

**Public Assessment Report
for paediatric studies submitted in accordance
with Article 45 of Regulation (EC) No1901/2006, as
amended**

**Zovirax
Vinherpes**

Aciclovir

DK/W/011/pdWS/001

Rapporteur:	Denmark
Finalisation procedure (day 120):	13-04-2011
Date of finalisation of PAR	28-06-2011

ADMINISTRATIVE INFORMATION

Invented name of the medicinal product(s):	Zovirax Vinherpes Suspension Forte Vinherpes Crema Vinherpes Inyectable
INN (or common name) of the active substance(s):	Aciclovir
MAH (s):	GlaxoSmithKline (GSK), Harlow, Essex, United Kingdom (Zovirax) Laboratories Esteve S.A.Barcelona, Spain
Pharmaco-therapeutic group (ATC Code):	J05AB01
Pharmaceutical form(s) and strength(s):	Zovirax, dispergible tablets 200mg, 400mg and 800mg Zovirax, tablets 200mg, 400mg and 800mg Zovirax, powder for injection, 250mg and 500mg Zovirax, oral suspension 200mg/5ml and 400mg/5ml Vinherpes Suspension Forte, Oral suspension, 400mg/5ml Zovirax 5% cream Vinherpes Crema, cream Vinherpes Inyectable, Lyophilisate powder for infusion (withdrawn in 2008)

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I. EXECUTIVE SUMMARY

Aciclovir was approved for marketing in the EU via the national procedure. The main indications are:

1. Treatment of herpes simplex virus infections in neonates, children and adolescents.
2. Treatment of varicella infections in children and adolescents.

In accordance with Article 45 of Regulation EC 1901/2006, GlaxoSmithKline (GSK) submitted a total of 13 previously unsubmitted paediatric studies on aciclovir (two studies on Zovirax cream, 5 studies on Zovirax oral formulations and 6 studies on Zovirax intravenous formulations) all completed prior to 26 January 2008. The studies were submitted also on behalf of the other MAH involved in the procedure, Laboratories Esteve S.A.

In addition to HSV and VZV treatment, aciclovir was previously investigated for use as CMV prophylaxis and GSK's core labelling indication includes the indication of "prophylaxis of CMV infection in bone marrow transplant recipients in children and adults". In the current submission, two studies examining this issue have been included. However, as this indication is not mentioned in most current EU SPC's and since aciclovir prophylaxis is now rarely used for this indication as much more effective drugs such as ganciclovir are now available, these studies will not be discussed in great detail.

Two open-label studies on aciclovir cream formulation were also submitted, however as these studies are of only minor interest without efficacy or relevant safety data, these studies will not be discussed here.

Although the submitted clinical studies were found to overall support the already existing information on indications, efficacy and safety of aciclovir for the treatment of HSV and VZV infections in children, two major concerns were raised by the Rapporteur in the preliminary assessment report (circulated 17 August 2010) after a critical review of the submitted studies. 3 MS agreed with the Rapporteur's conclusions, 1 MS partially agreed with the Rapporteur's conclusions.

A second round of assessment was carried out and the final assessment report was circulated 14 March 2011. The MAH's proposals for SmPC in response to the PPdAR were overall endorsed by the Rapporteur, however, the MAH was requested to provide updated recommendations for 4.2, Dosage in renal impairment, with special attention to dosage in infants.

Following the circulation of the final assessment report, a minor comment was received from a MS, while another MS agreed with the Rapporteur's assessment. The MAH's proposals for SmPC in response to the Rapporteur FPdAR / MS comments were fully endorsed by the Rapporteur and the procedure was finalised on 13 April 2011.

SmPC changes are proposed in section 4.1 and 5.2 for oral aciclovir and section 4.2 and 5.2 for IV aciclovir.

II. RECOMMENDATION¹

Type IB variation (C.I.3.a) to be requested from the MAH by 12 June 2011.

Changes in SPC sections 4.1 and 5.2 for oral acyclovir and SPC sections 4.2 and 5.2 for IV acyclovir are recommended (information in red underlined should be added, information in ~~blue strikethrough~~ should be deleted). PL should be changed accordingly.

Oral acyclovir

Section 4.1:

Zovirax Tablets are indicated for the treatment of herpes simplex virus infections of the skin and mucous membranes including initial and recurrent genital herpes (excluding neonatal HSV and severe HSV infections in immunocompromised children).

Section 5.2:

In neonates (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 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). 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).

IV acyclovir

Section 4.2:

Route of administration: Slow intravenous infusion over 1 hour.

A course of treatment with Zovirax I.V. usually lasts 5 days, but this may be adjusted according to the patient's condition and response to therapy. Treatment for herpes encephalitis usually lasts 10 days. Treatment for and neonatal herpes *Herpes simplex infections* usually lasts 14 days for mucocutaneous (skin-eye-mouth) infections and 21 days for disseminated or central nervous system disease ~~10 days~~.

The duration of prophylactic administration of Zovirax I.V. is determined by the duration of the period at risk.

Dosage in adults:

Patients with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections should be given Zovirax I.V. in doses of 5 mg/kg body weight every 8 hours provided renal function is not impaired (see Dosage in renal impairment).

Immunocompromised patients with *Varicella zoster* infections or patients with herpes encephalitis should be given Zovirax I.V. in doses of 10 mg/kg body weight every 8 hours provided renal function is not impaired (see Dosage in renal impairment).

In obese patients dosed with intravenous aciclovir based on their actual body weight, higher plasma concentrations may be obtained (see 5.2 Pharmacokinetic properties). Consideration should therefore be given to dosage reduction in obese patients and especially in those with renal impairment or the elderly.

¹ The recommendation from section V can be copied in this section.

Dosage in children: The dose of Zovirax I.V. for children aged between 3 months and 12 years is calculated on the basis of body surface area.

Children 3 months of age or older with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections should be given Zovirax I.V. in doses of 250 mg per square metre of body surface area every 8 hours if renal function is not impaired.

In immunocompromised children with *Varicella zoster* infections or children with herpes encephalitis, Zovirax I.V. should be given in doses of 500 mg per square metre body surface area every 8 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 Zovirax I.V. in neonates and infants up to 3 months of age is calculated on the basis of body weight.

The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 21 days for disseminated and CNS disease, or for 14 days for disease limited to the skin and mucous membranes.

Infants and children with impaired renal function require an appropriately modified dose, according to the degree of impairment (see Dosage in renal impairment).

~~Neonates and infants up to 3 months of age with *Herpes simplex* infections should be given Zovirax I.V. in doses of 10 mg/kg body weight every 8 hours. Treatment for neonatal herpes simplex infections usually lasts 10 days.~~

Dosage in the elderly:

The possibility of renal impairment in the elderly must be considered and dosage should be adjusted accordingly (see *Dosage in renal impairment* below).

Adequate hydration should be maintained.

Dosage in renal impairment:

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

Dosage adjustment for patients with renal impairment is based on creatinine clearance, in units of ml/min for adults and adolescents and in units of ml/min/1.73m² for infants and children less than 13 years of age. The following adjustments in dosage are suggested:

Dosage adjustments in adults and adolescents:

<u>Creatinine Clearance</u>	<u>Dosage</u>
25 to 50 ml/min	The dose recommended above (5 or 10 mg/kg body weight) should be given every 12 hours.
10 to 25 ml/min	The dose recommended above (5 or 10 mg/kg body weight) 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 body weight) should be halved and administered

	<p>every 24 hours.</p> <p>In patients receiving haemodialysis the dose recommended above (5 or 10 mg/kg body weight) should be halved and administered every 24 hours and after dialysis.</p>
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Dosage adjustments in infants and children:

<u>Creatinine Clearance</u>	<u>Dosage</u>
<u>25 to 50 ml/min/1.73 m²</u>	<u>The dose recommended above (250 or 500 mg/m² body surface area or 20 mg/kg body weight) should be given every 12 hours.</u>
<u>10 to 25 ml/min/1.73 m²</u>	<u>The dose recommended above (250 or 500 mg/m² body surface area or 20 mg/kg body weight) should be given every 24 hours.</u>
<u>0(anuric) to 10 ml/min/1.73 m²</u>	<p><u>In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommended above (250 or 500 mg/m² body surface area or 20 mg/kg body weight) should be halved and administered every 24 hours.</u></p> <p><u>In patients receiving haemodialysis the dose recommended above (250 or 500 mg/m² body surface area or 20 mg/kg body weight) should be halved and administered every 24 hours and after dialysis.</u></p>

Section 5.2:

In neonates (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 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). 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).

III. INTRODUCTION

Several MAHs submitted 13 completed paediatric studies for aciclovir, in accordance with Article 45 of the Regulation (EC)No 1901/2006, as amended on medicinal products for paediatric use.

In addition, the following documentation has been included as per the procedural guidance:

- An annex including SPC wording of sections 4.1 and 4.2 related to the paediatric use of the medicinal product

The MAH stated that the submitted paediatric studies do not influence the benefit risk for aciclovir and that there is no consequential regulatory action. However, as a result of this Paediatric Worksharing procedure SmPC changes are proposed in section 4.1 and 5.2 for oral aciclovir and section 4.2 and 5.2 for IV aciclovir.

IV. SCIENTIFIC DISCUSSION

IV.1 Preliminary scientific discussion

IV.1.1 Introduction

Aciclovir is a nucleoside (guanine analogue) antiviral drug, which antiviral activity depends upon metabolism within herpes infected cells to form sequentially the mono-, di- and triphosphates inhibiting essential processes in virus replication. The antiviral activity of acyclovir is primarily against the herpes group of viruses. It is a highly selective inhibitor of herpes simplex virus (HSV-1) and varicella-zoster virus (VZV), the activity is notably lesser against Epstein-Barr, and against cytomegalovirus (CMV).

Aciclovir has relatively low oral bioavailability and short plasma half-life. Comparatively large doses and frequent administration are required to maintain trough values for plasma concentrations of Aciclovir above the threshold required for virus inhibition. Hence, Aciclovir has limited oral bioavailability (15–20%).

Aciclovir first became available as a topical drug in 1982 and is now available for intravenous use and for use in the form of cream, eye ointment, tablets (200, 400 and 800 mg) and suspension (200 mg/5 ml or 400 mg/ 5ml)

In consideration of the rather poor bioavailability, Valaciclovir, a prodrug esterified version of acyclovir with better bioavailability which offers comparative systemic drug level to the intravenous formulation of acyclovir, was developed by GSK and has been available from 1995.

IV.1.2 Clinical studies submitted

Study Code	Study Title	GSK Report Number
Aciclovir - oral		
101-902	Zovirax treatment of varicella in otherwise normal adolescents and adults: Immediate versus delayed therapy and viral sensitivity.	RM1997/00394/00
P12-176	Treatment of chickenpox in children with Zovirax suspension in a double-blind, placebo controlled clinical trial.	THRS/88/0015-1
P12-183	Treatment of chickenpox in children with Zovirax suspension in a multicentre, double-blind, placebo controlled trial.	THRS/90/0006
P12-184	Treatment of chickenpox in adolescents with Zovirax tablets in a multicentre, double-blind, placebo controlled trial.	THRS/90/0008
P12-148	Pharmacokinetics of Zovirax oral suspension in paediatric patients with varicella zoster and herpes simplex viral infection.	TBZZ/86/0015
Aciclovir - intravenous		
NA	Collaborative study of neonatal herpes simplex virus infection: A controlled evaluation of acyclovir and Vira-A – Assessment of mortality and definition of morbidity with therapy.	THRS/88/0068/01
P12-142	Prophylaxis against CMV in bone marrow transplant recipients with intravenous Zovirax.	THRS/89/0079
H14-304	A multicentre, double-blind, controlled trial of prophylaxis against CMV infections in bone marrow transplant patients using intravenous Zovirax followed by oral Zovirax.	BQRT/94/0014
NA	A double-blind, placebo controlled study of intravenous Zovirax for varicella (zoster) virus infection in immunocompromised children.	BKCT/86/003
P12-22	Zovirax multiple-dose, pharmacokinetic analyses in paediatric patients with herpesvirus infections.	TEIN/81/0009
P12-23	Zovirax pharmacokinetics in neonatal patients with herpesvirus infections.	TBZZ/89/0002

Aciclovir 5% Cream

Aciclovir Cream		
Study Code	Study Title	GSK Report Number
ZOVA3005	A multicentre, open-label evaluation of the safety of aciclovir 5% cream for the treatment of recurrent herpes labialis infections in adolescents (12 – 17 years of age)	RM1999/00098/00
ZOVA3007	Actual use study of aciclovir 5% cream among unsupervised consumers 12 years of age and older	RM1999/00005/00

ACICLOVIR- ORAL STUDIES

Study 101-902: Zovirax treatment of varicella in otherwise normal adolescents and adults: Immediate versus delayed therapy and viral sensitivity (6).

Description

Double-blind randomized controlled trial in children, adolescents and adults with primary varicella zoster infection, comparing 5 to 7 days of acyclovir treatment and immediate versus delayed therapy.

Methods

Randomized, placebo-controlled, double blind trial in immunocompetent patients who were stratified by age at enrollment (children, 2 to 11 years; adolescents, >12 to 18 years; adults, >19 years) and duration of rash (<24 h vs. >24 to 48 h). Lesions were staged, counted and cultured; temperatures and symptoms were recorded daily.

Subjects presenting within 24 h of rash onset (Group A) were randomly assigned to 7 (group A1) or 5 (group A2) days of oral acyclovir treatment, 80 mg/kg/day up to a maximum of 3200 mg/day in four divided doses. Subjects whose rash was >24 to 48 h old were randomized to receive 5 days of acyclovir treatment beginning on the first (Group B1) or second study day (Group B2).

Results

Baseline data

Patient Age	A1	A2	B1	B2	Total
2-11 years	13	15	13	12	53
12-18 years	7	9	6	5	27
≥19 years	28	28	21	20	97
Subtotals	48	52	40	37	177

TABLE 1. Characteristics of subjects on enrollment

Characteristic	Children	Adolescents	Adults
No. of subjects	53	27	97
Age (yr)			
Mean (median in parentheses)	5.7 (5.4)	15.4 (15.0)	27.5 (26.6)
Range	2.1–11.8	12.2–18.9	19.4–48.0
Gender (no. male/no. female)	25/28	11/16	46/51
No. of subjects by race			
White	48	24	79
African American	3	2	3
Hispanic	2	1	15
Case order of chickenpox in household (% of total in parentheses)			
Primary	31 (58)	15 (56)	69 (71)
Secondary	18 (34)	10 (37)	23 (24)
Tertiary	4 (8)	2 (7)	5 (5)
No. with oral temperature $\geq 37.8^{\circ}\text{C}$ (% in parentheses)	22 (42)	14 (52)	40 (41)
Mean h of rash at enrollment (no. of subjects in parentheses)			
A1	13.2 (13)	15.4 (7)	12.8 (28)
A2	17.8 (15)	10.2 (9)	12.9 (28)
B1	32.6 (13)	33.9 (6)	32.6 (21)
B2	35.0 (12)	36.2 (5)	37.9 (20)
No. of facial and chest box lesions at entry			
Median (mean in parentheses)	19.0 (33.9)*†	53 (77.6)†	58 (98.5)*
Range	0–163	4.0–243	5–932

* $P < 0.001$ for children *vs.* adults.

† $P = 0.008$ for children *vs.* adolescents.

Efficacy results

In children and in adults no difference in rash progression, maximum number of lesions or duration of fever was observed between treatment groups, with 5 days of therapy being equivalent to 7 days. In children, adolescents and adults the clinical illness was shortest among patients who were assigned to acyclovir within the first 24 h of rash. Viruses shed during therapy remained susceptible to acyclovir and retained normal thymidine kinase function

Safety results

No placebo group was included in this trial. Adverse clinical events were reported by 10 of 177 subjects (5.6%), 3 of whom withdrew from the study prematurely. None of the adverse events was ascribed to study medication. No SAE were reported.

Discussion on clinical aspects

5 days were as effective as 7 days of therapy up to 72 hrs after rash onset. There were no safety signals. This study carries no new efficacy or safety information, but is limited by the absence of a placebo control group.

P12-76. Treatment of chickenpox in children with Zovirax suspension in a double-blind, placebo controlled clinical trial (7).

Methods

Study objective: To determine whether acyclovir administered orally affects the duration and severity of varicella in otherwise normal children .

Design: Randomized, placebo-controlled, double-blind trial.

Setting: Patients' residence and university hospital clinic.

Patients: One hundred five children between 5 and 16 years of age with laboratory- confirmed varicella entered the study. Of the 102 who were included in the final analysis, 50 received acyclovir and 52 received placebo.

Interventions: Placebo or acyclovir was given orally four times daily, for 5 to 7 days. The acyclovir dose was adjusted as follows: 5 to 7 years of age, 20 mg/kg; 7 to 12 years, 15 mg/kg; and 12 to 16 years, 10 mg/kg.

Efficacy results

Acyclovir recipients, compared with the placebo group, defervesced sooner (median, 1 day vs 2 days; $p = 0.001$), experienced onset of cutaneous healing sooner, as reflected by a decrease in number of lesions (median, 3 days vs 2 days; $p = 0.002$), and had fewer skin lesions (median, 500 vs 336; $p = 0.02$). Acyclovir did not significantly change the rate of complications of varicella (10% in the acyclovir group vs 13.5% among placebo subjects).

Safety results

Adverse drug effects were not observed. Acyclovir recipients had lower geometric mean serum antibody titers to varicella-zoster virus than their placebo counterparts 4 weeks after the onset of illness, but antibody titers in both groups were similar 1 year later.

Discussion on clinical aspects

Acyclovir appeared to be effective in reducing the number of days with fever and the maximum number of lesions among otherwise healthy children with chickenpox. No safety signals were observed.

Study P12-183. Treatment of chickenpox in children with Zovirax suspension in a multicentre, double-blind, placebo controlled trial (8).

Description

Multi-center, double-blind, placebo-controlled study involving 815 healthy children 2 to 12 years old who contracted chickenpox. Treatment with acyclovir was begun within the first 24 hours of rash and was administered orally in a dose of 20 mg per kilogram of body weight four times daily for five days.

Baseline data

Table 1. Demographic Characteristics of the Study Subjects.

CHARACTERISTIC	ACYCLOVIR GROUP (N = 367)	PLACEBO GROUP (N = 357)
Age (yr) — mean (median)	5.18 (5.00)	5.19 (5.00)
Sex — no. (%)		
Female	175 (47.7)	184 (51.5)
Male	192 (52.3)	173 (48.5)
Race — no. (%)		
Black	31 (8.4)	32 (9.0)
White	313 (85.3)	309 (86.6)
Other	23 (6.3)	16 (4.5)
Hours to enrollment — mean (median)*	14 (17.0)	15 (17.5)
Household occurrence — no. of cases (%)†		
Primary	202 (55.2)	197 (55.2)
Secondary	151 (41.3)	149 (41.7)
Tertiary	13 (3.6)	11 (3.1)
Lesions at entry — mean (median)	107 (62)	100 (64)
Fever on day 0‡ — no. (%)	169 (46.1)	185 (51.8)

*From the onset of the rash.

†Data were not available for one acyclovir recipient.

‡Fever was defined as a temperature of 37.8°C (100°F) or higher.

Efficacy results

Table 2. Cutaneous Events in the Study Subjects.

VARIABLE	ACYCLOVIR GROUP (N = 367)	PLACEBO GROUP (N = 357)	P VALUE
No. of lesions — mean (median)	294 (277)	347 (386)	<0.001
>500 lesions — no. (%) of patients	78 (21.3)	137 (38.4)	<0.001
Residual lesions on day 28* — mean (median)	13 (6)	33 (13)	<0.001

*Data were missing for one placebo recipient.

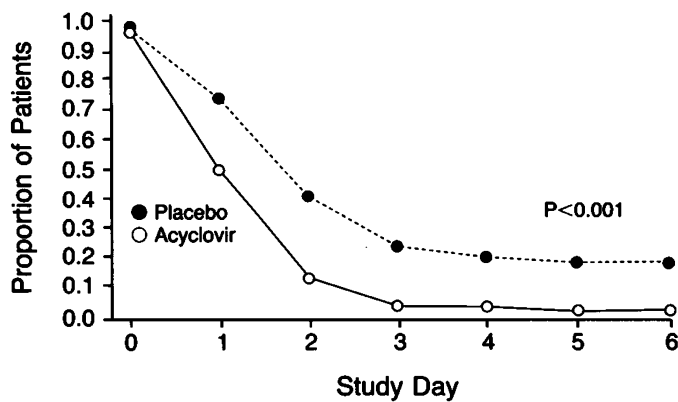


Figure 1. Proportion of Patients with Continued Formation of New Lesions.

Children treated with acyclovir had fewer varicella lesions than those given placebo (mean percent, as compared with 38 percent with placebo; $P < 0.001$). In over 95 percent of the recipients of acyclovir no new lesions formed after day 3, whereas new lesions were forming in 20 percent of the placebo recipients on day 6 or later. The recipients of acyclovir also had accelerated progression to the crusted and healed stages, less itching, and fewer residual lesions after 28 days. In the children treated with acyclovir the duration of fever and constitutional symptoms was limited to three to four days, whereas in 20 percent of the children given placebo illness lasted more than four days. There was no significant difference between groups in the distribution of 11 disease complications (10 bacterial skin infections and 1 case of transient cerebellar ataxia).

Safety results

No significant differences in clinical adverse effects or laboratory abnormalities between acyclovir treated and placebo-treated, no significant difference between groups in the titers of antibodies against Varicella Zoster virus.

Discussion on clinical aspects

This large and important randomized study confirms the efficacy and safety of acyclovir for primary varicella infection in children. No safety signals were observed.

Study P12-184. Treatment of chickenpox in adolescents with Zovirax tablets in a multicentre, double-blind, placebo controlled trial (9).

Description

Study objective: To determine whether orally administered acyclovir is of therapeutic benefit for varicella in otherwise healthy adolescents, and to compare the severity of the disease in adolescents with that in younger children.

Design: Multicenter, randomized, placebo-controlled, double-blind trial.

Setting: Patients' homes and university hospital clinics.

Patients: 68 adolescents, ages 13 to 18 with varicella were enrolled. Of the 62 adolescents with laboratory-confirmed varicella who were included in the final analysis, 34 received acyclovir and 31 received placebo.

Interventions: Placebo or an 800 mg acyclovir tablet was given orally four times daily for 5 days, beginning within 24 hours of onset of rash.

Efficacy results

Acyclovir recipients had significant reductions in times to cessation of new lesion formation ($p < 0.001$), maximum number of lesions ($p = 0.049$), and defervescence ($p = 0.045$). Mean constitutional illness score was significantly reduced on day 4 (0.5 vs 1.5, $p = 0.05$), as was the mean number of residual hypopigmented lesions present on 28-day follow-up examination (22.7 vs 92.7, $p = 0.018$). Comparison of placebo recipients with children 2 to 12 years of age participating in a companion study indicated that varicella is more severe in adolescents: mean maximum total lesions (421 vs 347, $p = 0.003$), mean maximum constitutional illness score (3.1 vs 2.2, $p = 0.032$), and mean number of residual lesions (92.7 vs 33.2, $p = 0.01$) were all greater in the adolescent population.

Safety results

Adverse experiences and varicella-zoster virus antibody titers measured 28 days after enrollment were similar in both treatment groups. Two complications, both bacterial superinfections, occurred in placebo recipients.

Discussion on clinical aspects

Limited by small study size, only adolescents were included, no new efficacy or safety information was provided.

Study P12-148. Pharmacokinetics of Zovirax oral suspension in paediatric patients with varicella zoster and herpes simplex viral infection(5).

Description

Open multicenter pharmacokinetic study of acyclovir oral suspension in pediatric patients with HSV or varicella zoster infection

Methods.

According to GSK submitted protocol, a total of 13 pediatric patients were included, however according to published information from this study (5), 18 patients were included?- GSK should explain this discrepancy. Summarized below are the main findings from the published study:

Oral acyclovir suspension was given to children less than 7 years of age who had HSV or VZV infections which were not of a life-threatening nature. Patients were excluded if their serum creatinine concentration was greater than 1.5 mg/dl or if the serum bilirubin or liver transaminase concentration was more than twice the normal value.

TABLE 1. Demographic information for patients

Sex ^a	Age	Wt (kg)	BSA ^b (m ²)	Viral disease	Underlying disease
F	3 wk	3.8	0.25	HSV suppression	Neonatal HSV
F	4 wk	3.4	0.23	HSV suppression	Neonatal HSV
M	7 wk	4.2	0.26	HSV suppression	Neonatal HSV
F	0.5 yr	5.9	0.33	Cutaneous HSV	Eczema
F	0.6 yr	7.8	0.41	Cutaneous HSV	Eczema
M	0.9 yr	8.8	0.44	HSV whitlow	None
F	1.5 yr	10.0	0.46	Recurrent HSV	Neonatal HSV
M	1.8 yr	10.0	0.49	HSV whitlow	None
M	2.0 yr	12.5	0.55	Herpes zoster	Asthma
F	2.3 yr	15.5	0.59	Varicella post-VZIG	Leukemia
M	3.5 yr	12.2	0.56	Varicella	Eczema
F	3.9 yr	15.2	0.65	Varicella postvaccine	Leukemia
F	4.1 yr	17.2	0.70	Varicella	Eczema
F	4.0 yr	14.0	0.63	Retinitis	Neonatal HSV
M	5.7 yr	23.6	0.85	Varicella post-VZIG	Leukemia
F	5.7 yr	19.0	0.80	Varicella post-VZIG	Wilms' tumor
F	6.2 yr	15.1	0.66	Herpes zoster	Leukemia
M	6.9 yr	24.3	0.90	Recurrent oral HSV	Nephrosis

^a F, Female; M, male.

^b BSA, Body surface area.

Treatments

According to the published study: Acyclovir (Zovirax) suspension (40 mg/ml) was given orally or by nasogastric tube at 300 or 600 mg/m² per dose. The doses were given four times daily at 0800, 1200, 1600, and 2000 h for 5 to 7 days. Thirteen children received 600 mg/M² per dose and five patients, including the three infants less than 2 months of age, received doses of 300 mg/M². All patients received four doses per day except for one infant who was given 300 mg/M² per dose three times per day.

Investigations:

Blood samples were analyzed for acyclovir concentrations by RIA immediately before one of the doses and 2 h after the dose on study day 2, 3, or 4. On the last day of acyclovir administration, blood samples were taken just before and at 1, 2, 3, 4, 6, and 8 h after the final dose.

Results

Aciclovir concentrations on day 2, 3 and 4 are shown below

TABLE 2. Acyclovir concentrations in plasma

Age group (n)	Dose (mg/m ²)	Acyclovir concn (µg/ml [mean ± SD])								
		Day 2, 3, or 4 ^a		Before last dose	Time (h) after last dose					
		Before	2 h		1	2	3	4	6	8
6 mo-4 yr (7) ^b	600	0.31 ± 0.07	1.03 ± 0.30	0.22 ± 0.20	0.53 ± 0.23	0.84 ± 0.35	0.90 ± 0.40	0.95 ± 0.49	0.60 ± 0.35	0.35 ± 0.17
4-7 yr (6) ^c	600	0.59 ± 0.44	0.97 ± 0.60	0.30 ± 0.14	0.73 ± 0.31	0.84 ± 0.30	0.85 ± 0.29	0.73 ± 0.29	0.51 ± 0.19	0.35 ± 0.20
Mean ± SD (13) 6 mo- 7 yr	600	0.45 ± 0.35	1.00 ± 0.47	0.25 ± 0.18	0.62 ± 0.28	0.84 ± 0.32	0.88 ± 0.34	0.85 ± 0.41	0.56 ± 0.27	0.35 ± 0.17
<2 mo (3)	300	1.56 ± 1.51	1.87 ± 1.34	0.69 ± 0.27	0.61 ± 0.16	1.48 ± 0.55	1.82 ± 1.16	1.88 ± 1.11	1.32 ± 0.90	0.84 ± 0.60
6 mo-4 yr (2)	300	1.05 ± 0.10	1.31 ± 0.09	0.49 ± 0.55	0.61 ± 0.19	0.77 ± 0.13	0.73 ± 0.14	0.52 ± 0.13	0.29 ± 0.13	0.21 ± 0.02

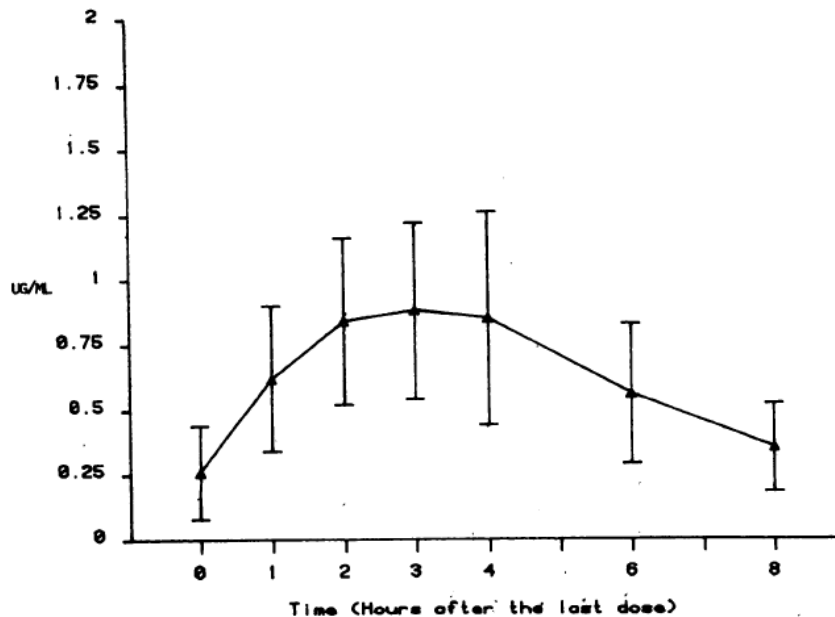
^a Samples were drawn on day 2, 3, or 4 just before and 2 h after dose 1, 2, 3, or 4.

^b One patient received an extra dose on the last day 3.5 h after the scheduled last dose; 4- to 8-h points were excluded from the mean.

^c Data for one patient for whom there were substantial deviations from the protocol dosing regimen were excluded from the means.

No significant differences were observed between the mean acyclovir concentrations in plasma after the last dose for patients less than 4 years of age and those, from 4 to 7 years old, who received doses of 600 mg/m².

The time profile of mean acyclovir concentrations in plasma after the last dose for all patients who received the 600 mg/m² dose regimen is shown below.



The mean values for all patients receiving 600 mg/m² per dose were as follows: C_{max}, 0.99 + 0.38, µg/ml (mean standard deviation); T_{max}, 3.0 ± 0.86 h; AUC, 5.56 ± 2.17 kg. h/ml; and t_{1/2}, 2.59 ± 0.78 h. The mean pharmacokinetic values were similar for children between 6 months and 4 years of age and children over 4 years old receiving the 600-mg/ m² dose. Three infants less than 2 months of age and two children between 2 months and 4 years of age were given acyclovir suspension at 300 mg/ m² per dose. The three infants who were less than 2 months of age achieved a higher mean C_{max}, 1.88, µg/ml, and had a somewhat longer mean t_{1/2}, 3.26 h, than did the older children receiving the same or a higher dose (Table 3).

By using interpolation and superimposition of mean data, the steady-state acyclovir concentrations in plasma were simulated for the 600-mg/m² dose (Fig. 2). The expected peak acyclovir concentrations after four consecutive doses given at 4-h intervals were approximately 0.9, 1.3, 1.4, and 1.5 µg/ml after successive doses during the day.

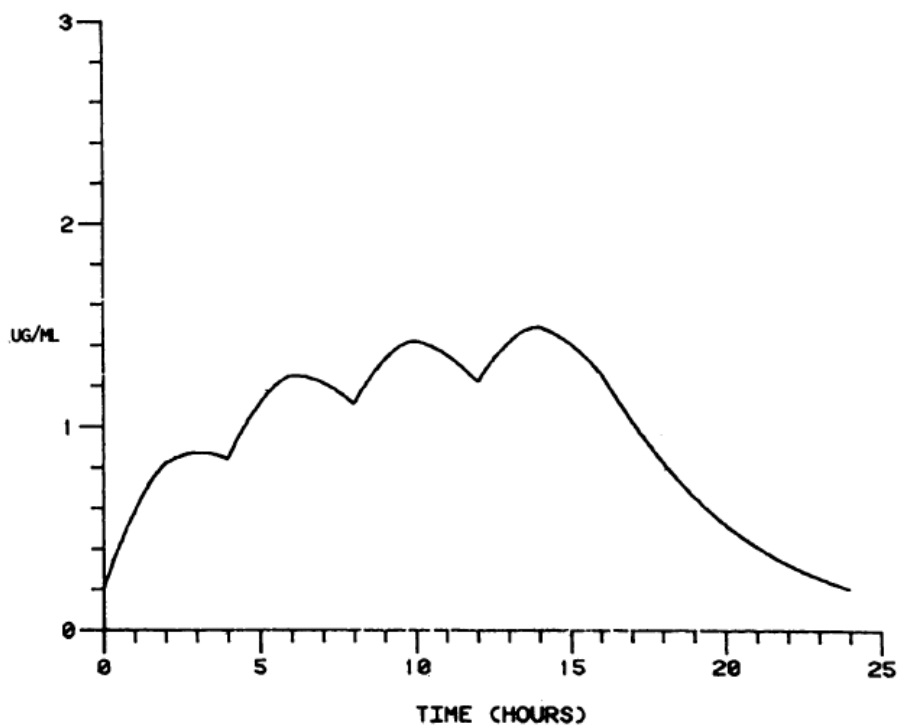


FIG. 2. Simulated steady-state acyclovir concentrations in plasma. The simulated steady-state acyclovir concentrations (micrograms per milliliter) in plasma plotted on the y axis were obtained by interpolation and superimposition of the mean data for 13 patients 6 months to 6.9 years of age who received 600 mg of acyclovir oral suspension per m² per dose. The times indicated on the x axis are based on four doses given every 4 h during the day (i.e., at h 0, 4, 8, and 12).

Safety findings

No safety information are included in the GSK submitted study report, however according to the published study report three patients experienced self-limited clinical reactions (mild diarrhea, mild vomiting or profuse diaphoresis) which did not require study discontinuation.

Discussion on clinical aspects

At present, suggested oral dosages for Zovirax(acyclovir) in UK and Ireland for children are:

Treatment of herpes simplex infections and prophylaxis of herpes simplex infections in the immunocompromised: Children aged two years and over should be given adult dosages and children below the age of two years should be given half the adult dose.

Treatment of varicella infections:

6 years and over: 800mg Zovirax four times daily.

2 to 5 years: 400mg Zovirax four times daily.

Under 2 years: 200mg Zovirax four times daily.

Treatment should continue for five days. Dosing may be more accurately calculated as 20mg/kg body weight (not to exceed 800mg) Zovirax four times daily.

The current PK study shows that acyclovir suspension at a dosage of 600 mg/m² four times daily in infants provides only approximately half of the systemic concentration available when acyclovir is given intravenously at 250 mg/m² three times daily. Oral acyclovir has a low oral bioavailability, which is between 10% and 30%. It is of concern that the achieved acyclovir concentrations with oral acyclovir may provide inadequate serum levels in some children with current dosage recommendations. More recent studies have shown relatively large inter-individual variability in the pharmacokinetic parameters for acyclovir in the pediatric population. It has been suggested that maximal efficacy is reached when the length of time that the acyclovir concentration remains above the IC₅₀ is greater than 12 h in each 24-h period of treatment. In treatment of VZV a higher acyclovir AUC is required because the IC₅₀ for VZV isolates is higher than HSV. The mean daily AUCs for acyclovir at the doses approved for the treatment of herpes zoster in adults are 107 µM·h (acyclovir at 800 mg five times per day) and 253 µM·h (valaciclovir at 1,000 mg q8h), respectively, with the latter treatment having a greater efficacy.

It is unclear if the peak concentrations (approximately 1.0 µg/ml) achieved in the current study with a dosage of 600 mg/m² are adequate for neonatal HSV, VZV or other severe herpes infections in children. For example a 2 year child has a approximate BSA area of 0.5 m², corresponding to 300 mg x 4, which in some cases may actually be a higher dose than the currently recommended dosage for a 2 year old. This seems to be a major concern, why further pharmacokinetic data and discussion is required from the MAH. Discussion of these aspects is critical. It should be noted that serum concentrations obtained by oral valaciclovir- the prodrug of acyclovir- provides much improved serum concentrations of acyclovir.

ACICLOVIR- INTRAVENOUS STUDIES

Study THRS/88/0068. Collaborative study of neonatal herpes simplex virus infection: A controlled evaluation of acyclovir and Vira-A – Assessment of mortality and definition of morbidity with therapy (4) .

Description

Multicenter randomized blinded study of neonatal HSV infection comparing intravenous vidarabine with acyclovir.

Methods

Study population

Newborns (babies less than one month of age) with virologically confirmed HSV infection were eligible for enrollment in this study. Babies were enrolled from 27 institutions from February 1981 to January 1988. Newborns were enrolled in the study irrespective of gestational age, birth weight, or concomitant medical problems.

Treatments:

Vidarabine was administered by continuous intravenous infusion over a 12-hour period at a dosage of 30 mg per kilogram of body weight per day and at a concentration no greater than 0.7 mg per milliliter in standard intravenous fluid. The dosage of acyclovir was 30 mg per kilogram per day divided into three doses that were given every eight hours in a minimal volume of 50 ml of standard intravenous fluid over a one-hour period. Therapy was continued for 10 days

Outcomes:

Newborns were classified as having disseminated infection if they had visceral-organ involvement, as manifested by hepatitis (defined as an aspartate aminotransferase level ≥ 2.5 times normal), HSV pneumonitis, or disseminated intravascular coagulopathy. Central nervous system disease was not considered disseminated involvement. Second, newborns were classified as having central nervous system infection if they had neurologic and cerebrospinal fluid abnormalities, such as pleocytosis ($\geq 50 \times 10^6$ white cells per liter for preterm babies and $> 20 \times 10^6$ white cells per liter for term infants) and proteinosis (> 1.2 g per liter for preterm babies and ≥ 0.90 g per liter for term infants), indicative of brain infection, with or without involvement of the skin, eyes, or mouth (mucous membranes). Clinical findings included hypotonia, seizures, and abnormal computed tomographic scans and electroencephalograms. Other diseases of the central nervous system, such as intraventricular hemorrhage, were recorded to prevent misclassification. Third, babies were classified as having infection confined to the skin, eyes, or mouth if they did not have evidence of other organ involvement.

During a minimum of 14 days of hospitalization (unless the subject died), newborns were assessed daily. Neurologic status was determined 3, 6, 12, and 24 months after enrollment in the study.

Statistical Methods: The total number of babies enrolled in the trial had the ability to detect a 25 percent difference between the two treatments at a significance level of 5 percent and a power of more than 90 percent. Primary response variables for evaluating drug efficacy were mortality and the morbidity of surviving patients.

Results

A total of 210 babies with virologically proved neonatal HSV infection were entered in the study. Eight babies had disease at birth (chorioretinitis, skin lesions or scarring, and hydrocephalus) and were excluded from efficacy analyses.¹² Ninety-five babies were randomly assigned to receive vidarabine, and 107 to receive acyclovir

Baseline data

Table 2. Characteristics of Newborns Treated with Vidarabine or Acyclovir, According to Extent of Disease.*

CHARACTERISTIC	VIDARABINE	ACYCLOVIR
	<i>no. of infants (%)</i>	
Skin, eye, or mouth infection (n = 85)	31	54
Age at presentation (days)	11.1±1.3	11.2±0.9
Duration of disease before treatment (days)†	4.8±1.0	4.8±0.6
No. premature	9 (29)	15 (28)
Maternal history of HSV‡	15 (48)	23 (43)
Cesarean-section delivery	8 (26)	6 (11)
Central nervous system infection (n = 71)	36	35
Age at presentation (days)	17.1±1.3	15.2±1.3
Duration of disease before treatment (days)†	4.7±0.5	5.0±0.7
No. premature	8 (22)	7 (20)
Maternal history of HSV‡	14 (39)	15 (43)
Cesarean-section delivery	7 (19)	6 (17)
Disseminated disease (n = 46)	28	18
Age at presentation (days)	11.0±0.9	10.3±1.1
Duration of disease before treatment (days)†	4.2±0.5	4.7±0.7
No. premature	8 (29)	4 (22)
Maternal history of HSV‡	10 (36)	6 (33)
Cesarean-section delivery	5 (18)	9 (50)§

*Plus-minus values are means ±SE.

†Defined as duration of any or all of the following symptoms before enrollment: vesicles, conjunctivitis, fever, seizures, pneumonitis, and disseminated intravascular coagulopathy. Fourteen patients without these symptoms had the duration of disease calculated on the basis of other symptoms.

‡Or that of a sexual partner with HSV infection.

§P≤0.05 for the comparison between groups.

Efficacy results

After adjustment for differences between groups in the extent of disease, there was no difference between vidarabine and acyclovir in either morbidity (P = 0.83) or mortality (P = 0.27). None of the 85 babies with disease confined to the skin, eyes, or mouth died. Of the 31 babies in this group who were treated with vidarabine and followed for a year, 88 percent (22 of 25) were judged to be developing normally after one year, as compared with 98 percent (45 of 46) of the 54 treated with acyclovir (95 percent confidence interval for the difference, -4 to 24). For the 71 babies with encephalitis, mortality was 14 percent with vidarabine (5 of 36) and with acyclovir (5 of 35); of the survivors, 43 percent (13 of 30) and 29 percent (8 of 28), respectively, were developing normally after one year (95 percent confidence interval for the difference, -11 to 39). For the 46 babies with disseminated disease, mortality was 50 percent (14 of 28) with vidarabine and 61 percent (11 of 18) with acyclovir (95 percent confidence interval for the difference, -20 to 40); of the survivors, 58 percent (7 of 12) and 60 percent (3 of 5), respectively, were judged to be developing normally after one year (95 percent confidence interval for the difference, -40 to 50).

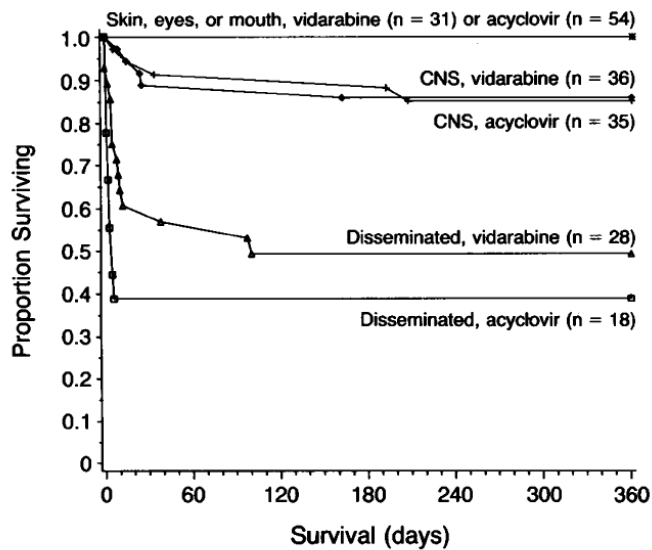


Figure 1. Survival of Babies with Neonatal HSV Infection, According to Treatment and the Extent of Disease.

The infection was classified as confined to the skin, eyes, or mouth; affecting the central nervous system (CNS); or producing disseminated disease. After adjustment for the extent of disease with use of a stratified analysis, the overall comparison of vidarabine with acyclovir was not statistically significant ($P = 0.27$) by a log-rank test. No comparison of treatments within disease categories was statistically significant.

Recurrent disease

Eight percent of the surviving babies (7 of 87) with encephalitis or disseminated disease appeared to have a recurrence of the disease within one month after completing therapy. Six babies received vidarabine, and one received acyclovir. All seven babies had relapse of central nervous system disease, as manifested by recurrent seizures and a more abnormal cerebrospinal fluid profile, with retrieval of HSV from the fluid. Recurrent skin lesions were common within one month after therapy was completed. Eight of 42 babies who received vidarabine (19 percent) had recurrent skin lesions, as compared with 17 of 49 acyclovir-treated babies (35 percent). There were no differences in the frequency of recurrent skin lesions according to the extent of disease or treatment group. Six months after therapy the rate of recurrence had increased to 46 percent in both groups.

Safety results

Four cases of adverse clinical reactions were attributed to vidarabine and three to acyclovir. These consisted of rash (one case in each group), diarrhea (one in the vidarabine group), tremulousness (two in the vidarabine group and one in the acyclovir group), and vomiting (one in the acyclovir group).

Discussion on clinical aspects

This study confirms the serious mortality and morbidity of neonatal HSV infection, particularly encephalitis. Overall acyclovir provided comparable efficacy to vidarabine. Although it is unclear if the "recurrent" cases reported represent recurrence or residual disease manifestations, in consideration of the apparent relatively high relapse rate for HSV encephalitis (8%), the chosen treatment duration (10 days) was probably too short. The current (UK) SPC for

zovirax states “Treatment for neonatal herpes simplex infections usually lasts 10 days.” Considering the recurrent disease observed in this study, the MAH should discuss if the current suggested treatment duration is adequate, particularly in case on HSV encephalitis. Of note, the acyclovir dosage for children investigated was 10 mg/kg tid

P12-142. Prophylaxis against CMV in bone marrow transplant recipients with intravenous Zovirax (10).

Description

Open label, parallel, untreated control group, acyclovir assigned according to CMV and HSV serology

Methods

Intravenous acyclovir 500 mg/m² every 8 hours for 5 days prior to bone marrow transplantation (BMT) continued for 30 days after BMT.

Study population

Treatment	Entered	Evaluated Efficacy	Evaluated Safety
ZOVIRAX	121	85	121
Control	82	78	82*

No adverse informations were collected, only some routine hematology and chemistry data.

Few children were included: Age 1-15 years, n=11, 16-20 years, n=6

Results

In CMV sero-positive patients, acyclovir treatment conferred a small morbidity and mortality advantage compared to no treatment.

Discussion on clinical aspects

Few children included, insufficient to evaluate efficacy. Rather poorly conducted study, with no safety information collected from the control group, the reported apparent efficacy of acyclovir for the prevention of CMV disease is now of only historical interest in view of the much more potent available drugs such as ganciclovir which now are used for this indication. Of note, the reported number of patients submitted in this GSK study report does not match up with the published information from the same trial.

H14-304. A multicentre, double-blind, controlled trial of prophylaxis against CMV infections in bone marrow transplant (BMT) patients using intravenous Zovirax followed by oral Zovirax (11).

Description

Objectives: 1. Determine efficacy of high dose iv acyclovir for prophylaxis of CMV reactivation following BMT. 2. Determine efficacy of subsequent long term(6 months) high dose oral acyclovir for prophylaxis of CMV reactivation

Methods

Recipients of HLA-matched related or unrelated allogeneic BMT who were seropositive for CMV or those with a seropositive donor when the marrow was unmanipulated were entered into a double-blind, double-dummy, randomised controlled study. We excluded patients aged under 2 years, those who had serum creatinine over 150 (imoI/L, those who had received other antiviral drugs or CMV-specific immunoglobulin, or those who were known from prior exposure to be sensitive to acyclovir. Patients were randomised into three groups(A, B or C):

Group	Creatinine clearance/age	Acyclovir		Acyclovir/placebo	
		- 5 to +30 days	Acyclovir dose (mg per day)	+ 1 to +6 mo	Acyclovir (mg per day)
A	< 50 mL/min	Intravenous	500 mg/m ² × 3	Oral acyclovir	800 × 4
	25–50 mL/min	Intravenous	500 mg/m ² × 2	Oral acyclovir	800 × 4
	10–25 mL/min	Intravenous	500 mg/m ² × 1	Oral acyclovir	800 × 3
	< 10 mL/min	Intravenous	Patient withdrawn*	Oral acyclovir	800 × 2
B	As for A	Intravenous	As for A	Oral placebo	.
C	≥10 yr	Oral	400 mg × 4	Oral placebo	.
	< 10 yr	Oral	200 mg × 4	Oral placebo	.

*If effect thought to be related to acyclovir.

Only 15 children, < 10 years, were included in this study

Statistical Methods

Intention to treat. Cox analysis.

Results

Intravenous acyclovir significantly reduced the probability of and delayed the onset of CMV infection. There was no further reduction in infection risk with the addition of long-term oral acyclovir. Time to CMV viraemia was delayed in the intravenous/oral acyclovir groups compared with controls. Extending the prophylaxis with oral acyclovir significantly improved survival: 79 of 105 recipients were still alive at 7 months compared with 60 of 102 controls (p=0.012). Although the intravenous/oral acyclovir group did significantly better than controls in terms of survival, the difference between the intravenous/oral acyclovir group and the intermediate group was of borderline statistical significance (p=0.054).

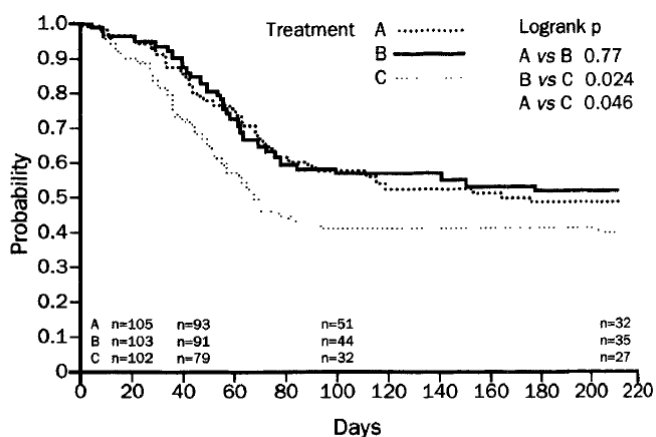


Figure 1: Kaplan-Meier estimates of probability of freedom from CMV infection after BMT

HSV disease

Among patients who have developed herpes simplex virus disease, the median time to onset of the disease in group C was 30 days and was delayed to 81 days in group A and to 46 days in B. The Kaplan-Meier probability of the disease at day 210 was reduced from 32% in C and 34% in B to 7% in A. 5 patients in group A who have developed the disease, 22 in B, and 21 in C were treated with acyclovir. The estimates of varicella-zoster virus disease at day 210 were 3%, 9%, and 9%, respectively.

Safety result

Adverse events that were possibly treatment related were similar in all three groups. The most commonly reported events were nausea, vomiting, elevated creatinine, and renal failure.

Discussion on clinical aspects

Too few paediatric subjects were included to evaluate efficacy. Interestingly, in relation to the aforementioned concern of a possible too low recommended oral dosage raised by the pharmacokinetic study, this study may suggest that the dosage of 200 mg x4 was inferior not only for CMV but also for HSV and VZV prophylaxis, unfortunately there were insufficient number of children included for conclusions.

BKCT/86/003 A double-blind, placebo controlled study of intravenous Zovirax for varicella (zoster) virus infection in immunocompromised children (12).

Description

Double-blind, randomized study conducted at two university hospitals in Hungary

Methods

Immunocompromised children of either sex who were between three months and 14 y of age and who presented with a clinical diagnosis of varicella were entered into the study. All patients had malignancies and were undergoing cytostatic chemotherapy. Patients were excluded from the trial if they had a body surface area $> 1.5\text{m}^2$, if their level of blood urea nitrogen was > 6.8 mmol/L, or if they were in the terminal stages of their underlying disease. Any child presenting

with fulminating varicella was treated with open iv acyclovir (i.e., known acyclovir rather than coded acyclovir or placebo) outside of the trial, as was any child with a large body surface area.

Table 1. Demographic characteristics of patients on entry.

Characteristics	Treatment group	
	Acyclovir (n = 25)	Placebo (n = 25)
Age (y)		
Mean	5.8	5.4
Range	1-14	2-14
Sex (male/female)	15/10	13/12
Duration of rash (h)		
0-24	10	10
25-48	6	5
49-72	7	7
>72	2	3
Underlying disease		
Acute lymphoid leukemia	10	11
Acute myeloid leukemia	2	1
Non-Hodgkins lymphoma	2	3
Neuroblastoma	4	4
Wilms' tumor	2	3
Burkitt's lymphoma	1	1
Other	4*	2†
Phase of illness		
Active (initial or relapse)	9	8
Remission	16	17

* Rhabdomyosarcoma, primary chronic polyarthritis, brain tumor, or sarcoma.

† Teratoma or fibrosarcoma nasi.

Results

Fifty immunocompromised children with varicella entered the study. Of these, 25 received iv acyclovir and 25 received iv placebo. One patient in the acyclovir group was withdrawn from treatment on day 2 at the request of his parents. He was monitored, however, up to day 6 and was included in the statistical analysis. Transfer to open treatment with acyclovir. One (4%) of the 25 acyclovir recipients and 12 (48%) of the 25 placebo recipients were withdrawn and were treated with open iv acyclovir

Efficacy results

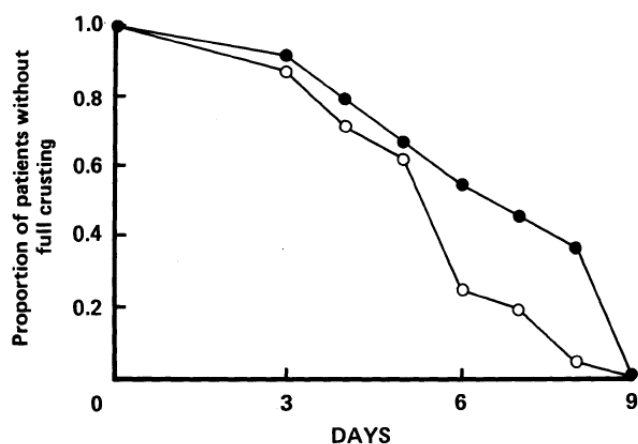


Figure 1. Time to full crusting in recipients of acyclovir (○) and recipients of placebo (●).

Table 2. Analysis of rash duration.

Parameter	Duration of rash in recipients of				P *
	Acyclovir		Placebo		
	Mean days (SE)	No. of patients	Mean days (SE)	No. of patients	
Time to cessation of macule/papule formation	3.9 (0.35)	24	4.6 (0.56)	10	.193
Time to cessation of vesicles	5.1 (0.36)	24	6.2 (0.66)	11	.056
Time to formation of first crust	2.7 (0.20)	23	2.6 (0.18)	8	.260
Time to full crusting	5.7 (0.36)	24	7.1 (0.58)	11	.013†
Time to last new lesion formation	2.8 (0.45)	22	2.7 (0.62)	11	.463

NOTE. All patients, except those who received open iv treatment with acyclovir, were included in this analysis.

* By Mantel-Cox test.

† Statistically significant.

Among those patients who did not receive open treatment, acyclovir significantly reduced time to full crusting ($P = .01$). Overall, acyclovir, as judged by the physician, significantly improved the patients' condition.

Safety results

No safety signals were observed.

Discussion on clinical aspects

The interpretation of this study is limited. Although reported as a randomized blinded study, the details of randomization and blinding seems inadequate in this study in which a very high number of patients were transferred to active acyclovir treatment from placebo.

Study P12-22, Zovirax multiple-dose, pharmacokinetic analyses in paediatric patients with herpesvirus infections (not previously published)

The pharmacokinetic disposition of acyclovir was investigated during an open uncontrolled multiple-dose study to evaluate pharmacokinetics, tolerance and evidence of antiviral effect in immunocompromised pediatric patients. The drug was administered by a 1-hour intravenous infusion at doses of 250 and 500 mg/m² BSA. For data analysis, patients were subdivided by age into four groups: group A (3 months to 2 years), group B (2 to 7 years), group C (7 to 12 years) and group D (12 to 17 years). The half-life of acyclovir was 1.88 ± 0.37 (n = 5), 2.16 ± 1.08 (n = 5), 2.81 ± 1.10 (n = 6) and 3.58 ± 0.59 (n = 3) for the four age groups, respectively. The total body clearance was 287 ± 108 , 366 ± 101 , 353 ± 145 and 263 ± 95 ml/min/1.73 m² for the four age groups. The change of total body clearance of acyclovir appears to correlate with the change of renal function (i.e. creatinine clearance) with age. Cerebrospinal fluid concentration in one patient (17.9 µM) was approximately 40% of predicted plasma concentration at the time of sampling.

Discussion on clinical aspects

In line with the remainder of the current application, the MAH has only submitted a poor quality pdf scans of this study report. Main findings in this study were unsurprisingly that clearance correlates with renal function and age. Safety was not assessed.

Study P12-23. Zovirax multiple-dose, pharmacokinetic analyses in paediatric patients with herpesvirus infections (not previously published).

Description

Multicenter, open, uncontrolled study of acyclovir in neonatal patients (birth to 3 months) with HSV type I/II or CMV infections.

Methods

Five, 10 mg/kg and 15 mg/kg acyclovir was infused over 1-hr periods every 8 hr, 5 to days for HSV infections and 10 days for CMV infections. Blood and urine samples were collected as described and acyclovir concentrations determined by RIA.

Results

Plasma drug concentrations

19 neonatal patients provide peak and trough acyclovir concentrations at steady state as shown in table 3, below:

Table 3

The Steady State Mean Peak (C_{max}^{ss}) and Trough (C_{min}^{ss})
Acyclovir Concentrations in neonatal patients receiving 5, 10 and 15 mg/kg t.i.d. (P12-23)

Dose (mg/kg)	Patient Initial	C_{max}^{ss} ($\mu\text{g/ml}$)	C_{min}^{ss}
5.0 (n = 7)	JSP	5.0	0.88
	MT	7.1	2.3
	CE	6.3	0.68
	TA	8.9	1.3
	TS	3.6	0.45
	RB	6.3	-
	CLM	5.1	1.3
	Mean \pm SD (Range)	6.04 \pm 1.7 (3.6-8.9)	0.98 \pm 0.72 (0.45-2.3)
10.0 (n = 7)	BGW	18.9	2.7
	MJ	13.2	2.5
	EP	14.3	2.8
	JB	12.6	1.15
	TG	13.3	3.04
	RT	13.9	-
	CM	11.3	0.72
	Mean \pm SD (Range)	13.9 \pm 2.4 (11.3-18.9)	2.2 \pm 1.0 (1.15-3.04)
15.0 (n = 5)	VW	25.7	7.3
	MC	15.6	1.5
	JC	19.5	2.1
	BBP*	33.2	19.4
	SR	20.6	1.33
	Mean \pm SD (Range)	20.4 \pm 4.2 (15.6-33.2)	3.0 \pm 2.8 (1.3-19.4)

*excluded from mean because of abnormally low CL_{tot} and long $t_{1/2}$

Both C_{max}^{ss} and C_{min}^{ss} values increased proportionally with dose.
As shown, mean C_{max}^{ss} values at 5, 10 and 15 mg/kg were approx 6, 14 and 20 $\mu\text{g/ml}$, respectively.

Pharmacokinetic analysis

Plasma concentration profiles were best fitted by a two-compartment open model. Mean total body clearance value normalized by body weight in neonatal patients is only about one-third of the of the mean value in adult and pediatric patients. However, the mean total body clearance value normalized by body weight is only about 15% less than the mean value found in adult patients, suggesting that average steady state concentration in neonatal patients may be comparable if weight normalized dosing is given.

**Comparison of Principal Pharmacokinetic Parameters[‡] in Neonatal,
Pediatric, and Adult Patients**

Age Group	n	(ml/min/1.73 m ²)	CL _{tot} (ml/min/70 kg)	t _{1/2β} (hr)	Vd _{ss} (l/kg)
neonates	12	99 ± 37	307 ± 111	3.80 ± 1.19	1.08 ± 0.35
1-2 yr	4	325 ± 76	728 ± 183	1.86 ± 0.42	1.01 ± 0.15
2-7 yr	5	366 ± 101	644 ± 183	2.16 ± 1.08	1.06 ± 0.33
7-12 yr	6	353 ± 142	484 ± 195	2.81 ± 1.10	1.00 ± 0.35
12-17 yr	3	263 ± 95	355 ± 150	3.58 ± 0.59	0.97 ± 0.35
Adult*	20	327 ± 80	352 ± 88	2.48 ± 0.64	0.77 ± 0.22

[‡]Mean ± S.D.

*Creatinine clearance > 80 ml/min/1.73 m²

Safety results

Aciclovir was well tolerated in neonates at doses up to 15 mg/kg without clinically significant toxicity.

Discussion on clinical aspects

This neonatal PK study suggests that 5 mg/kg may be inadequate and 15 mg/kg may be well tolerated. Recent pharmacokinetic studies have noted large and rather unpredictable inter-individual differences in clearance, particularly among neonates such as preterm infants, in which urinary excretion of acyclovir may be unpredictable (1;2). Zeng and co workers have proposed a one-compartment PK model, simulations using this model suggest that patients with good renal function and/or lower body weight have a relatively high risk of being underdosed. Considering the high mortality of neonatal HSV infection, the MAH should discuss possible improvements in the dosage selection for neonates.

IV.2 Rapporteur's overall conclusion and recommendation in Preliminary Paediatric AR

➤ Overall conclusion

Based on the studies submitted, the current recommended oral aciclovir dosage for children is questioned.

1. The submitted PK studies show that acyclovir suspension at a dosage of 600 mg/m² four times daily in infants provides only approximately half of the systemic concentration available when acyclovir is given intravenously at 250 mg/m² three times daily. Oral acyclovir has a low oral bioavailability which is between 10% and 30%. It is of concern that the achieved acyclovir concentrations with oral acyclovir may provide inadequate serum levels in some children with current dosage recommendations. More recent studies have shown relatively large inter-individual variability in the pharmacokinetic parameters

for acyclovir in the pediatric population. It has been suggested that maximal efficacy is reached when the length of time that the acyclovir concentration remains above the IC50 is greater than 12 h in each 24-h period of treatment. In treatment of VZV, a higher acyclovir AUC is required because the IC50 for VZV isolates is higher than for HSV. The mean daily AUCs for acyclovir at the doses approved for the treatment of herpes zoster in adults are 107 µM·h (acyclovir at 800 mg five times per day) and 253 µM·h (valaciclovir at 1,000 mg q8h), respectively, with the latter treatment having a greater efficacy. It should be noted that oral valaciclovir- the prodrug of acyclovir- provides much improved serum concentrations of acyclovir.

2. Based on the relatively high recurrence rate of serious HSV infection in a neonatal study after 10 days of acyclovir therapy, the MAH should discuss optimal treatment length for severe HSV/VZV infections such as HSV encephalitis.

➤ **Recommendation**

Based on the data submitted, the MAH should provide answers to the LOQ as part of this worksharing procedure. (See PPdAR “Request for supplementary information”)

IV.3 Request for supplementary information in Preliminary Paediatric AR

1. The submitted pharmacokinetic studies for oral acyclovir suggest that current dosage recommendations for children may provide inadequate serum levels of acyclovir in some neonates/children, particularly in case of VZV and/or serious herpes infections (please see discussion above), why the MAH is requested to provide additional clarification regarding dosage recommendations in neonates/children for oral acyclovir.

These concerns are supported by recent pharmacokinetic studies/simulations not included in the current submission (1-3).

2. In study THRS/88/0068 (4) investigating neonatal HSV, a relatively high relapse rate for HSV encephalitis (8%) following a total treatment duration of 10 days was observed. The current (UK) SPC for zovirax states “Treatment for neonatal herpes simplex infections usually lasts 10 days.” Considering the recurrent disease rate observed in this study, the MAA should discuss if the current suggested treatment duration in the SPC is adequate, particularly in case on HSV encephalitis. Probably the SPC needs clarification regarding the length of acyclovir treatment in cases of severe disease.

Other concerns

In the submission of Study P12-148 (Pharmacokinetics of Zovirax oral suspension in paediatric patients with varicella zoster and herpes simplex viral infection), a total of 13 pediatric patients were included, however according to published information (5) from this study, 18 patients were included?- the MAH should explain this discrepancy.

IV.4 Rapporteur's assessment of MAH responses to questions in the Rapporteur's Preliminary Paediatric AR

The MAH (GSK) has now responded to major objections pertaining to paediatric studies submitted in accordance with Article 45 of Regulation EC 1901/2006, as amended, for aciclovir (Zovirax). Please see the Rapporteur assessment of company responses below.

MAJOR CONCERN #1

The submitted pharmacokinetic studies for oral acyclovir suggest that current dosage recommendations for children may provide inadequate serum levels of acyclovir in some neonates/children, particularly in case of VZV and/or serious herpes infections (please see discussion below), why the MAH is requested to provide additional clarification regarding dosage recommendations in neonates/children for oral acyclovir.

These concerns are supported by recent pharmacokinetic studies/simulations not included in the current submission (1-3, see references in Section 2.1 below).

GSK Response

The stated concern relates to the use of oral acyclovir in neonates/children with varicella zoster virus (VZV) infections and/or serious herpes simplex virus (HSV) infections, and a suggestion that current dosage recommendations may be too low to provide adequate systemic concentrations in some pediatric patients. The rapporteur cites the following three publications as support for these concerns:

- (1) Tod M, Lokiec F, Bidault R, De Bony F, Petitjean O, Aujard Y. Pharmacokinetics of oral acyclovir in neonates and in infants: a population analysis. *Antimicrob Agents Chemother* 2001 January;45(1):150-7.
- (2) Zeng L, Nath CE, Blair EY, Shaw PJ, Stephen K, Earl JW et al. Population pharmacokinetics of acyclovir in children and young people with malignancy after administration of intravenous acyclovir or oral valacyclovir. *Antimicrob Agents Chemother* 2009 July;53(7):2918-27.
- (3) Smith JP, Weller S, Johnson B, Nicotera J, Luther JM, Haas DW. Pharmacokinetics of acyclovir and its metabolites in cerebrospinal fluid and systemic circulation after administration of high-dose valacyclovir in subjects with normal and impaired renal function. *Antimicrob Agents Chemother* 2010 March;54(3):1146-51.

The publication by Tod et al reported results from a population pharmacokinetic analysis of intravenous acyclovir and oral acyclovir in children. Consistent with all prior pharmacokinetic investigations, the authors found that acyclovir concentration-time profiles from IV administration were best fit with a two-compartment model and that acyclovir from oral administration could be well described with a one-compartment model. By simulating concentration-time profiles for different oral dosage regimens using their derived population PK parameters, the authors attempted to address adequacy of current oral acyclovir dosing recommendations based on the criteria that plasma concentrations should exceed IC₅₀ values of 2.5 µM (~0.56 µg/mL) for treatment of HSV and 5.0 µM (~1.12 µg/mL) for treatment of VZV infections for at least 12 hours in each 24-hour period of treatment. The authors do not cite a source for their choice of IC₅₀ values, but state that these represent a “worst-case for HSV strains

and a bad case for VZV strains”. Regarding the requirement that plasma concentrations exceed these IC50 values for 12 or more hours during the day, the authors state that this was suggested in articles published by Saiag et al [Saiag, 1999] and Spruance et al [Spruance, 1996]. However, in fact, neither of these publications makes any such statement or suggestion. Moreover, the Pharmacodynamic Effects sections of the Zovirax Global Data Sheet, International Product Information and SPCs all state “The relationship between the *in-vitro* determined sensitivity of HSV isolates and clinical response to aciclovir therapy is not clear.” Accordingly, the underlying basis for the recommendations by Tod et al for use of higher oral acyclovir doses in the treatment of HSV and VZV infections in children has not been established and is highly speculative.

The publication by Zeng et al, conducted in children with malignancies, describes results from population pharmacokinetic analysis of intravenous acyclovir and oral valacyclovir, the acyclovir pro-drug. In contrast to the modelling results of Tod et al and historical experience, Zeng et al used a one-compartmental model for IV acyclovir. A one-compartmental model was also used to characterize the pharmacokinetics of acyclovir from oral valacyclovir administration. Similar to analysis conducted by Tod et al, the authors performed simulations based on the population PK parameters to evaluate the portion of the day that acyclovir concentrations were above “threshold” IC50 values for HSV and VZV and the percentage of the simulated subjects for whom the time-above-threshold was greater than 12 hours in each 24-hours of treatment. Zeng et al cited the publication of Tod et al for choice of threshold IC50 values and also cited (erroneously, see above) the Saiag and Spruance references for needing the 12-hour duration. Although the study reported by Zeng et al did not include data from oral acyclovir administration (and, hence, is not clear how this pertains to Article 45 questions on oral acyclovir), there are several other problematic issues associated with the study. Perhaps most importantly, the authors indicated that the doses studied in the pediatric subjects with cancer (5mg/kg three times daily for IV acyclovir and 10mg/kg twice daily for oral valacyclovir) are recommended doses. Since valacyclovir is marketed in fixed dosage strengths of 250, 500 or 1000 mg tablets, it is not clear how they administered the drug as 10 mg/kg doses. Additionally, such a weight-based dose is not approved for this product at any dosing frequency for any indication in any patient population (the US FDA did recently approve use of an extemporaneously prepared valacyclovir suspension at a dose of 20mg/kg three times daily for treatment of chickenpox in immunocompetent children 2 to 18 years of age). And given that only about 70% of valacyclovir exists as acyclovir and that its bioavailability is approximately 50%, it is also not clear why a twice-daily 10mg/kg regimen (corresponding to about 7 mg/kg/day as systemically available acyclovir) was evaluated in comparison with a three-times daily regimen of 5 mg/kg intravenous acyclovir (15 mg/kg/day systemic acyclovir).

Lastly, the publication by Smith et al describes pharmacokinetic results from administration of high-dose valacyclovir in adults (at dosage regimens of valacyclovir approved for prophylaxis of cytomegalovirus [CMV] infection and disease in organ transplant recipients). This was a study of the CSF penetration of acyclovir and its metabolites. It did not include administration of oral acyclovir and did not include pediatric subjects. Accordingly, like the Zeng publication, it is not clear how this publication is relevant to Article 45 considerations regarding use of oral acyclovir in children. This publication did not suggest that recommended oral acyclovir doses in children may be inadequate.

In summary, the rapporteur’s concerns that currently recommended oral acyclovir dosing may be inadequate for some indications in infants and children appears to stem from simulations

performed by Tod et al and Zeng et al, and these authors' evaluations of the proportions of subjects who maintain acyclovir concentrations above certain IC50 values for at least 12 hours of the day. As noted, the authors selected IC50 values higher than average and provided no information to support a position that clinical efficacy is improved when acyclovir concentrations exceed the selected IC50s for greater than 12 hours of the day. Accordingly, the PK criteria selected by the authors seem quite arbitrary. Additionally, the Tod and Zeng publications did not include efficacy data from their study subjects and did not cite any historical clinical outcome data to support their time-above-IC50 criteria. Given these significant limitations and hypothetical nature of results presented in these publications, GSK believes that the clinical trials data and supporting information previously reviewed and approved by regulatory agencies are more robust than the theoretical simulations offered by the aforementioned citations and thus provide the relevant data to support the existing indications and associated oral acyclovir dosing.

Regarding serious or severe infections, GSK does believe that some clarity can be provided to the SPC to indicate that intravenous acyclovir should be used for the treatment of neonatal herpes and for the treatment of herpes encephalitis; that is, to clarify that oral acyclovir should not be used for treatment of these HSV manifestations (see also response to Major Concern #2). In the oral Zovirax SPC, the indication statement for treatment of herpes simplex virus infections states (can replace the word "Tablets" with "Suspension"):

"Zovirax Tablets are indicated for the treatment of herpes simplex virus infections of the skin and mucous membranes including initial and recurrent genital herpes."

This statement does not include treatment of HSV infections of the central nervous system (e.g., encephalitis, or neonatal HSV involving the CNS). Thus, the indication statement could be interpreted to include other types of neonatal HSV infection, such as that limited to skin, eyes and mouth (SEM) and perhaps some cases of disseminated neonatal HSV (see response to Major Concern #2). However, GSK believes that all neonatal HSV (as well as herpes simplex encephalitis in patients of all ages) should be treated with intravenous acyclovir. Accordingly, we propose to clarify the current indication statement as follows:

"Zovirax Tablets are indicated for the treatment of herpes simplex virus infections (excluding neonatal HSV) of the skin and mucous membranes including initial and recurrent genital herpes."

Rapporteur's comments

1) Dosage recommendation discussion:

After review of the discussed references from the paper by Tod et al. it is fully correct- as discussed by GSK- that the two cited papers by Saiag and Spruance references does not provide any clear evidence for improved efficacy according to the threshold IC50 values suggested by Tod. Point resolved

2) Wording of SPC regarding serious or severe infections:

GSK acknowledges the need for a clarification regarding the restriction of oral aciclovir to non-severe HSV infections, particularly that all neonatal HSV (as well as herpes simplex encephalitis in patients of all ages) should be treated with intravenous

acyclovir – the suggested rewording of the indication “Zovirax Tablets are indicated for the treatment of herpes simplex virus infections (excluding neonatal HSV) of the skin and mucous membranes including initial and recurrent genital herpes.” - is an improvement, but would suggest that the text is further amended to exclude also severe HSV infections in immunocompromised children, as such patients usually would usually be managed by treatment with intravenous acyclovir or valcyclovir. Therefore suggest the following change to 4.1:

“Zovirax Tablets are indicated for the treatment of herpes simplex virus infections (excluding neonatal HSV and severe HSV infections in immunocompromised children) of the skin and mucous membranes including initial and recurrent genital herpes.”

MAJOR CONCERN #2

In study THRS/88/0068 investigating neonatal HSV, a relatively high relapse rate for HSV encephalitis (8%) following a total treatment duration of 10 days was observed. The current (UK) SPC for zovirax states “Treatment for neonatal herpes simplex infections usually lasts 10 days”. Considering the recurrent disease rate observed in this study, the MAH should discuss if the current suggested treatment duration in the SPC is adequate, particularly in case on HSV encephalitis. Probably the SPC needs clarification regarding the length of acyclovir treatment in cases of severe disease.

GSK Response

GSK has been asked to discuss if the 10-day duration of IV acyclovir treatment for the management of neonatal HSV is adequate, particularly in the case of HSV encephalitis. GSK agrees the SPC needs to be updated regarding the duration of IV acyclovir treatment in the treatment of neonatal HSV infections.

In newborn infants, HSV infection can manifest as: (1) disseminated disease involving multiple organs, most prominently liver and lungs, but in 60% to 75% of cases also involving the central nervous system; (2) localized CNS disease, with or without skin involvement (CNS disease); or (3) disease localized to the skin, eyes, and mouth (SEM disease). Approximately 20% of cases of neonatal HSV manifest as disseminated disease, one third manifest as CNS disease, and 40% to 45% manifest as SEM disease. Approximately 60% of neonates with disseminated disease or CNS disease have skin lesions, and approximately 80% to 85% of neonates with SEM disease will have skin involvement [AAP, 2009].

Study THRS/88/0068 was conducted from February 1981 to January 1988 and compared vidarabine with acyclovir for the treatment of neonatal HSV infection [Whitley, 1991]. Babies less than one month of age with virologically confirmed HSV infection were randomly assigned to receive either IV vidarabine (30 mg/kg of body weight per day; n=95) or IV acyclovir (30 mg/kg/day; n=107) for 10 days and followed for up to 24 months. Results showed that among the surviving babies with encephalitis or disseminated disease, 8% (7/87) had a recurrence of CNS disease within one month after completing treatment. Six of these seven babies received vidarabine and one received acyclovir. Recurrent skin lesions also were common within one

month after therapy completed, with 19% and 35% of babies who received vidarabine and acyclovir, respectively, exhibiting recurrent skin lesions. At six months after treatment, the rate of recurrence increased to 46% in both treatment groups [Whitley, 1991].

Kimberlin and colleagues investigated high-dose IV acyclovir in the management of neonatal HSV infection in an open-label investigation of IV acyclovir at dosages higher than the 30 mg/kg/day regimen, and for longer than 10 days [Kimberlin, 2001]. Eighty-eight (88) infants aged ≤ 28 days and whose disease was considered to be caused by HSV were enrolled in the study and received IV acyclovir for 21 days. The first 16 patients were enrolled in 1989 and 1990 and received acyclovir 45 mg/kg/day; the other 72 patients were enrolled between 1990 and 1997 and received acyclovir 60 mg/kg/day.

Results from this study supported the use of a 21-day course of high-dose (60 mg/kg/day) intravenous acyclovir to treat neonatal CNS and disseminated disease.

In 1999, the International Herpes Management Forum (IHMF) published updated Treatment Guidelines for the management of neonatal herpes [IHMF, 1999]. The high risk of death or neurological damage with delayed or no treatment of neonatal HSV infection requires that diagnosis be pursued promptly whenever the infection is suspected and that empiric treatment with IV aciclovir be initiated at the time diagnostic tests are ordered [IHMF, 1999]. For the treatment of neonatal HSV infection, IHMF recommends IV acyclovir (20 mg/kg every 8 hours; Category 2 recommendation), and early administration which may improve long-term neurological outcome (Category 1 recommendation). The duration of IV aciclovir (20 mg/kg every 8 hours) treatment should be 14 days for disease limited to the skin, eyes or mouth [i.e. normal cerebrospinal fluid (CSF)], and 21 days for other forms of neonatal HSV infection (i.e. CNS disease, disseminated disease, abnormal CSF) (Category 1/2 recommendation) [IHMF, 1999; Kimberlin, written communication, 2010].

The IHMF Guidelines are supported in the “Red Book®”, the official policy statement of the American Academy of Pediatrics. From 2000 to present, the Red Book has provided US pediatric healthcare practitioners recommendations for the dose and duration of IV acyclovir for the management of neonatal herpes [Red Book, 2009].

The US Centers for Disease Control (CDC) also provide Treatment Guidelines for the management of neonatal HSV. Since 2002, CDC Guidelines have stated “The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 21 days for disseminated and CNS disease or for 14 days for disease limited to the skin and mucous membranes” [CDC, 2010]. This dosing is also recommended by the Paediatric Formulary Committee of the British National Formulary for Children [BNF, 2010].

In conclusion, GSK agrees the current SPC for acyclovir should be clarified regarding the dose and duration of IV acyclovir treatment in cases of severe neonatal herpes disease, as follows:

The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 21 days for disseminated and CNS disease, or for 14 days for disease limited to the skin and mucous membranes.

Rapporteur's comments

GSK agrees that the current SPC should be clarified regarding intravenous dose and duration according to current guidelines for severe neonatal herpes recommending a dosage of 20 mg/kg body weight i.v tid for 14-21 days as suggested- the proposed revised SPC text is now acceptable. Based on the revised dosage recommendation, dosage recommendations in renal impairment needs to be given; The MAH is requested to provide updated recommendations for 4.2, Dosage in renal impairment, with special attention to dosage in infants.

OTHER CONCERN

In the submission of Study P12-148 (Pharmacokinetics of Zovirax oral suspension in paediatric patients with varicella zoster and herpes simplex viral infection), a total of 13 paediatric patients were included, however according to published information from this study, 18 patients were included?- the MAH should explain this discrepancy.

GSK Response

We have searched the GSK electronic archives for information relating to this study, conducted approximately 25 years ago, and have not found specific information that would clearly explain the difference in number of subjects in the internal study reports (n=13) and the number of subjects included in the later publication (n=18). Study P12-148 was designed to obtain pharmacokinetic and safety data from administration of acyclovir oral suspension to children from 6 months to <7 years of age. However, the internal GSK Final Medical Report (GSK Doc. No. THRS/86/0001), dated 9 January 1986, noted that one two-week old infant received acyclovir oral suspension on a compassionate plea basis and that, although the patient did not satisfy inclusion criteria, pharmacokinetic sampling and safety evaluations were performed and the data for the subject were included in the report. Similarly, we speculate that data for 5 additional subjects, perhaps also treated on a compassionate plea basis, became available between the time of creation of the internal study report and the time of preparing the manuscript, which was submitted for publication in June 1987. In an effort to share all available data in paediatric subjects, the authors of the manuscript apparently elected to include results from the full cohort in the publication. Unfortunately we are not able to offer any additional information on this study based on our internal study searches.

Rapporteur's comments

Due to the absence of historical data: Point resolved.

IV.5 Rapporteur's overall conclusion and recommendation in Final Paediatric AR

Clarification of dosage recommendations for oral acyclovir in neonates/children: After re-review of the PK/PD literature for infants/children- supported by the answers from GSK there is currently no evidence for oral dosage changes in the absence of supportive clinical data.

GSK agrees that the current SPC for acyclovir should be clarified regarding

- 1) Changes to the indication of oral acyclovir, which clarify that oral acyclovir is mainly for use in non-severe skin and mucosa HSV infections
- 2) The dose and duration of IV acyclovir treatment in cases of severe neonatal herpes disease, as follows.

Regarding 1): The Rapporteur suggests that the proposed SPC 4.1 is further slightly amended as follows: “Zovirax Tablets are indicated for the treatment of herpes simplex virus infections (excluding neonatal HSV and severe HSV infections in immunocompromised children) of the skin and mucous membranes including initial and recurrent genital herpes.”

Regarding 2): The following suggestion to a change in the SPC, 4.2 is acceptable “The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 21 days for disseminated and CNS disease, or for 14 days for disease limited to the skin and mucous membranes.”

Based on the revised dosage recommendation, dosage recommendations in renal impairment needs to be given; The MAH is requested to provide updated recommendations for 4.2, Dosage in renal impairment, with special attention to dosage in infants.

IV.6 Rapporteur’s assessment of MAH responses to questions in the Rapporteur’s Final Paediatric AR / MS comments D115

GSK have now provided responses to the further questions of the Rapporteur’s final assessment report pertaining to paediatric studies submitted in accordance with Article 45 of Regulation EC 1901/2006, as amended, for aciclovir (Zovirax), 14 March 2011.

The questions have now all been resolved – please see our comments to GSK responses and the suggestions for changes in the SPC of oral and intravenous aciclovir with the final positive conclusion below.

Dosage recommendations

Clarification of dosage recommendations for oral acyclovir in neonates/children: After re-review of the PK/PD literature for infants/children- supported by the answers from GSK there is currently no evidence for oral dosage changes in the absence of supportive clinical data.

GSK agrees that the current SPC for acyclovir should be clarified regarding

1. Changes to the indication of oral acyclovir, which clarify that oral acyclovir is mainly for use in non-severe skin and mucosa HSV infections
2. The dose and duration of IV acyclovir treatment in cases of severe neonatal herpes disease, as follows.

Question 1:

The Rapporteur suggests that the proposed SPC 4.1 is further slightly amended as follows: “Zovirax Tablets are indicated for the treatment of herpes simplex virus infections (excluding neonatal HSV and severe HSV infections in immunocompromised children) of the skin and mucous membranes including initial and recurrent genital herpes.”

GSK Response

With a minor change in wording, GSK agrees to this change to the text in Section 4.1 of the SPC for Zovirax Tablets (see response to comment from MS; inserted here as Question 1a):

Question 1a (comment from MS on FPdAR):

Section 4.1

The additions (excluding neonatal HSV and severe HSV infections in immunocompromised children) are endorsed. It is for readability suggested to place them at the end of the sentence thus: “Zovirax Tablets are indicated for the treatment of herpes simplex virus infections of the skin and mucous membranes including initial and recurrent genital herpes (excluding neonatal HSV and severe HSV infections in immunocompromised children).”

GSK Response

GSK agrees to the wording as proposed by MS on their review of the rapporteur’s final assessment report. Specifically, we agree to the following wording for Section 4.1 for Zovirax tablets:

“Zovirax Tablets are indicated for the treatment of herpes simplex virus infections of the skin and mucous membranes including initial and recurrent genital herpes (excluding neonatal HSV and severe HSV infections in immunocompromised children).”

Rapporteur’s comment:

Issue resolved. The wording proposed by MS and accepted by GSK is endorsed.

Question 2:

The following suggestion to a change in the SPC, 4.2 is acceptable “The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 21 days for disseminated and CNS disease, or for 14 days for disease limited to the skin and mucous membranes.”

GSK Response

GSK agrees to this change to the text in Section 4.2 of the SPC for Zovirax I.V. relating to the treatment of neonatal HSV infection.

Also, the current text relating to neonates in SPC Section 5.2 (Pharmacokinetic properties) states: “In neonates (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 C_{ssmax} was found to be 61.2 micromolar (13.8 microgram/ml) and the C_{ssmin} to be 10.1 micromolar (2.3 microgram/ml).” GSK considers it appropriate to add information from the Kimberlin publication to provide some information relating to higher dose administration. Specifically, we propose that the following text be added after the existing sentence to both the I.V. and oral SPCs:

“A separate group of neonates treated with 15 mg/kg every 8 hours showed approximate dose proportional increases, with a C_{max} of 83.5 micromolar (18.8 microgram/ml) and C_{min} of 14.1 micromolar (3.2 microgram/ml).”

Rapporteur’s comment

The addition of the suggested supplementary text based on the Kimberlin publication is supported and accepted.

Question 3:

Based on the revised dosage recommendation, dosage recommendations in renal impairment needs to be given; The MAH is requested to provide updated recommendations for 4.2, Dosage in renal impairment, with special attention to dosage in infants.

GSK Response

The Rapporteur has agreed with the GSK proposal to modify intravenous aciclovir dosage from 10mg/kg three times daily to 20mg/kg three times daily in the treatment of neonatal herpes based on the important results demonstrating improved mortality and morbidity from investigation of the higher dose by the Collaborative Antiviral Study Group [Kimberlin, 2001] and as subsequently supported in various treatment guidelines.

Regarding dosage adjustments for infants with renal impairment, this is addressed in the Discussion section of the Kimberlin publication regarding high-dose (HD) aciclovir, which states:

“Guidelines for administering intravenous acyclovir in neonates with impaired renal function have been previously published and apply to the use of HD acyclovir as well.²⁰ In patients with moderately reduced creatinine clearance (serum creatinine 0.8-1.1 mg/dL [70-100 µmol/L]), the dosage (20 mg/kg) should be administered every 12 hours, and for neonates with reduced creatinine clearance (serum creatinine 1.2-1.5 mg/dL [110-130 µmol/L]) it should be administered every 24 hours. In renal failure (serum creatinine >1.5 mg/dL [130 µmol/L], or urine output <1 mL/kg/h), the dosage should be halved (10 mg/kg) and given every 24 hours.”

In proposing these guidelines, the authors cited a publication (Kimberlin reference 20, noted at end of first sentence in above paragraph) that developed dosage adjustment guidelines based on their study of the pharmacokinetics of intravenous aciclovir in 16 neonates with gestational ages from 27 to 40 weeks and various levels of renal dysfunction [Englund, 1991]. However, in addition to the serum creatinine ranges given in the Kimberlin publication, Table II of the Englund publication also included creatinine clearance ranges of 20-50 mL/min/1.73m² in association with the 0.8-1.1 mg/dL serum creatinine range and 10-25 mL/min/1.73m² in association with the 1.2-1.5 mg/dL creatinine range.

Both of these publications noted that the pharmacokinetic results in their studies were generally consistent with results from previous publications of intravenous aciclovir administration to neonates [Hintz, 1982; Blum, 1982]. However, the Englund publication is the only one that provided information allowing correlation of pharmacokinetic results with renal function within the infant age group. Accordingly, GSK has no basis to offer alternative dosage adjustment

guidelines for IV aciclovir in infants with renal impairment and proposes that they be included in Section 4.2 of the SPC.

Additionally, since creatinine clearance in infants and children is generally reported in units normalized to body surface area (i.e., mL/min/1.73m²), we propose that the dosage adjustment guidance for this population be separated from that for adolescents and adults having creatinine clearance reported as mL/min:

Dosage adjustments in adults and adolescents:

<u>Creatinine Clearance</u>	<u>Dosage</u>
25 to 50 ml/min	The dose recommended above (5 or 10 mg/kg body weight) should be given every 12 hours.
10 to 25 ml/min	The dose recommended above (5 or 10 mg/kg body weight) 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 body weight) should be halved and administered every 24 hours. In patients receiving haemodialysis the dose recommended above (5 or 10 mg/kg body weight) should be halved and administered every 24 hours and after dialysis.

Dosage adjustments in infants and children:

<u>Creatinine Clearance</u>	<u>Dosage</u>
25 to 50 ml/min/1.73 m ²	The dose recommended above (250 or 500 mg/m ² body surface area or 20 mg/kg body weight) should be given every 12 hours.
10 to 25 ml/min/1.73 m ²	The dose recommended above (250 or 500 mg/m ² body surface area or 20 mg/kg body weight) should be given every 24 hours.
0(anuric) to 10 ml/min/1.73 m ²	In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommended above (250 or 500 mg/m ² body surface area or 20 mg/kg body weight) should be halved and administered every 24 hours. In patients receiving haemodialysis the dose recommended above (250 or 500 mg/m ² body surface area or 20 mg/kg body weight) should be halved and administered every 24 hours and after dialysis.

Please refer to the changes-marked SPC for full text changes associated with this response.

Rapporteur's comment

Appropriate and improved guidance for dosage adjustment in neonates with renal impairment have been provided. The table and text is fully acceptable and endorsed.

V. RAPPORTEUR'S OVERALL CONCLUSION AND RECOMMENDATION

➤ Overall conclusion

The suggested changes to the SPC of oral and i.v formulations of aciclovir (Zovirax) are endorsed

➤ Recommendation

Type IB variation (C.I.3.a) to be requested from the MAH by 12 June 2011.

Changes in SPC sections 4.1 and 5.2 for oral acyclovir and SPC sections 4.2 and 5.2 for IV acyclovir are recommended (information in red underlined should be added, information in blue strikethrough should be deleted). PL should be changed accordingly

Oral acyclovir

Section 4.1:

Zovirax Tablets are indicated for the treatment of herpes simplex virus infections of the skin and mucous membranes including initial and recurrent genital herpes (excluding neonatal HSV and severe HSV infections in immunocompromised children).

Section 5.2:

In neonates (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 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). 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).

IV acyclovir

Section 4.2:

Route of administration: Slow intravenous infusion over 1 hour.

A course of treatment with Zovirax I.V. usually lasts 5 days, but this may be adjusted according to the patient's condition and response to therapy. Treatment for herpes encephalitis usually lasts 10 days. Treatment for ~~and~~ neonatal herpes ~~Herpes simplex~~

infections usually lasts 14 days for mucocutaneous (skin-eye-mouth) infections and 21 days for disseminated or central nervous system disease~~10 days.~~

The duration of prophylactic administration of Zovirax I.V. is determined by the duration of the period at risk.

Dosage in adults:

Patients with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections should be given Zovirax I.V. in doses of 5 mg/kg body weight every 8 hours provided renal function is not impaired (see Dosage in renal impairment).

Immunocompromised patients with *Varicella zoster* infections or patients with herpes encephalitis should be given Zovirax I.V. in doses of 10 mg/kg body weight every 8 hours provided renal function is not impaired (see Dosage in renal impairment).

In obese patients dosed with intravenous aciclovir based on their actual body weight, higher plasma concentrations may be obtained (see 5.2 Pharmacokinetic properties). Consideration should therefore be given to dosage reduction in obese patients and especially in those with renal impairment or the elderly.

Dosage in children: The dose of Zovirax I.V. for children aged between 3 months and 12 years is calculated on the basis of body surface area.

Children 3 months of age or older with *Herpes simplex* (except herpes encephalitis) or *Varicella zoster* infections should be given Zovirax I.V. in doses of 250 mg per square metre of body surface area every 8 hours if renal function is not impaired.

In immunocompromised children with *Varicella zoster* infections or children with herpes encephalitis, Zovirax I.V. should be given in doses of 500 mg per square metre body surface area every 8 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 Zovirax I.V. in neonates and infants up to 3 months of age is calculated on the basis of body weight.

The recommended regimen for infants treated for known or suspected neonatal herpes is acyclovir 20 mg/kg body weight IV every 8 hours for 21 days for disseminated and CNS disease, or for 14 days for disease limited to the skin and mucous membranes.

Infants and children with impaired renal function require an appropriately modified dose, according to the degree of impairment (see Dosage in renal impairment).

~~Neonates and infants up to 3 months of age with *Herpes simplex* infections should be given Zovirax I.V. in doses of 10 mg/kg body weight every 8 hours. Treatment for neonatal herpes simplex infections usually lasts 10 days.~~

Dosage in the elderly:

The possibility of renal impairment in the elderly must be considered and dosage should be adjusted accordingly (see *Dosage in renal impairment* below).

Adequate hydration should be maintained.

Dosage in renal impairment:

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

Dosage adjustment for patients with renal impairment is based on creatinine clearance, in units of ml/min for adults and adolescents and in units of ml/min/1.73m² for infants and children less than 13 years of age. The following adjustments in dosage are suggested:

Dosage adjustments in adults and adolescents:

<u>Creatinine Clearance</u>	<u>Dosage</u>
25 to 50 ml/min	The dose recommended above (5 or 10 mg/kg body weight) should be given every 12 hours.
10 to 25 ml/min	The dose recommended above (5 or 10 mg/kg body weight) should be given every 24 hours.
0(anuric) to 10 ml/min	<p>In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommended above (5 or 10 mg/kg body weight) should be halved and administered every 24 hours.</p> <p>In patients receiving haemodialysis the dose recommended above (5 or 10 mg/kg body weight) should be halved and administered every 24 hours and after dialysis.</p>

Dosage adjustments in infants and children:

<u>Creatinine Clearance</u>	<u>Dosage</u>
<u>25 to 50 ml/min/1.73 m²</u>	<u>The dose recommended above (250 or 500 mg/m² body surface area or 20 mg/kg body weight) should be given every 12 hours.</u>
<u>10 to 25 ml/min/1.73 m²</u>	<u>The dose recommended above (250 or 500 mg/m² body surface area or 20 mg/kg body weight) should be given every 24 hours.</u>
<u>0(anuric) to 10 ml/min/1.73 m²</u>	<p><u>In patients receiving continuous ambulatory peritoneal dialysis (CAPD) the dose recommended above (250 or 500 mg/m² body surface area or 20 mg/kg body weight) should be halved and administered every 24 hours.</u></p> <p><u>In patients receiving haemodialysis the dose recommended above (250 or 500 mg/m² body surface area or 20 mg/kg body weight) should be halved and administered every 24 hours and after dialysis.</u></p>

Section 5.2:

In neonates (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 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). A separate group of neonates treated with 15 mg/kg every 8 hours showed approximate dose proportional increases, with a C_{max} of 83.5 micromolar (18.8 microgram/ml) and C_{min} of 14.1 micromolar (3.2 microgram/ml).

VI. REQUEST FOR SUPPLEMENTARY INFORMATION

Not applicable.

VII. LIST OF MEDICINAL PRODUCTS AND MARKETING AUTHORISATION HOLDERS INVOLVED

The list can be taken from the spreadsheet compiled from the EMEA