Orchidia Pharmaceutical Ind.

SAE

Ganvir

Sterile Ophthalmic Gel

1. Name of the medicinal product

GANVIR ~~eye~~ gel.
ophthalmic

2. Qualitative and quantitative composition

Active Ingredient.

Ganciclovir 0.15%.

3. Pharmaceutical form

~~Eye~~ gel.
ophthalmic

4. Clinical particulars

4.1 Therapeutic indications

Treatment of acute herpetic keratitis (dendritic and geographic ulcers).

4.2 Posology and method of administration

Instil one drop of gel in the inferior conjunctival sac of the eye to be treated, 5 times a day until complete corneal reepithelialisation. Then 3 instillations a day for 7 days after healing. The treatment does not usually exceed 21 days.

Use in the elderly:

The dosage in the elderly is the same as in adults (see above). There is no need to adjust the dosage in the elderly as inclinical trials patients up to the age of 85 years have been treated and no specific health concerns were observed.

Use in children:

GANVIR eye gel is not recommended for use in children.

Only limited clinical trial data are available (7 children, range 2-14 years).

Orchidia Pharma Scientific Office:
117 AL Thawra St., Heliopolis, P.O. Box 11341 Cairo, Egypt. Tel. : +202 22916920 Fax : +202 22914210
E-mail: info@orchidiapharma.com www.orchidiapharma.com

4.3 Contraindications

Hypersensitivity to ganciclovir or acyclovir or to any other ingredients of the product.

4.4 Special warnings and precautions for use

The following special warnings and precautions for use should be borne in mind, although systemic effects after ocularinstillation are very unlikely. In preclinical testing ganciclovir given systemically caused aspermatogenesis, mutagenicity,teratogenicity, carcinogenicity and suppression of female fertility. These effects in animal studies have been observed atplasma concentrations far exceeding those being seen in humans after therapeutic use of GANVIR Eye Gel .However, ganciclovir should be considered a potential carcinogen and teratogen in humans.

Benzalkonium chloride :

- May cause eye irritation
- Avoid contact with soft contact lenses
- Remove contact lenses prior to application and wait at least 15 minutes before reinsertion, known to discolor soft contact lenses.

4.5 Interaction with other medicinal products and other forms of interaction

In case of any additional local ocular treatment there should be an application interval of at least 5 minutes between the twomedications. GANVIR Eye Gel should be the last medication instilled.

Although the quantities of ganciclovir passing into the general circulation after ophthalmic use are small, the risk of druginteractions cannot be ruled out.

Interactions with ganciclovir administered systemically have been observed:

Binding of ganciclovir to plasma proteins is only about 1-2% and drug interactions involving binding site displacement are notanticipated.

It is possible that drugs which inhibit replication of rapidly dividing cell populations such as bone marrow, spermatogonia andgerminal layers of skin and gastrointestinal mucosa might have combined additive toxic effects when used concomitantlywith, before or after ganciclovir. Because of the possibility of additive toxicity with co-administration of drugs such as dapsone,pentamidine, flucystosine, vincristine, vinblastine, adriamycin, amphotericin B, trimethoprim/sulpha combinations or othernucleoside analogues, combination with ganciclovir therapy should be used only if the potential benefits outweigh the risks.

Since both zidovudine and ganciclovir can result in neutropenia, it is recommended that these two drugs should not be givenconcomitantly during induction treatment with ganciclovir. Maintenance ganciclovir treatment plus zidovudine at therecommended dose resulted in severe neutropenia in most patients studied to date.

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generalised seizures have been reported in patients taking ganciclovir and imipenem-cilastatin concomitantly.

It is also possible that probenecid, as well as other drugs which inhibit renal tubular secretion or resorption, may reduce renalclearance of ganciclovir and could increase the plasma half-life of ganciclovir.

4.6 Pregnancy and lactation

Teratogenicity has been observed in animal studies with systemic ganciclovir. There is no experience regarding the safety of GANVIR eye gel in human pregnancy or lactation. Administration during pregnancy and lactation is therefore notrecommended, except for compelling reasons.

4.7 Effects on ability to drive and use machines

Patients should refrain from driving a vehicle or operating machines on the occurrence of any visual disturbance or othervisual symptomatology.

4.8 Undesirable effects

In some cases, adverse events which did not result in a treatment interruption were observed in relation to the use of GANVIR eye gel: burning sensations or brief tingling sensations, superficial punctate keratitis, visual disturbance on application.

4.9 Overdose

There is practically no risk of adverse events due to accidental oral ingestion since a bottle of 5g contains 7.5mg ganciclovircompared to the daily adult i.v. dose of 500-1000mg.

In the unlikely event of overdose, dialysis and hydration may be of benefit in reducing drug plasma levels.

Toxic manifestations seen in animals given very high single intravenous doses of ganciclovir (500mg/kg) included emesis,hypersalivation, anorexia, bloody diarrhoea, inactivity, cytopenia, abnormal liver function tests and BUN, testicular atrophy anddeath.

5. Pharmacological properties

5.1 Pharmacodynamic properties

GANVIR is a formulation of 0.15% ganciclovir in a transparent aqueous gel with a hydrophilic polymer base.

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ganciclovir, 9-(1,3-dihydroxy-2-propoxymethyl)guanine or DHPG, is a broadspectrum virustatic agent which inhibits thereplication of viruses, including viruses of the herpes group, both in vivo and in vitro: herpes simplex types 1 and 2 (HSV),cytomegalovirus (CMV), Epstein-Barr virus (EBV), herpes zoster (HZV).

The mean effective dose (ED50) in vitro of ganciclovir on ocular clinical isolates of the herpes simplex virus is on average 0.23µg/ml (0.06 - 0.50).

Ganciclovir inhibits in vitro the replication of various adenovirus serotypes.

The ED50 is 1.8 to 4.0 µg/ml for Ad 8 and Ad 19, those most frequently seen in ophthalmology.

Herpetic viruses induce one or more cellular kinases in the host cells, which phosphorylise the ganciclovir into itstriphosphate derivative. This phosphorylation is carried out mainly in infected cells, as the concentrations of ganciclovir-triphosphatein non-infected cells are 10 times lower.

Ganciclovir-triphosphate works as an antiviral agent by inhibiting the synthesis of viral DNA in two ways: competitive inhibitionof viral DNA polymerases and direct incorporation into viral DNA which has the effect of stopping its elongation.

5.2 Pharmacokinetic properties

Studies of ocular pharmacokinetics in rabbits have shown a rapid and relevant penetration of ganciclovir into the cornea andthe anterior segment of the eye, allowing concentrations higher than the effective antiviral concentrations over several hours.

In fact, after instillation of one drop of ganciclovir gel, the concentrations (Cmax) of ganciclovir measured in the cornea(17µg/g), the conjunctiva (160µg/g), the aqueous humour (1µg/ml) and the iris/ciliary body (4µg/g), are higher than the inhibitoryconcentrations for herpes simplex viruses 1 and 2 (< 0.5µg/ml) over more than 4 hours.

The repeated instillation 4 times a day for 12 days in rabbits with herpetickeratitis does not result in an accumulation ofganciclovir in the plasma.

In man, after daily ocular instillations repeated 5 times a day for 11 to 15 days in the course of treatment of superficial herpetickeratitis, plasma levels determined by means of a precise analytical method (quantification limit: 0.005µg/ml) are very low: onaverage 0.013µg/ml (0 - 0.037) which is 640 times lower than levels following a one hour iv infusion of 5mg/kg (Cmax = 8.0µg/ml). The oral bioavailability of ganciclovir is approximately 6% when taken with food. Ganciclovir has a half life of 2.9 hours,the systemic clearance is 3.64 ml/min/kg and the major route of excretion of ganciclovir is via glomerular filtration ofunchanged drug.

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6. Pharmaceutical particulars

6.1 List of excipients

Benzalkonium chloride

Carbopol 974P

Mannitol

1N Sodium hydroxide

Water for injection

الإدارة المركزية للشئون الصيدلية
الإدارة العامة للتسجيل
إدارة إستقبال الأدوية البشرية
وارد برقم : 3

6.2 Special precautions for storage

~~Do not store above 30°C.~~ Store at temperature not exceeding 30 C°, after opening, Store at temperature not exceeding 30 C° for 30 days

6.3 Nature and contents of container

A carton box containing white (LDPE) plastic bottle with white (HDPE) dropper covered with white (PP) plastic cap containing 6gm gel and insert leaflet.

Manufactured by

Orchidia Pharmaceuticals Industries

Industrial Zone-AlObour City, Egypt.

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