in both immunocompromised and non immunocompromised patients, including the neonate and infant up to three months of age.

PHARMACEUTICAL ASSESSMENT

ACTIVE SUBSTANCE

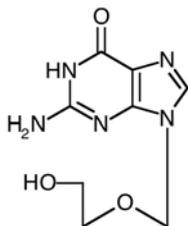
Aciclovir

Nomenclature:

INN: Aciclovir

Chemical name: 2-amino-9-[(2-hydroxyethoxy)methyl]-3,9-dihydro-6H-purin-6-one

Structure:



Molecular formula: $C_8H_{11}N_5O_3$

Molecular weight: 225.2

CAS No: 59277-89-3

Physical form: A white or almost white crystalline powder

Solubility: Slightly soluble in water, very slightly soluble in alcohol, freely soluble in dimethyl sulfoxide

The active substance aciclovir is the subject of a Ph. Eur. monograph.

Synthesis of the drug substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specifications are in place for all starting materials and reagents, as well as for working and reference standards used, and these are supported by relevant certificates of analysis.

Confirmation has been provided that the materials used are not derived from animals or animals susceptible to BSE and TSE and therefore comply with the TSE requirements.

An appropriate active substance specification has been provided based on the European Pharmacopeia monograph, and in line with the Certificate of Suitability

The Certificate of Suitability states that the drug substance is adequately controlled by the Ph.Eur. drug substance monograph if supplemented by additional tests for:

- 1,6-bis(2-amino-1,9-dihydro-6H-6-oxo-purin-9-yl)-2,5-dioxahexane. (NMT 0.2%)
- Any other detectable impurity (NMT 0.1%)
- Ethanol (NMT 1000ppm)

The supplementary tests for impurities are conducted using the method described in the Ph. Eur. monograph. Residual ethanol is determined using a satisfactory in-house method.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

The manufacture and quality of active substance manufactured by the active substance manufacturer is controlled by a Certificate of Suitability.

Active aciclovir is stored in appropriate packaging. It is packed in two sealed polyethylene bags placed within a “Kraft-lined” drum which protects the product from light, dust and humidity during handling, storage, transport and distribution. Either black or transparent bags are used – this is not considered to be critical as the opaque secondary packaging would provide absolute protection from light and thickness is consistent. Specifications and Certificates of Analysis for all packaging components used have been provided. The polyethylene bags in direct contact with the drug substance satisfy Directive 2002/72/EC (as amended), and are suitable for contact with foodstuffs.

Batch analysis data are provided and comply with the proposed specification.

Appropriate stability data have been generated for active substance stored in the proposed packaging. This data demonstrates the stability of the active substance and supports a retest period of 60 months, when stored in the proposed packaging.

DRUG PRODUCT

Description & Composition

The product is presented as a lyophilised powder for solution for infusion, containing the active ingredient, aciclovir.

Other ingredients consist of pharmaceutical excipients, namely sodium hydroxide and water for injections. Appropriate justification for the inclusion of each excipient has been provided.

All excipients used comply with their respective European Pharmacopoeial monographs. Satisfactory Certificates of Analysis have been provided for all excipients.

The applicant has provided a declaration confirming that there are no materials of human or animal origin contained in or used in the manufacturing process for the proposed product.

There were no novel excipients used and no overages.

Impurity profiles

Impurity profiles for the drug product were found to be superior to those for the reference product, and all the impurities are within the specification limits.

Pharmaceutical development

Details of the pharmaceutical development of the drug product have been supplied and are satisfactory.

Manufacture

A description and flow-chart of the manufacturing method has been provided.

In-process controls have been provided and are appropriate considering the nature of the product and the method of manufacture. Process validation has been carried out on validation batches. The results are satisfactory.

Finished product specification

The finished product specification complies with the Ph. Eur. general monograph for parenteral preparations and the BP monograph for aciclovir infusion, and is satisfactory. Acceptance limits have been justified with respect to conventional pharmaceutical requirements and, where appropriate, safety. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any standards used.

Container Closure System

The drug product is presented as a powder supplied in Type I transparent, colourless, 10ml glass vials with Ph. Eur. Type I chlorobutyl rubber stoppers and polypropylene flip-off caps. The primary packaging satisfies Directive 2002/72/EC (as amended), and is suitable for contact with parenteral and ophthalmic preparations. Specifications and Certificates of Analysis for all packaging components used have been provided. These are satisfactory. The product is licensed for packs of one, five or ten vials, although the PL Holder has stated that not all pack sizes may be marketed.

Stability

Finished product stability studies have been conducted in accordance with current guidelines and results were within the proposed specification limits. Based on the results, a shelf-life of 36 months has been set, with storage instruction 'Do not store above 25°C'. This is satisfactory. For reconstituted solutions, the shelf life is 24 hours at a temperature of 2-8°C. The storage instruction is 'Do not store above 25°C'.

Bioequivalence Study

Bioequivalence studies are not necessary to support this application for a parenteral product.

EXPERT REPORT

The quality overview is written by an appropriately qualified expert and is satisfactory. A satisfactory Curriculum Vitae has been provided for the pharmaceutical expert.

PRODUCT INFORMATION:**Summary of Product Characteristics**

The approved SPC is satisfactory.

Patient Information Leaflet

The approved PIL is in line with the final SPC and is satisfactory.

Labelling

Colour mock-ups of the labelling have been provided. The labelling is satisfactory.

Conclusion

The proposed product has been shown to be a generic version of the reference product, with respect to qualitative and quantitative content of the active substance, and the pharmaceutical form. The test product is pharmaceutically equivalent to the reference product which has been licensed in the UK for over 10 years. Given the route of administration and pharmaceutical form, it is not necessary to demonstrate bioequivalence of the proposed product to the reference product.

The quality grounds for this application are considered adequate. It is recommended that a Marketing Authorisation is granted.

PRECLINICAL ASSESSMENT

The application was submitted as a national, abridged, standard application, according to Article 10.1 (a) (iii) first paragraph (now article 10(1)) of Directive 2001/83/EC, as amended.

No new preclinical data have been supplied with this application and none are required for an application of this type. A preclinical expert report has been written by a suitably qualified person and is satisfactory.

CLINICAL ASSESSMENT

INDICATIONS

Aciclovir 250mg Powder for Solution for Infusion is indicated for the prophylaxis and treatment of *Herpes simplex* infections in immunocompromised patients. It is also used for the treatment of severe initial genital herpes in the non-immunocompromised, *Herpes simplex* infections in the neonate and infant up to three months of age, herpes encephalitis, and *Varicella zoster* infections.

CLINICAL PHARMACOLOGY

No new data are submitted and none are required for this type of application.

EFFICACY

No new data are submitted and none are required for this type of application. Efficacy is reviewed in the clinical expert report

SAFETY

No new data are submitted and none are required for this type of application. Safety is reviewed in the clinical expert report

EXPERT REPORT

The expert report is written by a medically qualified pharmaceutical consultant and is satisfactory. A suitable Curriculum Vitae has been provided for the clinical expert.

CONCLUSION

The grounds for establishing the proposed product as a generic version of the reference product, Zovirax IV 250mg (PL 00003/0159), are considered adequate. The product literature is approved.

The grant of a marketing authorisation is recommended.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Aciclovir 250mg Powder for Solution for Infusion are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

The applicant's Aciclovir 250mg Powder for Solution for Infusion (PL 20851/0005) has been demonstrated to be a generic version of the reference product Zovirax IV 250mg (PL 00003/0159).

No new or unexpected safety concerns arise from this application.

PRODUCT LITERATURE

The approved SPC, PIL and labelling are satisfactory and consistent with that for the innovator product.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. The qualitative and quantitative assessment supports the claim that the applicant's product and the innovator product are interchangeable. Extensive clinical experience with aciclovir is considered to have demonstrated the therapeutic value of the active substance. The risk benefit is, therefore, considered to be positive.

**ACICLOVIR 250MG POWDER FOR SOLUTION FOR INFUSION
(ACICLOVIR)****PL 20851/0005****STEPS TAKEN FOR ASSESSMENT**

- 1 The MHRA received the marketing authorisation application on 10th June 2005
- 2 Following standard checks and communication with the applicant the MHRA considered the application valid on 9th August 2005
- 3 Following assessment of the application the MHRA requested further information relating to the clinical dossier on 15th November 2005
- 4 The applicant responded to the MHRA's requests, providing further information for the clinical sections on 15th November 2005
- 5 Following assessment of the response and application the MHRA requested further information relating to the clinical and quality sections on 25th November 2005
- 6 The applicant responded to the MHRA's request, providing further information for the clinical and quality sections on 1st February 2006
- 7 Following assessment of the response the MHRA requested further information relating to the clinical sections on 2nd March 2006
- 8 The applicant responded to the MHRA's requests, providing further information for the clinical sections on 11th July 2006
- 9 Following assessment of the response and application the MHRA requested further information relating to the quality sections on 13th October 2006, 3rd April 2007, and 25th July 2007
- 10 The applicant responded to the MHRA's requests, providing further information for the quality sections on 21st October 2006, 2nd July 2007, and 2nd October 2007
- 11 The application was determined on 4th December 2007

SUMMARY OF PRODUCT CHARACTERISTICS

The UK Summary of Product Characteristics (SPC) for Aciclovir 250mg Powder for Solution for Infusion is as follows:

1 NAME OF THE MEDICINAL PRODUCT

Aciclovir 250mg Powder for Solution for Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 250mg of aciclovir as the sodium salt

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for infusion.

White powder.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Aciclovir for infusion is indicated for the treatment of *Herpes simplex* infections in immunocompromised patients and severe initial genital herpes in the non-immunocompromised.

Aciclovir for infusion is indicated for the prophylaxis of *Herpes simplex* infections in immunocompromised patients.

Aciclovir for infusion is indicated for the treatment of *Varicella zoster* infections.

Aciclovir for infusion is indicated for the treatment of herpes encephalitis.

Aciclovir for infusion is indicated for the treatment of *Herpes simplex* infections in the neonate and infant up to three months of age.

4.2 POSOLOGY AND METHOD OF ADMINISTRATION

Route of administration: Slow intravenous infusion.

A course of treatment with aciclovir for infusion usually lasts five days, but this may be adjusted according to the patient's condition and response to therapy. Treatment for herpes encephalitis and neonatal *Herpes simplex* infections usually lasts ten days.

The duration of prophylactic administration of aciclovir for infusion is determined by the duration of the period at risk.

Dosage

Dosage in adults:

Patients with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections should be given aciclovir for infusion in doses of 5mg/kg bodyweight every eight hours.

Immunocompromised patients with *Varicella zoster* infections or patients with herpes encephalitis should be given aciclovir for infusion in doses of 10mg/kg bodyweight every eight hours provided renal function is not impaired (see Dosage in renal impairment).

Dosage in children:

The dose of aciclovir for infusion for children aged between three months and 12 years is calculated on the basis of body surface area.

Children with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections should be given aciclovir for infusion in doses of 250 mg per square metre of body surface area every eight hours.

In immunocompromised children with *Varicella zoster* infections or children with herpes encephalitis, aciclovir for infusion should be given in doses of 500 mg per square metre body surface area every eight hours if renal function is not impaired.

Children with impaired renal function require an appropriately modified dose, according to the degree of impairment.

The dosage of aciclovir for infusion in neonates and infants up to three months of age is calculated on the basis of bodyweight.

Neonates and infants up to three months of age with *Herpes simplex* infections should be given aciclovir for infusion in doses of 10 mg/kg bodyweight every eight hours. Treatment for neonatal *Herpes simplex* infections usually lasts ten days.

Dosage in the elderly:

In the elderly, total aciclovir body clearance declines in parallel with creatinine clearance. Special attention should be given to dosage reduction in elderly patients with impaired creatinine clearance.

Dosage in renal impairment:

Caution is advised when administering aciclovir for infusion to patients with impaired renal function. The following adjustments in dosage are suggested:

Creatinine Clearance

25 to 50 ml/min: The dose recommended above (5 or 10 mg/kg bodyweight) should be given every 12 hours.

10 to 25 ml/min: The dose recommended above (5 or 10 mg/kg bodyweight) should be given every 24 hours.

0 (anuric) to 10 ml/min: In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommended above (5 or 10 mg/kg bodyweight) should be halved and administered every 24 hours. In patients receiving haemodialysis the dose recommended above (5 or 10 mg/kg bodyweight) should be halved and administered every 24 hours and after dialysis.

Administration

The required dose of aciclovir for infusion should be administered by slow intravenous infusion over a one-hour period.

After reconstitution aciclovir for infusion may be administered by a controlled-rate infusion pump.

Alternatively, the reconstituted solution may be further diluted to give an aciclovir concentration of not greater than 5 mg/ml (0.5% w/v) for administration by infusion.

For instructions on reconstitution and dilution of the product before administration see section 6.6.

4.3 CONTRAINDICATIONS

Aciclovir for infusion is contraindicated in patients known to be previously hypersensitive to aciclovir or valaciclovir.

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

The dose of aciclovir for infusion must be adjusted in patients with impaired renal function in order to avoid accumulation of aciclovir in the body (see Dosage in renal impairment).

In patients receiving aciclovir for infusion at higher doses (e.g. for herpes encephalitis), specific care regarding renal function should be taken, particularly when patients are dehydrated or have any renal impairment.

Reconstituted aciclovir for infusion has a pH of approximately 11.0 and should not be administered by mouth.

Aciclovir for infusion contains no antimicrobial preservative. Reconstitution and dilution should therefore be carried out under full aseptic conditions immediately before use and any unused solution discarded. The reconstituted or diluted solutions should not be refrigerated.

This vial contains approximately 26mg of sodium in total. The sodium content should be taken into consideration when prescribing to patients requiring sodium restriction.

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. Probenecid and cimetidine increase the AUC of aciclovir by this mechanism, and reduce aciclovir renal clearance. However no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.

In patients receiving intravenous aciclovir, caution is required during concurrent administration with drugs which compete with aciclovir for elimination, because of the potential for increased plasma levels of one or both drugs 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 the drugs are co-administered.

Care is also required (with monitoring for changes in renal function) if administering intravenous aciclovir with drugs which affect other aspects of renal physiology (e.g. ciclosporin, tacrolimus).

4.6 PREGNANCY AND LACTATION

A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of aciclovir. The birth defects described amongst aciclovir exposed subjects have not shown any uniqueness or consistent pattern to suggest a common cause. Caution should be exercised by balancing the potential benefits of treatment against any possible hazard.

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

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Aciclovir can cause reversible neurological reactions such as confusion, hallucinations, agitation, tremors, somnolence, psychosis and coma, which can all affect the ability to drive and use machinery.

4.8 UNDESIRABLE EFFECTS

Gastrointestinal: Nausea and vomiting have been reported.

Haematological: Decreases in haematological indices (anaemia, thrombocytopenia, leucopenia).

Hypersensitivity and Skin: Rashes including photosensitivity, urticaria, pruritus, fevers and rarely dyspnoea, angioedema and anaphylaxis.

Severe local inflammatory reactions sometimes leading to breakdown of the skin have occurred when formulations of aciclovir for intravenous use have been inadvertently infused into extravascular tissues.

Kidney: Rapid increases in blood urea and creatinine levels may occasionally occur in patients given aciclovir for infusion. This is believed to be related to peak plasma levels and the state of hydration of the patient. To avoid this effect the drug should not be given as an intravenous bolus injection but by slow infusion over a one hour period.

Adequate hydration of the patient should be maintained. Renal impairment developing during treatment with aciclovir for infusion usually responds rapidly to rehydration of the patient and/or dosage reduction or withdrawal of the drug. Progression to acute renal failure, however, can occur in exceptional cases.

Liver: Reversible increases in bilirubin and liver-related enzymes. Hepatitis and jaundice have been reported on very rare occasions.

Neurological: Reversible neurological reactions such as confusion, hallucinations, agitation, tremors, somnolence, psychosis, convulsions and coma have been associated with aciclovir for infusion therapy, usually in medically complicated cases.

4.9 OVERDOSE

Overdosage of intravenous aciclovir has resulted in elevations of serum creatinine, blood urea nitrogen and subsequent renal failure. Neurological effects including confusion, hallucinations, agitation, seizures and coma have been described in association with overdosage. Haemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered an option in the management of overdose of this drug.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

ATC Code: J05A B01, Direct Acting Antiviral

Aciclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against human herpes viruses, including *Herpes simplex virus* (HSV) types 1 and 2 and *Varicella zoster virus* (VZV), Epstein Barr virus (EBV) and Cytomegalovirus (CMV). In cell culture aciclovir has the greatest antiviral activity against HSV-1, followed (in decreasing order of potency) by HSV-2, VZV, EBV, and CMV.

The inhibitory activity of aciclovir for HSV-1, HSV-2, VZV and EBV is highly selective. The enzyme thymidine kinase (TK) of normal, uninfected cells does not use aciclovir effectively as a substrate, hence toxicity to mammalian host cells is low; however, TK encoded by HSV, VZV and EBV converts aciclovir to aciclovir monophosphate, a nucleoside analogue, which is further converted to the diphosphate and finally to the triphosphate by cellular enzymes. Aciclovir triphosphate interferes with the viral DNA polymerase and inhibits viral DNA replication with resultant chain termination following its incorporation into the viral DNA.

5.2 PHARMACOKINETIC PROPERTIES

In adults, the terminal plasma half-life of aciclovir after administration of aciclovir for infusion is about 2.9 hours. Most of the drug is excreted unchanged by the kidney. Renal clearance of aciclovir is substantially greater than creatinine clearance, indicating that tubular secretion, in addition to glomerular filtration, contributes to the renal elimination of the drug.

9-carboxymethoxymethylguanine is the only significant metabolite of aciclovir and accounts for 10 to 15% of the dose excreted in the urine.

When aciclovir is given one hour after 1g of probenecid the terminal half-life and the area under the plasma concentration time curve, are extended by 18% and 40% respectively.

In adults, mean steady state peak plasma concentrations (C^{ss}_{max}) following a one-hour infusion of 2.5 mg/kg, 5 mg/kg, and 10 mg/kg were 22.7 micromolar (5.1 microgram/ml), 43.6 micromolar (9.8 microgram/ml), and 92 micromolar (20.7 microgram/ml) respectively. The corresponding trough levels (C^{ss}_{min}) 7 hours later were 2.2 micromolar (0.5 microgram/ml), 3.1 micromolar (0.7 microgram/ml) and 10.2 micromolar (2.3 microgram/ml) respectively. In children over one year of age similar mean peak (C^{ss}_{max}) and trough (C^{ss}_{min}) levels were observed when a dose of 250 mg/m² was substituted for 5 mg/kg and a dose of 500 mg/m² was substituted for 10 mg/kg. In neonates (0 to three months of age) treated with doses of 10 mg/kg administered by infusion over a one-hour period every 8 hours the C^{ss}_{max} was found to be 61.2 micromolar (13.8 microgram/ml) and the C^{ss}_{min} to be 10.1 micromolar (2.3 microgram/ml).

The terminal plasma half-life in these patients was 3.8 hours. In the elderly, total body clearance falls with increasing age and is associated with decreases in creatinine clearance although there is little change in the terminal plasma half-life.

In patients with chronic renal failure the mean terminal half-life was found to be 19.5 hours. The mean aciclovir half-life during haemodialysis was 5.7 hours. Plasma aciclovir levels dropped approximately 60% during dialysis.

Cerebrospinal fluid levels are approximately 50% of corresponding plasma levels.

Plasma protein binding is relatively low (9 to 33%) and drug interactions involving binding site displacement are not anticipated.

5.3 PRECLINICAL SAFETY DATA

The results of a wide range of mutagenicity test *in vitro* and *in vivo* indicate that aciclovir is unlikely to pose a genetic risk to man.

Aciclovir was not found to be carcinogenic in long-term studies in the rat and the mouse.

Systemic administration of aciclovir in internationally accepted standard tests did not produce embryotoxic or teratogenic effects in rabbits, rats 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.

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. Two-generation studies in mice did not reveal any effect of (orally administered) aciclovir on fertility.

There is no experience of the effect of aciclovir for infusion on human fertility. Aciclovir tablets have been shown to have no definitive effect upon sperm count, morphology or motility in man.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Sodium hydroxide

6.2 INCOMPATIBILITIES

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 SHELF LIFE

Unopened - Three years

For reconstituted solutions, chemical and physical in-use stability has been demonstrated for at least 24 hours at 25°C. From a microbiological point of view, once opened, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Following dilution using the fluids detailed in section 6.6, chemical and physical in-use stability has been demonstrated for up to 12 hours at 25°C. From a microbiological point of view the diluted solution should be used immediately. If not used immediately in-use storage times and conditions are the responsibility of the user.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Unopened: Do not store above 25°C.

Keep the vials in the outer carton.

After reconstitution: Do not store above 25°C (see 6.3 Shelf Life).

6.5 NATURE AND CONTENTS OF CONTAINER

Packs* of one, five or ten Type I colourless glass 10ml vials stoppered with a chlorobutyl stopper and an aluminium and polypropylene flip-off cap.

*Not all pack sizes may be marketed

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL*Reconstitution:*

Aciclovir 250mg for infusion should be reconstituted using 10ml of either Water for Injections PhEur or Sodium Chloride Intravenous Infusion BP (0.9% w/v) to provide a solution containing 25mg aciclovir per ml.

From the calculated dose, determine the appropriate number and strength of vials to be used. To reconstitute each vial add the recommended volume of infusion fluid and shake gently until the contents of the vial have dissolved completely.

The reconstituted solution appears light yellow and slightly opalescent.

After reconstitution aciclovir powder for solution for infusion may be administered by a controlled-rate infusion pump.

Alternatively, the reconstituted solution may be further diluted to give an aciclovir concentration of not greater than 5 mg/ml (0.5% w/v) for administration by infusion:

For further dilution, add the required volume of reconstituted solution to the chosen infusion solution, as recommended below, and shake well to ensure adequate mixing occurs.

For children and neonates, where it is advisable to keep the volume of infusion fluid to a minimum, it is recommended that dilution is on the basis of 4ml reconstituted solution (100mg aciclovir) added to 20 ml of infusion fluid.

For adults, it is recommended that infusion bags containing 100ml of infusion fluid are used, even when this would give an aciclovir concentration substantially below 0.5% w/v. Thus, one 100 ml infusion bag may be used for any dose between 250mg and 500mg aciclovir (10 and 20 ml of reconstituted solution) but a second bag must be used for doses between 500 and 1000mg.

When diluted in accordance with the recommended schedules, aciclovir for infusion is known to be compatible with the following infusion fluids:

- sodium chloride intravenous infusion BP (0.45% and 0.9% w/v);
- sodium chloride (0.18% w/v) and glucose (4% w/v) intravenous infusion BP
- sodium chloride (0.45% w/v) and glucose (2.5% w/v) intravenous infusion BP
- compound sodium lactate intravenous infusion BP (Hartmann's Solution).

Aciclovir for infusion, when diluted in accordance with the above schedule will give an aciclovir concentration not greater than 0.5% w/v.

Since no antimicrobial preservative is included, reconstitution and dilution must be carried out under full aseptic conditions, immediately before use, and any unused solution discarded.

Should any visible turbidity or crystallisation appear in the solution before or during infusion, the preparation should be discarded.

7 MARKETING AUTHORISATION HOLDER

Wockhardt UK Limited
Ash Road North
Wrexham LL13 9UF
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PI 20851/0005

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

04/12/2007

10 DATE OF REVISION OF THE TEXT

04/12/2007

PRODUCT INFORMATION LEAFLETS

Patient Information Leaflet Aciclovir 250 mg Powder For Solution For Infusion

Read all of this leaflet carefully before you start using this medicine.

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

The name of your medicine is Aciclovir 250 mg Powder for Solution for Infusion.

In the rest of this leaflet Aciclovir 250 mg Powder for Solution for Infusion is called Aciclovir for Infusion.

In this leaflet:

1. What aciclovir for infusion is and what it is used for
2. Before you are given aciclovir for infusion
3. How aciclovir for infusion will be given to you
4. Possible side effects
5. How to store aciclovir for infusion

Each vial contains the active ingredient, aciclovir (as the sodium salt), as a powder for solution for intravenous infusion.

The other ingredient is sodium hydroxide.

Aciclovir for Infusion is Manufactured by Laboratorio Reig Jofré, Gran Capitán nº 10, 08970 Sant Joan Despí, Barcelona, Spain for the Marketing Authorisation holder Wockhardt UK Ltd, Ash Road North, Wrexham, LL13 9UF, UK (PL 20851/0005).

1. WHAT ACICLOVIR FOR INFUSION IS AND WHAT IT IS USED FOR

Aciclovir 250mg for infusion is a white powder for solution for infusion (powder for infusion). This means it is a powder to which sterile water or a sterile salt solution has to be added to before it can be used. Once made up, the solution can be given by a controlled-rate infusion pump. Alternatively, the solution can also have more liquid added to make it weaker so that it can then be given to you as a drip (an infusion).

The powder comes in a glass vial with a rubber cap and metal/plastic seal. It is available in packs of 1, 5 or 10 vials.

Aciclovir belongs to a group of medicines called antivirals. These medicines work by stopping viruses from spreading in the body.

Aciclovir for infusion is used to treat herpes infections in babies and patients with a low resistance to disease, encephalitis (inflammation of the brain) caused by herpes virus, and severe infections of the genitals caused by herpes

virus. It is also used to prevent repeated herpes infections in people who have a low resistance to disease.

Aciclovir for infusion is also used to treat chickenpox and "shingles".

Doctors sometimes prescribe this medicine for other purposes. If you think this applies to you, ask your doctor.

2. BEFORE YOU ARE GIVEN ACICLOVIR FOR INFUSION

Do not take aciclovir for infusion if:

- You have been told you are allergic to aciclovir or valaciclovir. Make sure to tell your doctor or pharmacist before they give you this medicine.

Take special care with aciclovir for infusion:

- If you have kidney problems. Make sure you tell your doctor and they may need to modify the doses according to how your kidneys may be working.
- If you are dehydrated (extremely thirsty)
- If you are on a low sodium diet: aciclovir for infusion contains approximately 26mg of sodium per vial. If you are on a low sodium diet make sure you tell your doctor or pharmacist.

Taking other medicines

Taking another medicine while you are being given aciclovir for infusion can affect how it or the other medicine works. Please inform your doctor or pharmacist if you are taking or have recently taken any other medicines, even those you may have bought yourself without a prescription. Please check with your doctor if you are taking any of the following (or any other medication):

- Probenecid, a drug used to prevent gout.
- Cimetidine, an anti-ulcer drug.
- Drugs used in transplant patients (i.e. Mycophenolate mofetil, ciclosporin and tacrolimus).

Pregnancy and breast-feeding

Aciclovir for infusion should not be given to you if you are pregnant unless your doctor considers it essential. You should let your doctor know if you think you may be pregnant or are trying for a baby.

You should let your doctor know if you are breast-feeding or want to start breast-feeding while you are having treatment with aciclovir for infusion.

Driving and using machines:

Aciclovir for infusion can cause confusion, hallucinations, agitation, tremor and somnolence which may affect your ability to drive or use machines. If you are affected, do not drive or operate machinery.

Important information about some of the ingredients of aciclovir for infusion:

Each vial contains 26mg of sodium. You should tell your doctor or pharmacist if you are on a controlled sodium diet.

3. HOW TO TAKE ACICLOVIR FOR INFUSION

Always take aciclovir for infusion exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Your doctor or nurse will prepare your injection by diluting it, either in the vial or in another container. The mixture is given by slow intravenous **infusion** over an hour using a syringe-pump or with a drip.

- The usual adult dose of aciclovir for infusion for the treatment of herpes infections, chickenpox or "shingles" is 5mg per kg bodyweight every eight hours for five days.
- This dose is doubled to 10mg per kg every eight hours for patients with chickenpox or "shingles" and low resistance to disease and patients suffering from herpes encephalitis (the latter may need ten days treatment).
- In babies up to three months old, the dose for the treatment of herpes infections is 10mg per kg of bodyweight every eight hours, usually for ten days.
- For children aged 3 months to 12 years, the dose for the treatment of chickenpox or herpes infections is 250mg per m² of body surface area, usually for five days. This can be doubled to 500mg per m² of body surface area every eight hours for children with chickenpox and low resistance to disease or with herpes encephalitis.

Dosage will be reduced if you have severe kidney problems or are elderly.

It is important to drink plenty of water after you have been given aciclovir infusion.

Your doctor will decide the dose which is best for you. If you do not understand, or are in any doubt, ask your doctor or nurse.

If you take more aciclovir for infusion than you should

A doctor or a nurse will usually give you this medicine. If you take too much aciclovir for infusion you may feel confused or agitated, or suffer from hallucinations (imagining things) or seizures. If you have taken too much medicine, you may be put on a kidney machine to reduce the amount of aciclovir for infusion in your blood. If you think you may have received too much aciclovir for infusion, please tell your doctor or nurse at once.

If you forget to take aciclovir for infusion

A doctor or a nurse will usually give you this medicine. If you think you have missed a dose, please tell your doctor or nurse.

4. POSSIBLE SIDE EFFECTS

Like many medicines, aciclovir for infusion may cause side effects in some patients, particularly when it is first administered, although not everybody gets them. These include:

- Feeling sick, being sick, anaemia and other blood problems (which could cause unexplained bleeding or bruising, sore throats or mouth ulcers, or low resistance to infections)
- Allergic reactions including rashes, sensitivity to light, itching, fever, breathing problems and swelling, liver and kidney problems
- There may be some increases in levels of chemicals in the blood, indicating kidney or liver disturbances

- Rarely yellowing of the skin, tiredness, confusion, hallucinations, feeling agitated, shaking, fits, mental disturbance and loss of consciousness have been reported, particularly in patients with other medical problems
- Local inflammation has been reported at the site of injection.

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.

5. HOW TO STORE ACICLOVIR FOR INFUSION

Keep your medicine out of the reach and sight of children. Do not use your medicine after the expiry date given on the carton and the label on the small glass container (vial). The expiry date is the last day of the month written on the packaging.

Your doctor, nurse or pharmacist will usually be responsible for storing and preparing aciclovir before use and for checking that the vials have not passed their expiry date.

Do not store above 25°C. Keep the vials in the outer carton, in order to protect from light.

Once the powder has been made into a solution the product can be stored for at least 24 hours at 25°C.

From a microbiological point of view, once opened, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Medicines should not be disposed of via wastewater or household waste. If you have been asked to dispose of this medicine ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

This leaflet was prepared in September 2007

To listen to or request a copy of this leaflet in Braille, large print or audio please call, free of charge: **0800 198 5000 (UK Only)**

Please be ready to give the following information:

Product Name Aciclovir 250mg Powder for Solution for Infusion

Reference Number 20851/0005

This is a service provided by the Royal National Institute of the Blind.

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MEDICAL INFORMATION LEAFLET

THE FOLLOWING INFORMATION IS INTENDED FOR HEALTHCARE PROFESSIONALS ONLY:

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Aciclovir 250mg Powder for Solution for Infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 250mg of aciclovir as the sodium salt
For a full list of excipients, see section 6.1

3. PHARMACEUTICAL FORM

Powder for solution for infusion.
White powder.

4. CLINICAL PARTICULARS

4.1. Therapeutic indications

Aciclovir for infusion is indicated for the treatment of *Herpes simplex* infections in immunocompromised patients and severe initial genital herpes in the non-immunocompromised.

Aciclovir for infusion is indicated for the prophylaxis of *Herpes simplex* infections in immunocompromised patients.

Aciclovir for infusion is indicated for the treatment of *Varicella zoster* infections.

Aciclovir for infusion is indicated for the treatment of herpes encephalitis.

Aciclovir for infusion is indicated for the treatment of *Herpes simplex* infections in the neonate and infant up to three months of age.

4.2 Posology and method of administration

Route of administration:
Slow intravenous infusion

A course of treatment with aciclovir for infusion usually lasts five days, but this may be adjusted according to the patient's condition and response to therapy. Treatment for herpes encephalitis and neonatal *Herpes simplex* infections usually lasts ten days.

The duration of prophylactic administration of aciclovir for infusion is determined by the duration of the period at risk.

Dosage

Dosage in adults:

Patients with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections should be given aciclovir for infusion in doses of 5mg/kg bodyweight every eight hours.

Immunocompromised patients with *Varicella zoster* infections or patients with herpes encephalitis should be

Administration

The required dose of aciclovir for infusion should be administered by slow intravenous infusion over a one-hour period.

After reconstitution aciclovir for infusion may be administered by a controlled-rate infusion pump.

Alternatively, the reconstituted solution may be further diluted to give an aciclovir concentration of not greater than 5 mg/ml (0.5% w/v) for administration by infusion.

For instructions on reconstitution and dilution of the product before administration see section 6.6.

4.3. Contraindications

Aciclovir for infusion is contraindicated in patients known to be previously hypersensitive to aciclovir or valaciclovir.

4.4. Special warnings and precautions for use

The dose of aciclovir for infusion must be adjusted in patients with impaired renal function in order to avoid accumulation of aciclovir in the body (see Dosage in renal impairment).

In patients receiving aciclovir for infusion at higher doses (e.g. for herpes encephalitis), specific care regarding renal function should be taken, particularly when patients are dehydrated or have any renal impairment.

Reconstituted aciclovir for infusion has a pH of approximately 11.0 and should not be administered by mouth.

Aciclovir for infusion contains no antimicrobial preservative. Reconstitution and dilution should therefore be carried out under full aseptic conditions immediately before use and any unused solution discarded. The reconstituted or diluted solutions should not be refrigerated.

This vial contains approximately 26mg of sodium in total. The sodium content should be taken into consideration when prescribing to patients requiring sodium restriction.

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. Probenecid and cimetidine increase the AUC of aciclovir by this mechanism, and reduce aciclovir renal clearance. However no dosage adjustment is necessary because of the wide therapeutic index of aciclovir.

In patients receiving intravenous aciclovir, caution is required during concurrent administration with drugs which compete with aciclovir for elimination, because of the potential for increased plasma levels of one or both drugs 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 the drugs are co-administered.

given aciclovir for infusion in doses of 10mg/kg bodyweight every eight hours provided renal function is not impaired (see Dosage in renal impairment).

Dosage in children:

The dose of aciclovir for infusion for children aged between three months and 12 years is calculated on the basis of body surface area.

Children with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections should be given aciclovir for infusion in doses of 250 mg per square metre of body surface area every eight hours.

In immunocompromised children with *Varicella zoster* infections or children with herpes encephalitis, aciclovir for infusion should be given in doses of 500 mg per square metre body surface area every eight hours if renal function is not impaired.

Children with impaired renal function require an appropriately modified dose, according to the degree of impairment.

The dosage of aciclovir for infusion in neonates and infants up to three months of age is calculated on the basis of bodyweight.

Neonates and infants up to three months of age with *Herpes simplex* infections should be given aciclovir for infusion in doses of 10 mg/kg bodyweight every eight hours. Treatment for neonatal *Herpes simplex* infections usually lasts ten days.

Dosage in the elderly:

In the elderly, total aciclovir body clearance declines in parallel with creatinine clearance. Special attention should be given to dosage reduction in elderly patients with impaired creatinine clearance.

Dosage in renal impairment:

Caution is advised when administering aciclovir for infusion to patients with impaired renal function. The following adjustments in dosage are suggested:

Creatinine Clearance

25 to 50 ml/min: The dose recommended above (5 or 10 mg/kg bodyweight) should be given every 12 hours.

10 to 25 ml/min: The dose recommended above (5 or 10 mg/kg bodyweight) should be given every 24 hours.

0 (anuric) to 10 ml/min: In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommended above (5 or 10 mg/kg bodyweight) should be halved and administered every 24 hours. In patients receiving haemodialysis the dose recommended above (5 or 10 mg/kg bodyweight) should be halved and administered every 24 hours and after dialysis.

Care is also required (with monitoring for changes in renal function) if administering intravenous aciclovir with drugs which affect other aspects of renal physiology (e.g. ciclosporin, tacrolimus).

4.6. Pregnancy and lactation

A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of aciclovir. The birth defects described amongst aciclovir exposed subjects have not shown any uniqueness or consistent pattern to suggest a common cause. Caution should be exercised by balancing the potential benefits of treatment against any possible hazard.

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

4.7. Effects on ability to drive and use machines

Aciclovir can cause reversible neurological reactions such as confusion, hallucinations, agitation, tremors, somnolence, psychosis and coma, which can all affect the ability to drive and use machinery.

4.8. Undesirable effects

Gastrointestinal: Nausea and vomiting have been reported.

Haematological: Decreases in haematological indices (anaemia, thrombocytopenia, leucopenia).

Hypersensitivity and Skin: Rashes including photosensitivity, urticaria, pruritus, fevers and rarely dyspnoea, angioedema and anaphylaxis.

Severe local inflammatory reactions sometimes leading to breakdown of the skin have occurred when formulations of aciclovir for intravenous use have been inadvertently infused into extravascular tissues.

Kidney: Rapid increases in blood urea and creatinine levels may occasionally occur in patients given aciclovir for infusion. This is believed to be related to peak plasma levels and the state of hydration of the patient. To avoid this effect the drug should not be given as an intravenous bolus injection but by slow infusion over a one hour period.

Adequate hydration of the patient should be maintained. Renal impairment developing during treatment with aciclovir for infusion usually responds rapidly to rehydration of the patient and/or dosage reduction or withdrawal of the drug. Progression to acute renal failure, however, can occur in exceptional cases.

Liver: Reversible increases in bilirubin and liver-related enzymes. Hepatitis and jaundice have been reported on very rare occasions.

Neurological: Reversible neurological reactions such as confusion, hallucinations, agitation, tremors, somnolence, psychosis, convulsions and coma have been associated with aciclovir for infusion therapy, usually in medically complicated cases.

4.9. Overdose

Overdosage of intravenous aciclovir has resulted in elevations of serum creatinine, blood urea nitrogen and subsequent renal failure. Neurological effects including confusion, hallucinations, agitation, seizures and coma have been described in association with overdosage. Haemodialysis significantly enhances the removal of aciclovir from the blood and may, therefore, be considered an option in the management of overdose of this drug.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

ATC Code: J05A B01, Direct Acting Antiviral

Aciclovir is a synthetic purine nucleoside analogue with *in vitro* and *in vivo* inhibitory activity against human herpes viruses, including *Herpes simplex virus* (HSV) types 1 and 2 and *Varicella zoster virus* (VZV), Epstein Barr virus (EBV) and *Cytomegalovirus* (CMV). In cell culture aciclovir has the greatest antiviral activity against HSV-1, followed (in decreasing order of potency) by HSV-2, VZV, EBV, and CMV.

The inhibitory activity of aciclovir for HSV-1, HSV-2, VZV and EBV is highly selective. The enzyme thymidine kinase (TK) of normal, uninfected cells does not use aciclovir effectively as a substrate, hence toxicity to mammalian host cells is low; however, TK encoded by HSV, VZV and EBV converts aciclovir to aciclovir monophosphate, a nucleoside analogue, which is further converted to the diphosphate and finally to the triphosphate by cellular enzymes. Aciclovir triphosphate interferes with the viral DNA polymerase and inhibits viral DNA replication with resultant chain termination following its incorporation into the viral DNA.

5.2. Pharmacokinetic properties

In adults, the terminal plasma half-life of aciclovir after administration of aciclovir for infusion is about 2.9 hours. Most of the drug is excreted unchanged by the kidney. Renal clearance of aciclovir is substantially greater than creatinine clearance, indicating that tubular secretion, in addition to glomerular filtration, contributes to the renal elimination of the drug.

9-carboxymethoxymethylguanine is the only significant metabolite of aciclovir and accounts for 10 to 15% of the dose excreted in the urine.

When aciclovir is given one hour after 1g of probenecid the terminal half-life and the area under the plasma concentration time curve, are extended by 18% and 40% respectively.

In adults, mean steady state peak plasma concentrations ($C_{max,ss}$) following a one-hour infusion of 2.5 mg/kg, 5 mg/kg, and 10 mg/kg were 22.7 micromolar (5.1 microgram/ml), 43.6 micromolar (9.8 microgram/ml), and 92 micromolar (20.7 microgram/ml) respectively. The corresponding trough levels ($C_{min,ss}$) 7 hours later were 2.2 micromolar (0.5 microgram/ml), 3.1 micromolar (0.7 microgram/ml) and 10.2 micromolar (2.3 microgram/ml)

6.3. Shelf life

Unopened - Three years

For reconstituted solutions, chemical and physical in-use stability has been demonstrated for at least 24 hours at 25°C. From a microbiological point of view, once opened, the product should be used immediately.

If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at 2-8°C, unless reconstitution has taken place in controlled and validated aseptic conditions.

Following dilution using the fluids detailed in section 6.6, chemical and physical in-use stability has been demonstrated for up to 12 hours at 25°C. From a microbiological point of view the diluted solution should be used immediately. If not used immediately in-use storage times and conditions are the responsibility of the user.

6.4. Special precautions for storage

Unopened: Do not store above 25°C

Keep the vials in the outer carton.

After reconstitution: Do not store above 25°C (see 6.3 Shelf Life).

6.5. Nature and contents of container

Packs* of one, five or ten Type I colourless glass 10ml vials stoppered with a chlorobutyl stopper and an aluminium and polypropylene flip-off cap.

*Not all pack sizes may be marketed

6.6. Instructions for use and handling

Reconstitution:

Aciclovir 250mg for infusion should be reconstituted using 10ml of either Water for Injections PhEur or Sodium Chloride Intravenous Infusion BP (0.9% w/v) to provide a solution containing 25mg aciclovir per ml.

From the calculated dose, determine the appropriate number and strength of vials to be used. To reconstitute each vial add the recommended volume of infusion fluid and shake gently until the contents of the vial have dissolved completely.

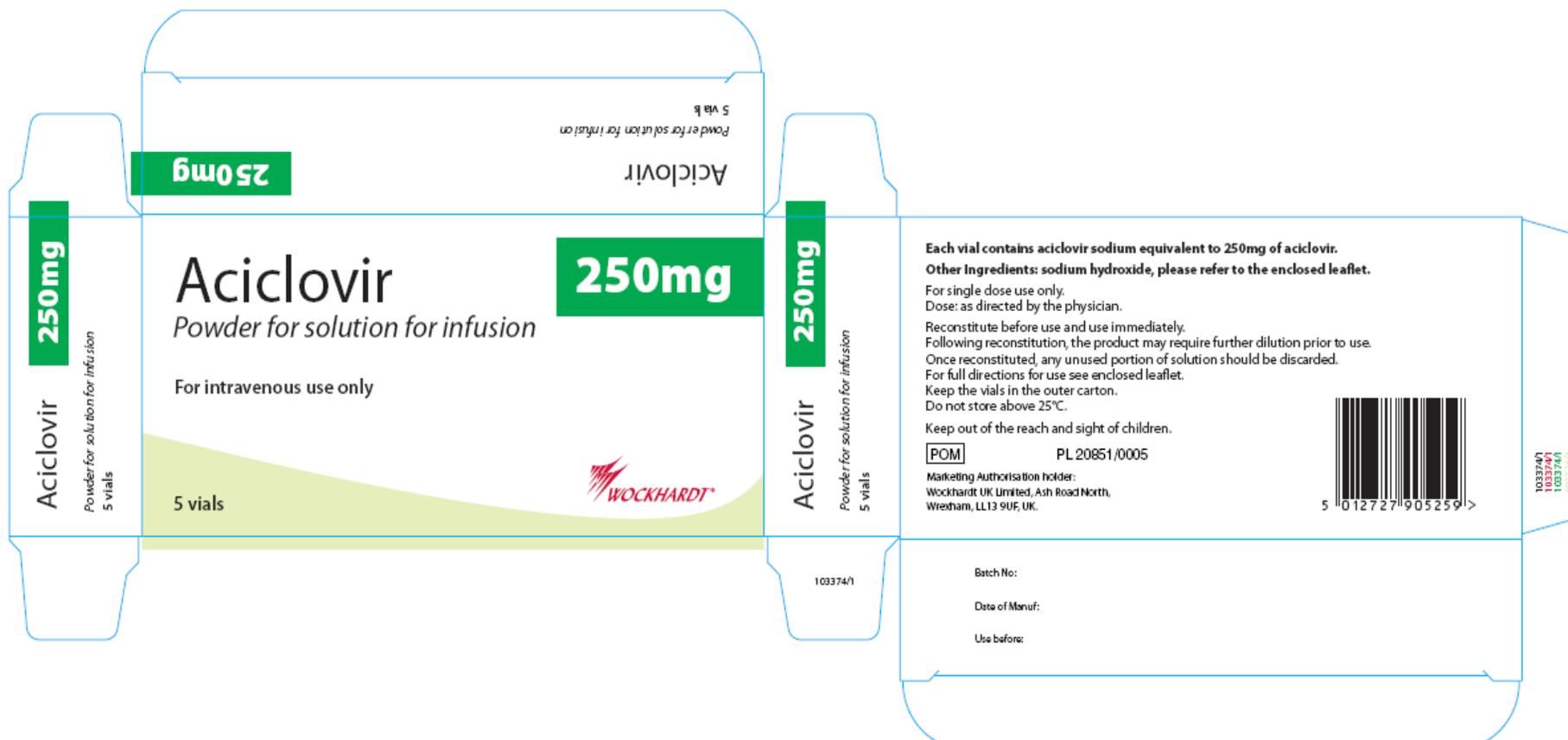
The reconstituted solution appears light yellow and slightly opalescent.

After reconstitution aciclovir powder for solution for infusion may be administered by a controlled-rate infusion pump. Alternatively, the reconstituted solution may be further diluted to give an aciclovir concentration of not greater than 5 mg/ml (0.5% w/v) for administration by infusion. For further dilution, add the required volume of reconstituted solution to the chosen infusion solution, as recommended below, and shake well to ensure adequate mixing occurs.

For children and neonates, where it is advisable to keep the volume of infusion fluid to a minimum, it is recommended that dilution is on the basis of 4ml reconstituted solution (100mg aciclovir) added to 20 ml of infusion fluid.

LABELLING

Carton



Label

Other ingredients: sodium hydroxide, please refer to the enclosed leaflet.
For single dose use only
Dose: as directed by the physician
Keep out of the reach and sight of children
Do not store above 25 °C
Reconstitute before use and use immediately.
Following reconstitution, the product may require further dilution prior to use.
Once reconstituted, any unused portion of solution should be discarded.
For full directions for use see enclosed leaflet. PL 20851/0005

Aciclovir

250mg

Powder for solution for infusion
Each vial contains aciclovir sodium equivalent to 250mg of aciclovir

For intravenous use only

Marketing Authorisation holder:
Wockhardt UK Limited,
Ash Road North, Wrexham,
LL13 9UF, United Kingdom

Batch no:
Manuf. date:
Expiry date:

POM