דצמבר 2021

הנדון:
Zovirax Tablets 200 mg, 400 mg/ זובירקס טבליות 200 מ"ג, 400 מ"ג
Zovirax Tablets Dispersible 800 mg / זובירקס טבליות מסיסות 800 מ"ג
Aciclovir
Tablets / Dispersible Tablets

רופא/ה נכבד/ה, רוקח/ת נכבד/ה,

חברת גלקסוסמיתקליין ישראל בע"מ (GSK) מבקשת להודיע על עדכון העלונים לרופא ולצרכן של התכשירים שבנדון.

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

טקסט חדש מסומן בקו תחתי. טקסט שנמחק מסומן ~~בקו חציה~~. טקסט המהווה החמרה מודגש בצהוב.

ההתוויות הרשומות לתכשירים בישראל:

Zovirax Tablets 200mg,
Zovirax Tablets 400mg:

- 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).
- Zovirax Tablets are indicated for the suppression (prevention of recurrences) of recurrent herpessimplex infections in immunocompetent patients.
- Zovirax Tablets are indicated for the prophylaxis of herpes simplex infections in immunocompromised patients.
- Zovirax Tablets are indicated for the treatment of varicella (chickenpox) and herpes zoster (shingles) infections.

Zovirax Tablets Dispersible 800 mg:
Zovirax tablets 800 mg are indicated for the treatment of varicella (chickenpox) and herpes zoster (shingles) infections (excluding neonatal HSV and severe HSV infections in immunocompromised children).
Zovirax 800mg tablets is recommended in children over the age of 6.

עדכונים בעלון לרופא:

4.4. Special Warnings and Precautions for Use

…

This medicine contains less than 1 mmol sodium (23 mg) per dosage unit, that is to say essentially 'sodium-free'.

5.2. Pharmacokinetic Properties

~~Zovirax Tablets 200mg, Zovirax Tablets 400mg:~~

~~Mean steady state peak plasma concentrations (C^{SS}max) following doses of 200 mg administered four-hourly were 3.1 microMol (0.7 micrograms/ml) and equivalent trough plasma levels (C^{SS}min) were 1.8 microMol (0.4 micrograms/ml). Corresponding C^{SS}max levels following doses of 400 mg and 800 mg administered four-hourly were 5.3 microMol (1.2 micrograms/ml) and 8 microMol (1.8 micrograms/ml) respectively and equivalent C^{SS}min levels were 2.7 microMol (0.6 micrograms/ml) and 4 microMol (0.9 micrograms/ml).~~

~~Zovirax Dispersible Tablets 800mg:~~

~~Mean steady state peak plasma concentrations (C^{SS}max) following doses of 800 mg Aciclovir administered four-hourly were 8 microMol (1.8 micrograms/ml) and equivalent trough plasma levels were 4 microMol (0.9 micrograms/ml).~~

~~In adults the terminal plasma half-life of aciclovir after administrations of intravenous aciclovir is about 2.9 hours. Most of the drug is excreted unchanged by the kidney. Renal clearance of aciclovir is substantially greater than creatinine clearance, indicating that tubular secretion, in addition to glomerular filtration contributes to the renal elimination of the drug. 9-carboxymethoxymethylguanine is the only significant metabolite of aciclovir, and accounts for approximately 10 - 15% of the administered 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 is 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 microMol (5.1 micrograms/ml), 43.6 microMol (9.8 micrograms/ml) and 92 microMol (20.7 micrograms/ml), respectively. The corresponding trough levels (C^{SS}min) 7 hours later were 2.2 microMol (0.5 micrograms/ml), 3.1 microMol (0.7 micrograms/ml), and 10.2 microMol (2.3 micrograms/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 and young infants (0 to 3 months of age) treated with doses of 10 mg/kg administered by infusion over a one-hour period every 8 hours the C^{SS}max was found to be 61.2 microMol (13.8 micrograms/ml) and C^{SS}min to be 10.1 microMol (2.3 micrograms/ml). The terminal plasma half-life in these patients was 3.8 hours. 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). In the elderly, total body clearance falls with increasing age associated with decreases in creatinine clearance although there is little change in the terminal plasma half-life.~~

~~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.~~

Zovirax Tablets 200mg, Zovirax Tablets 400mg:

Acyclovir is incompletely absorbed from the GI tract. Approximately 20% is absorbed shortly after administration. When the dose is increased to 600 mg or more, acyclovir is absorbed relatively less well.
The maximum steady-state plasma concentration ($C_{ss\ max}$) after a 200-mg dose given at four-hour intervals was 3 micromol/L, and the lowest concentration ($C_{ss\ min}$) was 1.6 micromol/L. Corresponding concentrations after a 800-mg dose were 6.9 and 3.5 micromol/L, respectively. Most of it is excreted unchanged via the kidneys.

When a group of neonates were treated with acyclovir 15 mg/kg every eight hours, an approximate dose-dependent increase was observed, with a C_{max} of 83.5 micromol/L (18.8 micrograms/mL) and a C_{min} of 14.1 micromol/L (3.2 micrograms/mL).

As renal excretion of acyclovir exceeds creatinine clearance, elimination is likely to occur by both glomerular filtration and tubular secretion. Acyclovir has a plasma half-life of approximately three hours in patients with normal renal function. Acyclovir's only significant metabolite is 9-carboxymethoxymethylguanine, which makes up 10–15% of the excreted drug in the urine. In chronic renal failure, the mean terminal half-life of the drug is on average 19.5 hours. The mean concentration of acyclovir decreases by approximately 60% during dialysis.

In the elderly, total clearance decreases with age, associated with a decrease in creatinine clearance. However, the terminal half-life does not change much. Administration of acyclovir and zidovudine to HIV patients did not cause any measurable changes in the pharmacokinetics of any of the substances. No mutagenicity was observed in the studies on nine of eleven microbial or mammalian cells. An effect was observed in two studies on mammalian cells, but in this case the concentrations were at least x times higher than the plasma concentrations in humans (x depends on the route of administration: 25-fold after i.v. and 150-fold after oral administration).

Zovirax Tablets Dispersible 800mg:
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} concentration 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 concentration are approximately 50% of corresponding plasma concentration 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.
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.

There are no pharmacokinetic data for the oral formulation in neonates. The only available pharmacokinetic data are for the IV formulation in this age group

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.

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 concentration ~~levels~~ dropped approximately 60% during dialysis.

6.2. Incompatibilities

There are no special requirements for use on handling of this product. ~~None known.~~

עדכונים בעלון לצרכן:

2. לפני שימוש בתרופה

...

מידע חשוב על חלק מהמרכיבים של התרופה

זובירקס מכילה פחות מ-1mmol נתרן (23 מ"ג) לטבליה, לכן ניתן לומר כי היא למעשה נטולת נתרן.

...

העלון לרופא והעלון לצרכן נשלחו לפרסום במאגר התרופות שבאתר משרד הבריאות:
https://www.old.health.gov.il/units/pharmacy/trufot/index.asp?safa=h וניתן לקבלם מודפסים על-ידי פניה לחברת גלקסוסמיתקליין רח' בזל 25 פתח תקוה בטלפון: 03-9297100.

בברכה,
שני לוי
רוקחת ממונה