תאריך : דצמבר 2021

הנדון: <u>זובירקס IV / Zovirax IV</u>
Aciclovir 250 mg/vial
Powder for solution for infusion

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

חברת גלקסוסמיתקליין ישראל בע"מ (GSK) מבקשת להודיע על עדכון העלון לרופא של Zovirax IV.

בהודעה זו כלולים השינויים המהותיים בלבד. בעלונים ישנם שינויים נוספים.

טקסט חדש מסומן <u>בקו תחתי</u>. טקסט שנמחק מסומן ~~בקו חציה~~. טקסט המהווה החמרה מודגש בצהוב.

ההתוויה הרשומה לתכשיר בישראל:
Zovirax I.V. is indicated for the treatment of Herpes simplex infections in immunocompromised patients and severe initial genital herpes in the non-immunocompromised.
Zovirax I.V. is indicated for the prophylaxis of Herpes simplex infections in immunocompromised patients.
Zovirax I.V. is indicated for the treatment of Varicella zoster infections.
Zovirax I.V. is indicated for the treatment of herpes encephalitis.
Zovirax I.V. is indicated for the treatment of Herpes simplex infections in the neonate and infant up to 3 months of age.

העדכונים בעלון לרופא-

4.4 Special warnings and precautions for use

…
<u>Use in patients with renal impairment and in elderly patients:</u>
…
Reconstituted Zovirax I.V. has a pH of approximately 11 and should not be administered by mouth. Product contains sodium (~~26mg, approx. 1,13mmol~~ <u>28.03 mg sodium per vial</u>). To be taken into consideration by patients on a controlled sodium diet.
…

5.2 Pharmacokinetic properties

~~In adults, the terminal plasma half-life of aciclovir after administration of Zovirax I.V. is about 2.9 hours. Most of the drug is excreted unchanged by the kidney. Renal clearance of aciclovir is substantially greater than creatinine clearance, indicating that tubular secretion, in addition to glomerular filtration, contributes to the renal elimination of the drug. 9-carboxymethoxy-methylguanine is the only significant metabolite of aciclovir and accounts for 10 to 15% of the dose excreted in the urine.~~
~~When aciclovir is given one hour after 1 gram of probenecid, the terminal half-life and the area under the plasma concentration time curve, are extended by 18% and 40% respectively.~~
~~In adults, mean steady state peak plasma concentrations (C^{ss}max) following a one-hour infusion of 2.5 mg/kg, 5 mg/kg and 10 mg/kg were 22.7 micromolar (5.1 microgram/ml), 43.6 micromolar (9.8 microgram/ml) and 92 micromolar (20.7 microgram/ml) respectively. The corresponding trough levels (C^{ss}min) 7 hours later were 2.2 micromolar (0.5 microgram/ml), 3.1 micromolar (0.7 microgram/ml) and 10.2 micromolar (2.3 microgram/ml) respectively. In children over 1 year of age~~

~~similar mean peak (C^{ss}max) and trough (C^{ss}min) levels were observed when a dose of 250 mg/m^2 was substituted for 5 mg/kg and a dose of 500 mg/m^2 was substituted for 10 mg/kg. 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).~~

Absorption

Aciclovir is only partially absorbed from the gut. The average oral bioavailability varies between 10 and 20%. Under fasting conditions, mean peak concentrations (C_{max}) of 0.4 microgram/ml are achieved at approximately 1.6 hours after a 200 mg dose administered as oral suspension or capsule. Mean peak plasma concentrations (C_{ssmax}) increase to 0.7 microgram/ml (3.1 micromoles) at steady state following doses of 200 mg administered every four hours. A less than proportional increase is observed for C_{ssmax} concentrations following doses of 400 mg and 800 mg administered four-hourly, with values reaching 1.2 and 1.8 microgram/ml (5.3 and 8 micromoles), respectively.

Distribution

The mean volume of distribution of 26 L indicates that aciclovir is distributed within total body water. Apparent values after oral administration (Vd/F) ranged from 2.3 to 17.8 L/kg. As plasma protein binding is relatively low (9 to 33%), drug interactions involving binding site displacement are not anticipated. Cerebrospinal fluid concentrations are approximately 50% of corresponding plasma concentrations at steady-state.

Metabolism

Aciclovir is predominantly excreted unchanged by the kidney. The only significant urinary metabolite is 9-[(carboxymethoxy) methyl]guanine, and accounts for 10-15% of the dose excreted in the urine.

Elimination

In adults mean systemic exposure (AUC0-∞) to aciclovir ranges between 1.9 and 2.2 microgram*h/mL after a 200 mg dose. At this dose, the mean terminal plasma half-life after oral administration has been shown to vary between 2.8 and 4.1 hours.

In adults, the terminal plasma half-life of aciclovir after administration of Zovirax I.V. is about 2.9 hours. Renal clearance of aciclovir (CLr= 14.3 L/h) is substantially greater than creatinine clearance, indicating that tubular secretion, in addition to glomerular filtration, contributes to the renal elimination of the drug. The half-life and total clearance of aciclovir are dependent on renal function. Therefore, dosage adjustment is recommended for renally impaired patients.

In adults, mean steady state peak plasma concentrations (C^{ss}max) following a one-hour infusion of 2.5 mg/kg, 5 mg/kg and 10 mg/kg were 22.7 micromolar (5.1 microgram/ml), 43.6 micromolar (9.8 microgram/ml) and 92 micromolar (20.7 microgram/ml) respectively. The corresponding trough concentrations (C^{ss}min) 7 hours later were 2.2 micromolar (0.5 microgram/ml), 3.1 micromolar (0.7 microgram/ml) and 10.2 micromolar (2.3 microgram/ml) respectively. In children over 1 year of age similar mean peak (C^{ss}max) and trough (C^{ss}min) concentrations were observed when a dose of-250 mg/m^2 was substituted for 5 mg/kg and a dose of 500 mg/m^2 was substituted for 10 mg/kg.

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). The terminal plasma half-life in these patients was 3.8 hours.

~~The terminal plasma half-life in these patients was 3.8 hours.~~

Special Patient Populations

Elderly

In the elderly patients with normal renal function total clearance falls with increasing age due to decreases in creatinine clearance. However, the possibility of renal impairment in the elderly must be considered and the dosage should be adjusted accordingly.

~~In the elderly, total body clearance falls with increasing age and is associated with decreases in creatinine clearance although there is little change in the terminal plasma half-life.~~

Renal impairment

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

Weight

In a clinical study in which morbidly obese female patients (n=7) were dosed with intravenous aciclovir based on their actual body weight, plasma concentrations were found to be approximately twice that of normal weight patients (n=5), consistent with the difference in body weight between the two groups.

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

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

…

6.2 Incompatibilities

The reconstituted concentrate and diluted solution for infusion must not be mixed with other medicinal products except those mentioned in Section 6.6. ~~None known~~

העלון לרופא והעלון לצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
ניתן לקבלם מודפסים על-ידי פניה לחברת גלקסוסמיתקליין https://data.health.gov.il/Drugs/index.html#!/byDrug
רח' בזל 25 פתח תקוה בטלפון: 03-9297100.

בברכה,
שני לוי
רוקחת ממונה