VIRGAN 1.5 mg/g eye gel

1. NAME OF THE MEDICINAL PRODUCT
VIRGAN 1.5 mg/g eye gel

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
1 g gel contains 1.5 mg Ganciclovir.
Excipient with known effect: Benzalkonium chloride (75 µg/g)
For full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Eye gel
Colourless opalescent gel.

4. CLINICAL PARTICULARS
4.1 Therapeutic indications
Virgan is indicated for the treatment of superficial acute herpes simplex keratitis (dendritic and geographic ulcers) (see section 4.4.).

4.2 Posology and method of administration
Posology
1 drop 5 times daily until complete corneal re-epithelialization, then 1 drop 3 times daily for 7 days.
Treatment duration does not generally exceed 21 days.
Paediatric population
Use of the medicinal product in children under 18 years is not recommended since no specific studies have been conducted.

Method of administration
By ocular instillation in the inferior conjunctival cul-de-sac of the affected eye.

4.3 Contraindications
Hypersensitivity to the active subtance, aciclovir or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use
This medicinal product is not indicated in the treatment of cytomegalovirus (CMV) retina infections.
Efficacy in other viral types of keratoconjunctivitis has not been demonstrated.
No specific clinical studies were performed in immunodepressed subjects.
This medicine contains 2.625 micrograms benzalkonium chloride in each drop of gel which is equivalent to 0.075 mg/g.
Benzalkonium chloride may be absorbed by soft contact lenses and may change the colour of the contact lenses. Contact lenses should be removed before using this medicine and put back 15 minutes afterwards.
Benzalkonium chloride may also cause eye irritation, especially with dry eyes or disorders of the cornea. Patients should be instructed to talk to a doctor if they feel abnormal eye sensation, stinging or pain in the eye after using this medicine. Avoid contact with soft contact lenses.

4.5 Interaction with other medicinal products and other forms of interaction
If more than one topical ophthalmic drug is being used, the drugs should be administered at least fifteen minutes apart. Virgan should be instilled last.
Although the quantities of ganciclovir passing into the general circulation after ophthalmic use are small, the risk of drug interactions cannot be ruled out.

Interactions with ganciclovir administered systemically have been observed.
Binding of ganciclovir to plasma proteins is only 1-2% and drug interactions involving binding site displacement are not anticipated.

It is possible that drugs which inhibit replication of rapidly dividing cell populations such as bone marrow, spermatogonia and geminal layers of skin and gastrointestinal mucosa might have combined additive toxic effects when used concomitantly with, before or after ganciclovir. Because of the possibility of additive toxicity with the co-administration of drugs such as dapsone, pentamidine, fluocytosine, vincristine, vinblastine, adriamycin, amphotericim B, trimethoprim/sulpha combinations or other nucleoside 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 given concomitantly during induction treatment with ganciclovir. Maintenance ganciclovir treatment plus zidovudine at the recommended dose resulted in severe neutropenia in most patients studied to date.

Generalized 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 renal clearance of ganciclovir and could increase the plasma half-life of ganciclovir.

4.6 Fertility, pregnancy and lactation

There is insufficient experience regarding administration during pregnancy or lactation for evaluating the safety of VIRGAN during these periods.

Teratogenicity and effect on fertility have been observed in animal studies with orally or intravenous administered ganciclovir. Furthermore ganciclovir had shown potential genotoxicity with low safety margin (see section 5.3).

Consequently, administration during pregnancy or lactation is therefore not recommended, except in the absence of an alternative treatment. For women of childbearing age, contraceptives measures should be used during treatment and for up to six months thereafter.

Due to the genotoxic effect in animal studies, men taking VIRGAN are advised to use local contraceptive measure (as condom) during treatment and for up to three months thereafter.

4.7 Effects on ability to drive and use machines

The patient should refrain from driving or operating machines on the occurrence of any visual disturbance on application.

4.8 Undesirable effects

The following adverse reactions were reported during four clinical trials with VIRGAN 1.5 mg/g eye gel (three phase IIB trials and one Phase III trial)

Adverse events are categorized by frequency as follows: very common (≥ 1/10), common (≥ 1/100 to <1/10), uncommon (≥ 1/1,000 to <1/100), rare (≥ 1/10,000 to <1/1,000) and very rare (<1/10,000). Not known (cannot be estimated from the available data).

Eye disorders

Very common:

Transient burning or stinging sensations, eye irritation, blurred vision.

Common:

Superficial punctate keratitis, conjunctival hyperaemia.

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

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

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

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
VIRGAN ® is a formulation of 0.15% ganciclovir in a transparent aqueous gel with a hydrophilic polymer base.

Pharmacotherapeutic group: Antiinfectives, antivirals; ATC code: S01AD09
Ganciclovir, 9-[(1 ,3-dihydroxy-2-propoxy)methyl]guanine or DHPG, is a broad-spectrum virustatic agent which inhibits the replication of viruses, including viruses of the *Herpes* group, both *in vivo* and *in vitro*: herpes simplex type 1 and 2 (HSV), cytomegalovirus (CMV), Epstein-Barr virus (EBV) and Herpes zester (HZV).

The mean effective dose (ED50) *in vitro* of ganciclovir on ocular clinical isolates of the herpes simplex virus is on average 0.23 µg/ml (0.60-0.50). 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 its triphosphate derivative. This phosphorylation is carried out mainly in infected cells, as the concentrations of ganciclovir-triphosphate in non-infected cells are 10 times lower.

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

5.2 Pharmacokinetic properties
In humans after ocular instillation 5 times daily for 11 to 15 days during treatment of superficial herpetic keratitis, the plasma levels determined by means of a sensitive analytical method (quantification limit: 0.005 µg/ml) are very low: 0.013 µg/ml on average (0-0.037).
Ocular pharmacokinetics studies in rabbits evidenced rapid and relevant penetration of ganciclovir into the cornea and the anterior segment of the eye, allowing concentrations higher than the median effective doses (ED50) for several hours.

5.3 Preclinical safety data
Carcinogenic and mutagenic potential
Carcinogenic effects in animals were only seen following long term systemic exposure (20 mg/kg orally) with 50-fold the systemic exposure of patients treated with VIRGAN.
Ganciclovir was only positive in three of five different types of genotoxicity assay. Positive results were obtained in the most sensitive assay (mouse lymphoma) at 7,500-fold the systemic exposure in

patients treated with VIRGAN, and in the mouse micronucleus assay at 50 mg/kg/iv corresponding to 15,000 times the plasma levels during ocular therapy with VIRGAN.

Reproduction, fertility

Intravenous and oral studies with ganciclovir in animals resulted in testicular and ovarian suppression with consequential effects on fertility. Toxicity to the male reproductive system occurred following the systemic exposure of 12-fold in dogs and 19-fold in mice of the systemic exposure of patients treated with VIRGAN. There was impairment of reproductive performance in male mice at 60-fold the systemic exposure of VIRGAN patients. Impairment of reproductive performance in female mice occurred at 3000-fold the systemic exposure of patients treated with VIRGAN. Teratogenic effects in rabbits occurred at 100-fold the systemic exposure in patients treated with VIRGAN.

Ocular toxicity

Ocular use of VIRGAN during 28 days in rabbits, with 5 instillations per day, did not demonstrate any local or systemic toxic effect.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Carbomer (Carbopol 974P), Sorbitol, Sodium hydroxide (pH adjuster), Benzalkonium chloride and water for injections.

6.2 Shelf life

Before opening: 3 years.
After opening: 4 weeks.

6.3 Special precautions for storage

Do not store above 30°C

6.4 Nature and contents of container

Tube (LDPE/copolymer/aluminium/copolymer/HDPE) with a nozzle (HDPE) and screw cap (HDPE).
Pack size: 1 tube of 5 g eye gel.

7. NAME AND ADDRESS OF MANUFACTURER

FARMILA-THEA FARMACEUTICI SpA, Via Enrico Fermi, 50 SETTIMO MILANESE (MI) ITALY

8. DATE OF REVISION OF THE TEXT

July 2024