Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Zovirax Duo 50 mg/g and 10 mg/g Cream

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

1 gram cream contains 50 mg aciclovir and 10 mg hydrocortisone.

Excipients with known effect: 67,5 mg cetostearyl alcohol, 8 mg sodium laurilsulphate and 200 mg propylene glycol / gram cream.

For the full list of excipients, see section 6.

3 PHARMACEUTICAL FORM

Cream
White to yellowish cream

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of early signs and symptoms of recurrent herpes labialis (cold sores) to reduce the progression of cold sore episodes to ulcerative lesions in immunocompetent adults and adolescents (12 years of age and older).

4.2 Posology and method of administration

Posology.

Adults and adolescents (12 years of age and older).

Zoviduo should be applied five times per day for 5 days, (i.e. approximately every 3-4 hours omitting the night time application). Treatment should be initiated as early as possible, preferably immediately after the first signs or symptoms. A sufficient quantity of the cream should be applied each time to cover the affected area including the outer margin of the lesions, if present.

Treat for 5 days. If lesions are still present 5 days after completed treatment, users should be advised to consult a doctor.

Paediatric population

The safety and efficacy of Zoviduo in children below 12 years have not yet been established.

Method of administration

Cutaneous use only.

Users should wash their hands before and after applying the cream and avoid unnecessary rubbing of the lesions or touching them with a towel, to avoid aggravating or transferring the infection.

4.3 Contraindications

Hypersensitivity to the active substances, valaciclovir or to any of the excipients listed in section 6.1.

Use for skin lesions caused by any virus other than herpes simplex, or for fungal, bacterial or parasitic skin infections.

4.4 Special warnings and precautions for use

For cutaneous use only: to be applied to lesions on the lips and skin close to the lips. It is not recommended for application to mucous membranes (e.g.in the eye or inside the mouth or nose or on the genitals).

Zoviduo should not be used to treat genital herpes.

Particular care should be taken to avoid contact with the eye.

In patients with severe recurrent herpes labialis, other underlying disease should be excluded.

Do not use with occlusive dressings, such as plasters or specialised cold sore patches/plasters.

Zoviduo is not recommended for use by immunocompromised patients due to the possibility of pseudo-opportunistic infections or drug resistant strains which require systemic antiviral therapy**.** Immunocompromised patients should be advised to consult a doctor concerning the treatment of any infection.

Cold sore sufferers should be advised to avoid transmitting the virus, particularly when active lesions are present (e.g. wash hands before and after application).

Long-term continuous use should be avoided. Do not use for longer than 5 days.

Treatment of patients with concomitant dermatitis of other origin has not been studied.

Contains cetostearyl alcohol which may cause local skin reactions (e.g. contact dermatitis).
This medicine contains 200mg/g of propylene glycol

This medicine contains 8mg/g of sodium laurilsulfate. Sodium laurilsulfate may cause local skin reactions (such as stinging or burning sensation) or increase skin reactions caused by other products when applied on the same area.

Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed wth Zovirax Duo.

4.6 Fertility, pregnancy and lactation

<u>Pregnancy</u>

The use of Zovirax Duo should be considered only when the potential benefits outweigh the possibility of unknown risks. However, the systemic exposure to aciclovir and hydrocortisone from topical application of the cream is very low.

A post-marketing aciclovir pregnancy registry has documented pregnancy outcomes in women exposed to any formulation of aciclovir. The registry findings have not shown an increase in the number of birth defects amongst subjects exposed to aciclovir compared with the general population.

Extensive clinical data available with hydrocortisone do not indicate an increased risk of teratogenicity with the clinical use of topical corticosteroids. Adverse findings with regards to developmental toxicity have been observed in animal studies at low exposures.

Breast-feeding

Aciclovir and hydrocortisone pass into milk after systemic administration. However, the dosage received by a nursing infant following maternal use of Zovirax Duo would be insignificant.Zovirax Duo should however not be used during lactation unless clearly necessary.

Fertility

There are no data in humans to evaluate the effect of topical Zovirax Duo on fertility.

4.7 Effects on ability to drive and use machines

Zovirax Duo has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: 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), very rare (<1/10,000) and not known (cannot be estimated from the available data).

System Organ Class	Adverse Reaction/Event	Frequency
Skin and subcutaneous tissue disorders	Drying or flaking of the skin	Common
	Transient burning, tingling or stinging (following application of the product) Itching	Uncommon
	Erythema Pigmentation changes Contact dermatitis following application has been observed when applied under occlusion in dermal safety studies. Where sensitivity tests have been conducted, the reactive substance was hydrocortisone or a component of the cream base. Application site reactions including signs and symptoms of inflammation.	Rare
Immune system disorders	Immediate hypersensitivity reactions including angioedema	Very rare
Eye disorder	Vision, blurred	Not known

Based on post-marketing experience with single active aciclovir, immediate hypersensitivity reactions including angioedema have been identified as a very rare adverse reaction.

Paediatric population

The safety profile in adolescents (12-17 years) was similar to that in adults.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: www.hpra.ie; E-mail: medsafety@hpra.ie.

4.9 Overdose

No untoward effects would be expected if the entire contents of a 2 g tube of Zovirax Duo cream were ingested orally, or applied topically due to minimal systemic exposure. In the event of a suspected overdose treatment should be symptomatic.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antivirals, ATC code: D06BB53.

Zovirax Duo is a combination of aciclovir 5% w/w and hydrocortisone 1% w/w.

Mechanism of action

Aciclovir is an antiviral agent which is highly active *in vitro* against herpes simplex virus (HSV) types 1 and 2. Aciclovir is phosphorylated after entry into herpes infected cells to the active compound aciclovir triphosphate. The first step in this process is dependent on the presence of the HSV-coded enzyme thymidine kinase. Aciclovir triphosphate acts as an inhibitor of, and substrate for the herpes-specified DNA polymerase, preventing further viral DNA synthesis without affecting normal cellular processes.

Hydrocortisone is a mild corticosteroid that exerts a range of immunomodulatory effects. When applied topically, its primary role is to control various inflammatory skin disorders.

Zovirax Duo, which combines the antiviral activity of aciclovir and the anti-inflammatory action of hydrocortisone, reduces the progression of cold sore episodes intoulcerative lesions. The exact mechanism for this is not fully characterised but is thought to be mediated through clearance of the virus and mitigating the local inflammatory response in the lip leading to lessening of the signs and symptoms.

Clinical efficacy and safety

Adults:

In a double-blind, randomised clinical study 1443 subjects with recurrent labial herpes were treated either with Zovirax Duo, aciclovir 5% in vehicle cream or vehicle cream alone. The primary endpoint was prevention of progression of cold sores episodes to ulcerative lesions. Among subjects treated with Zovirax Duo 58% developed ulcerative lesions compared with 65% in subjects treated with 5% aciclovir in Zovirax Duo vehicle ($p=0.014$) and 74% in subjects treated with vehicle cream alone ($p<0.0001$). In those subjects that developed ulcerative lesions, the mean episode duration was 5.7, 5.9 and 6.5 days, for Zovirax Duo cream, aciclovir 5% in vehicle cream or vehicle alone, respectively ($p=0.008$ for the comparison between Zovirax Duo with vehicle cream alone).

Paediatric population

An open label safety study in adolescents with recurrent herpes labialis was conducted in 254 subjects between 12-17 years. Therapy was applied using the same dosing regimen as in adults and subjects were followed for adverse events. The safety and efficacy profile was similar to that observed in adults.

Immunocompromised patients

Safety was studied in a randomised, double-blind clinical study in 107 adult subjects with mild to moderate immunosuppression treated with either Zovirax Duo cream or aciclovir 5% in vehicle cream. Safety and frequency of recurrences during a follow-up period of 1 year after treatment of a herpes simplex virus recurrence were similar between the two treatment groups.

5.2 Pharmacokinetic properties

No clinical pharmacokinetic studies have been performed with Zovirax Duo.

Absorption

Due to limited absorption, the systemic exposure of aciclovir is expected to be low following topical administration of aciclovir and hydrocortisone cream.

Glucocorticoids have the ability to penetrate stratum corneum of the epidermis and affect the deeper cell layers. Usually only a small proportion of the dose is absorbed, and it is thus not expected to affect the hormonal balance. The systemic effect of glucocorticoids can occur in the event of increased absorption, (e.g. when applied on large inflamed areas of skin, or on skin of which the stratum corneum of the epidermis is damaged). Occlusive bandages increase absorption.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction, genotoxicity and carcinogenicity.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Cetostearyl alcohol
Liquid paraffin
Poloxamer 188
Propylene glycol
Isopropyl myristate
Sodium laurilsulfate
White soft paraffin
Citric acid monohydrate
Sodium hydroxide (for pH adjustments)
Hydrochloric acid (for pH adjustments)
Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

Shelf life after first opening: 3 months.

6.4 Special precautions for storage

Store below 25°C. Do not refrigerate or freeze.

6.5 Nature and contents of container

2 g aluminium laminated HDPE tube with a HDPE cap or a 2g aluminium tube with an internal epoxy phenolic lacquer and a HDPE screw-cap.

6.6 Special precautions for disposal and other handling

Any unused medicinal or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

PA0678/143/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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Date of last renewal: 1st March 2022

10 DATE OF REVISION OF THE TEXT

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