SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

VIRGAN 0.15% w/w eye gel.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 g gel contains 1.5 mg ganciclovir (0.15% w/w)

Excipient with known effect: benzalkonium chloride (75 µg/g)

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Eye gel. Colourless opalescent gel.

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 re-epithelialisation. 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 in clinical trials patients up to the age of 85 years have been treated and no specific health concerns were observed.

Use in children:

Use of the medicinal product in children under 18 years is not recommended since no specific studies have been conducted.

Method of administration

Ocular instillation.

4.3 Contraindications

Hypersensitivity to ganciclovir or acyclovir 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.

Benzalkonium chloride may cause eye irritation. Avoid contact with soft contact lenses. Remove contact lenses prior to application and wait at least 15 min before reinsertion. Known to discolour 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 about 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 germinal 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 co-administration of drugs such as dapsone, pentamidine, flucystosine, vincristine, vinblastine, adriamycin, amphotericin 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.

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

4.6 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.

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

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

4.8 Undesirable effects

Eye disorders
- Very common (>1/10): Transient burning or stinging sensations
- Common (>1/100, <1/10): Superficial punctate keratitis.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme. Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

There is practically no risk of adverse events due to accidental oral ingestion since a tube of 5g contains 7.5mg ganciclovir compared 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 and death.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antiinfectives, antivirals; ATC code: S01AD09

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

Ganciclovir, 9-(1,3-dihydroxy-2-propoxymethyl)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 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 0.23 μg/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 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 agent by inhibiting the synthesis of viral DNA in two ways: competitive inhibition of 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 and the 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/g) and the iris/ciliary body (4μg/g), are higher than the inhibitory concentrations 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 herpetic keratitis does not result in an accumulation of ganciclovir 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 herpetic keratitis, plasma levels determined by means of a precise analytical method (quantification limit: 0.005μg/ml) are very low: on average 0.013μg/ml (0 - 0.037) which is 640 times lower than levels following a one hour iv infusion of 5mg/kg (Cmax = 8.0 μg/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 of unchanged drug.

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. Ganciclovir had no effect on developing mouse foetuses at daily intravenous doses of 36mg/kg, but caused maternal/foetal toxicity and embryo death at daily doses of 108mg/kg. 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

Benzalkonium chloride
Carbomer 974P
Sorbitol
Sodium hydroxide
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

In the unopened container: 3 years.

In the opened container : 4 weeks.

6.4 Special precautions for storage

Do not store above 25°C.

6.5 Nature and contents of container

5g tube (polyethylene-aluminium) with dropper nozzle (polyethylene) and screw cap (polyethylene).

6.6 Special precautions for disposal and other handling

No special requirements for disposal.
Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER(S)

PL 20162/0006

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

First Authorisation: 21/07/2000

Renewal: 20/07/2005

10 DATE OF REVISION OF THE TEXT

10/01/2016