Agenzia Italiana del Farmaco

AIFA

Public Assessment Report

Decentralised Procedure

ZOFTACOT

(Hydrocortisone sodium phosphate)
3.35 mg/ml, Eye drops, solution in single-dose container

Applicant: Laboratoires Théa

Italian Marketing Authorisation Number: 044061

European procedure number: IT/H/0413/001/DC

TABLE OF CONTENTS

Module 1

Information about the Initial Procedure

Product Name	ZOFTACOT
Type of application	Article 10.3 of Directive 2001/83/EC as amended
Active Substance	Hydrocortisone sodium phosphate
Form	Eye drops, solution in single-dose container
Strength	3.35 mg/ml
MA Holder	Laboratoires Théa 12, rue Louis Blériot 63017 Clermont-Ferrand Cedex 2 - FRANCE
Reference Member State (RMS)	IT
Concerned Memember States (CMS)	AT BE BG CY CZ DE DK EL ES FI FR HR IE IS LU NL NO PL PT RO SE SI SK UK
Procedure number	IT/H/0413/001/DC
Timetable	End of procedure: Day 210 – 14/03/2017

Module 2

Summary of Product Characteristics

In accordance with Directive 2010/84/EU, the Italian version of the Summaries of Product Characteristics (SmPCs) for products granted Marketing Authorisations at a national level would be available on the AIFA website once the marketing Authorization will be granted.

Here is reported the English version of the SmPC approved at European level.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

ZOFTACOT 3.35 mg/ml eye drops, solution in single-dose container

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml eye drops, solution contains 3.35 mg of hydrocortisone sodium phosphate.
One drop contains approximately 0.12 mg of hydrocortisone sodium phosphate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Eye drops, solution in single-dose container.

The solution is a practically clear, colourless to slightly yellow solution, practically free from particles.
pH: 6.9 - 7.5
Osmolality: 280-320 mosmol/kg

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of mild non-infectious allergic or inflammatory conjunctival diseases.

4.2 Posology and method of administration

Posology
The recommended dosage is 2 drops 2 to 4 times daily in the affected eye.
The duration of this dosing regimen will generally vary from a few days to a maximum of 14 days. Gradual tapering off up to one administration every other day may be recommended in order to avoid a relapse.

In case of insufficient response, a more potent corticosteroid should be used.

Paediatric population
The safety and efficacy have not been established in the paediatric population. See section 4.4.

Elderly
No dose adjustment is necessary in elderly patients.

Method of administration
Ocular use.

A single-dose container contains enough solution to treat both eyes.
For single use only.

This medicinal product is a sterile solution that does not contain a preservative. The solution from one individual single-dose container is to be used immediately after opening for administration to the affected eye(s) (see section 6.3).

Patients should be instructed:
- to avoid contact between the dropper tip and the eye or eyelids,
- to use the eye drops, solution immediately after first opening of the single-dose container and to discard the single-dose container after use.

Nasolacrimal occlusion by compression of lacrimal ducts for one minute may reduce systemic absorption.

In case of concomitant treatment with other eye drops, solution, instillations should be spaced out by 5 minutes.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- Known glucocorticosteroid-induced ocular hypertension and other forms of ocular hypertension;
- Acute herpes simplex virus infection and most of the other corneal viral infections at the acute stage of ulceration (except when combined with specific chemiotherapeutic agents for herpes virus); conjunctivitis with ulcerative keratitis even at the initial stage (positive fluorescein test);
- Ocular tuberculosis;
- Ocular mycosis;
- Acute ocular purulent infection, purulent conjunctivitis and purulent blepharitis, stye and herpes infection that may be masked or aggravated by anti-inflammatory drugs.

4.4 Special warnings and precautions for use

Topical steroids should never be given for an undiagnosed red eye.

Use of this medicinal product is not recommended for the treatment of viral herpes keratitis, but it may be used if required only with a combined antiviral treatment and under close supervision of an ophthalmologist.

Thinning of the cornea and sclera (caused by diseases) may increase the risk of perforations with the use of topical steroids.

Any fungal infection should be suspected in cases of corneal ulceration where a steroid has or had been used for a long period.

Patients should be monitored at frequent intervals during treatment with hydrocortisone eye drops. Prolonged use of corticosteroid treatment has shown to cause ocular hypertension/glaucoma especially for

patients with previous IOP increase induced by steroids or with pre-existing high IOP or glaucoma, (see sections 4.3 and 4.8) and also cataract formation, especially in children and elderly population.

The use of corticosteroids may also result in opportunistic ocular infections due to the suppression of host response or to the delay of their healing. In addition, topical ocular corticosteroids may promote, aggravate or mask signs and symptoms of opportunistic eye infections.

Wearing of contact lenses during treatment with corticosteroid eye drops should be avoided.

Paediatric population
In children, long-term continuous corticosteroid therapy may produce adrenal suppression (see section 4.2).
The ocular hypertensive response to topical corticosteroids in children occurs more frequently, more severely, and more rapidly than that reported in adults.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.
Co-treatment with CYP3A inhibitors, including cobicistat-containing products, is expected to increase the risk of systemic side-effects. The combination should be avoided unless the benefit outweighs the increased risk of systemic corticosteroid side-effects, in which case patients should be monitored for systemic corticosteroid side-effects.

4.6 Fertility, pregnancy and lactation

Pregnancy
There are no or limited amount of data from the use of ZOFTACOT in pregnant women. Corticosteroids cross the placenta. Studies in animals have shown reproductive toxicity including formation of cleft palates (see section 5.3). The clinical relevance of this observation is unknown. After systemic administration of higher doses of corticosteroids, effects on the unborn/neonate (intra-uterine growth inhibition, inhibition of the function of the adrenal cortex) have been reported. However, these effects have not been observed after ocular use.
ZOFTACOT is not recommended during pregnancy, unless clearly necessary.

Breastfeeding
Systemically administered glucocorticoids are excreted in breast milk and may cause suppression of growth or of endogenous corticosteroid production or may have other undesirable effects.
It is unknown whether ZOFTACOT is excreted in human milk.
A risk to the newborns/infants cannot be excluded.

Fertility
There are no data on potential effects of hydrocortisone sodium phosphate 3.35 mg/ml on fertility.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.
Temporarily blurred vision or other visual disturbances may affect the ability to drive or use machines. If blurred vision occurs, the patient must wait until the vision is clear before driving or using machines.

4.8 Undesirable effects

List of adverse reactions:

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); very rare (<1/10,000); not known (frequency cannot be estimated from available data).

Hydrocortisone
Eye disorders:
- Not known: Burning*, stinging*.

Corticoid class effects
The following adverse drug reactions have not been observed with hydrocortisone, but are known with other topical corticosteroids.
Eye disorders:
- Not known: Allergic and hypersensitivity reactions, delayed wound healing, posterior capsular cataract*, opportunistic infections (herpes simplex infection, fungal infection, see Section 4.4), glaucoma*, mydriasis, ptosis, corticosteroid-induced uveitis, changes in corneal thickness*, crystalline keratopathy.

* *see section Description of selected adverse reactions*

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

Description of selected adverse reactions:
Burning and stinging may occur immediately after instillation. These events are usually mild and transient and have no consequences.

Prolonged use of corticosteroid treatment has shown to cause in ocular hypertension/glaucoma (especially for patient with previous IOP increase induced by steroids or with pre-existing high IOP or glaucoma, or family history of high IOP or glaucoma) and also cataract formation. Children and elderly patients may be particularly susceptible to steroid-induced IOP rise (see section 4.4).
Increase of intra-ocular pressure induced by corticosteroid topical treatment has been generally observed within 2 weeks of treatment (see section 4.4).
Diabetics are also more prone to develop subcapsular cataracts following topical steroid administration.
In diseases causing thinning of the cornea, topical use of steroids could lead to perforation in some cases (see section 4.4).

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 national reporting system listed in Appendix V.

4.9 Overdose

In the case of topical overdosage associated with prolonged eye irritation, the eye(s) should be rinsed with sterile water.

Prolonged overdosages could produce ocular hypertension. In this case, it is necessary to discontinue treatment.

The symptomatology due to accidental ingestion is not known. As with other corticosteroids however, the physician may consider gastric lavage or emesis.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: ANTIINFLAMMATORY AGENTS – Corticosteroids, plain, ATC code: S01BA02

Mechanism of action
Hydrocortisone or cortisol is a glucocorticoid secreted from the adrenal gland and equipped with anti-inflammatory activity capable of releasing and inducing the synthesis of the specific PLA2 inhibitor (lipocortin) therefore blocking the arachidonate cascade and the formation of phlogogenic factors, like prostaglandins, thromboxanes, (SRS-A) leukotrienes. Such a mechanism of action explains the anti-inflammatory and anti-allergic activity of hydrocortisone.

5.2 Pharmacokinetic properties

A pharmacokinetic study in rabbits performed with ZOFTACOT has shown that after administration, hydrocortisone rapidly diffused in the aqueous humour, cornea and conjunctivae. The penetration of hydrocortisone was the highest in the cornea, followed by the conjunctivae, and is very low in the aqueous humour. A weak systemic passage of hydrocortisone was also observed (< 2% of applied dose).

5.3 Preclinical safety data

Prolonged repeated administration of hydrocortisone via the systemic route in animals reduced body weight gain, increased neoglucogenesis and hyperglycaemia, thymolysis and ocular hypertension.

Reproductive toxicity
In mice, ocularly administered hydrocortisone has been shown to produce foetal resorptions and cleft palate. In rabbits, ocular use of hydrocortisone produced foetal resorptions and multiple abnormalities involving the head and abdomen.
In addition, intra-uterine growth inhibition and changes of functional development of the central nervous system have been reported after administration of corticosteroids to pregnant animals.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients
Disodium phosphate dodecahydrate,
sodium dihydrogen phosphate monohydrate,
sodium chloride,
disodium edetate,
hydrochloric acid (for pH adjustment),
water for injections.

6.2 Incompatibilities

Incompatibility with other drugs is not known.

6.3 Shelf life

2 years in the outer packaging.
After first opening of the sachet: use the single-dose containers within 1 month.
After first opening of the single-dose container: use immediately and discard the single-dose container after use.
Since sterility cannot be maintained after the individual single-dose container is opened, any remaining contents must be discarded immediately after administration.

6.4 Special precautions for storage

Do not store above 25°C.
Keep the single-dose containers in the sachet, in order to protect from light.
For storage after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

10 single-dose containers (LDPE) containing 0.4 ml of eye drops, solution are overwrapped in a sachet composed of four layers made of paper/polyethylene/aluminium/ethylene copolymer.

A pack size contains 10 (1x10), 20 (2x10), 30 (3x10) or 60 (6 x 10) single-dose containers.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal <and other handling>

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

7. MARKETING AUTHORISATION HOLDER

Laboratoires THEA
12, rue Louis Blériot
63017 Clermont-Ferrand Cedex 2
France

8. MARKETING AUTHORISATION NUMBER(S)

[To be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: {DD month YYYY}
[To be completed nationally]

10. DATE OF REVISION OF THE TEXT

[To be completed nationally]

Detailed information on this medicinal product is available on the website of {name of MS/Agency}.

Module 3

Package Leaflets

In accordance with Directive 2010/84/EU, the Italian version of the package leaflet for products granted Marketing Authorisations at a national level would be available on the AIFA website once the marketing Authorization will be granted.

Here is reported the English version of the PIL approved at European level.

1.3.1 Package leaflet: Information for the user

Zoftacot 3.35 mg/ml eye drops, solution in single-dose container
Hydrocortisone sodium phosphate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Zoftacot is and what it is used for

This medicine is an eye drops solution in single-dose container, which contains a substance called hydrocortisone. This substance is a corticosteroid which inhibits inflammatory symptoms.

It is used to treat mild allergic or inflammation conditions of the superficial part of your eye(s) (conjunctives).

The eye should not be infected (see Do not use Zoftacot).

2. What you need to know before you use Zoftacot

Do not use Zoftacot:
- If you are allergic to the active substance (hydrocortisone) or any of the other ingredients of this medicine (listed in section 6).
- If you have high pressure inside the eye (ocular hypertension), known to be due to glucosteroids (family of corticosteroids) or to other causes.

- If you have acute herpes virus infections and most of other viral diseases at the stage of ulceration (unless the infection is being treated with an anti-infective treatment for herpes virus).
- If you have conjunctivitis with ulcerative cornea inflammation (keratitis) even at initial stage.
- If you have a bacterial eye infection (acute purulent infection, conjunctivitis, blepharitis and stye).
- If you have a fungal infections of the eye (ocular mycosis).
- If you have a bacterial infection called tuberculosis which affects your eye (ocular tuberculosis).

Warnings and precautions
- Talk to your doctor, pharmacist or nurse before using this medicine.
- If you have a red eye that has not been diagnosed, do not use this medicine.
- If you have a viral eye infection (herpes), only use this medicine if the infection is being treated with an anti-infective treatment and close monitoring of your eyes is required.
- If you have a disease that causes thinning of the outer part of your eye (cornea and sclera), there may be a higher risk of perforation due to the use of topical corticosteroids applied to the eye.
- If you have or have been used a corticosteroid medicine for a long time and have an eye wound (corneal ulcer), a fungal infection may be suspected.
- A close regular monitoring of your eyes is required during your treatment. Prolonged use of corticosteroids has shown to cause an increase of the pressure inside the eye and of the onset of glaucoma, especially in patients who already suffer from high intraocular pressure or who are at risk of developping such condition with local steroid treatment (see Possible side effects) and to cause a clouding of the lens in the eye (cataract), in particular in children and elderly population.
- The use of corticosteroids can cause opportunistic ocular infections. In addition, topical ocular corticosteroids may promote, aggravate or mask signs and symptoms of opportunistic eye infections.
- You should avoid wearing contact lenses during the treament with this medicine.

Children
There is no data on safety and efficacy in children.
Continual, long-term treatment with corticosteroids in children may produce adrenal suppression.
The increase of the eye pressure in children occurs more frequently, more severely, and more rapidly than in adults.

Other medicines and Zoftacot
Please tell your doctor or pharmacist if you are using, have recently used or might use any other medicines, including medicines obtained without a prescription.

Some medicines may increase the effects of Zoftacot and your doctor may wish to monitor you carefully if you are taking theses medicines (including some medicines for HIV: ritonavir, cobicistat).

Pregnancy and breastfeeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.
- The use of this medicine during pregnancy is not recommended except when judged necessary by your doctor and under strict supervision.
- It is not known whether this medicine passes into breast milk. Your doctor will decide if you can use this medicine during breastfeeding or not.

Driving and using machines
Temporary blurred vision, or other sight defects may affect the ability to drive or use machines. Do not drive or use machines until normal vision has returned.

3. How to use Zoftacot

Dose
Always use this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

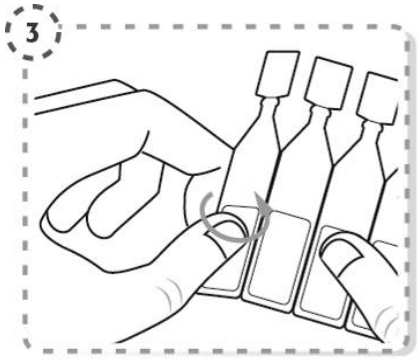
The recommended dose is 2 drops in the affected eye(s), 2 to 4 times a day, depending on the prescription. Gradual dose reduction is recommended in order to avoid relapse. The duration treatment usually varies from few days to a maximum of 14 days.

The same dose is used for both adults and the elderly.

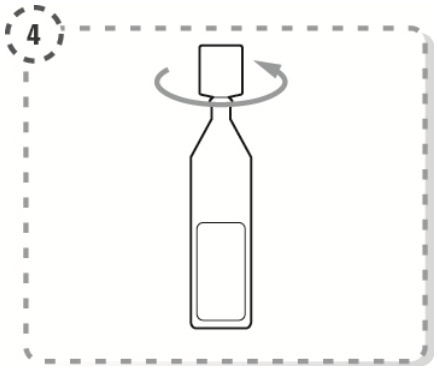
Use in children
The efficacy and the safety in children have not been established.

How to use the drops
This medicine is intended to be administered into the eye.

Please follow these instructions to use the drops:
1. Wash your hands and sit or stand comfortably.
2. Open the sachet containing 10 single-dose containers. Write down the date of first opening on the sachet.
3. Break off one single-dose container from the strip.

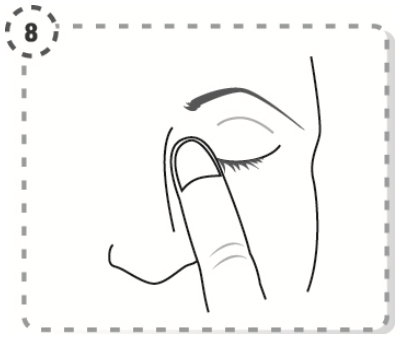


4. Twist open the top of the single-dose container as shown. Do not touch the tip after opening the container.



5. Use your finger to gently pull down the lower eyelid of your affected eye.
6. Place the tip of the single-dose container close to, but not touching your eye.
7. Squeeze the single-dose container gently so that two drops go into your eye, then release the lower eyelid.

8. Press a finger against the corner of the affected eye by the nose. Hold for 1 minute while keeping the eye closed.



9. Repeat in your other eye if your doctor has told you to do this. Each single-dose container contains enough solution for both eyes.

10. Discard the single-dose container after use. Do not keep it to use it again.

11. Place the unopened single-dose containers back in the sachet. Place the opened sachet in the carton. The unopened containers must be used within one month after opening of the sachet.

If you are using any other medicine to be applied to the eye, you should wait 5 minutes between each application.

If you use more Zoftacot than you should

Rinse the eye with sterile water if you have applied too much product to your eye and there is a prolonged irritation.

Contact immediately your doctor or your pharmacist.

If you forget to use Zoftacot

Do not take a double dose to make up for a forgotten dose.

If you stop using Zoftacot

Do not stop using the treatment abruptly. Always consult your doctor if you are considering stopping the treatment.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Not known: frequency cannot be estimated from the available data

- transient eye discomfort (burning, stinging) after application.

The following side effects were reported with medicines of the same group (corticosteroids) when used for treating eye conditions.
Not known: frequency cannot be estimated from the available data

- allergic reactions,
- delayed wound healing,
- clouding of the lens in the eye (posterior capsular cataract),
- opportunistic infections (viral like herpes, fungal infection),
- increase of pressure in your eye (glaucoma),
- dilation of the pupil (mydriasis),
- drooping eyelids (ptosis),
- inflammation inside your eye (uveitis),
- changes in the thickness of the front of the eye (cornea),
- inflammation of the cornea (crystalline keratopathy).

In very rare cases, some patients with severe damage to the clear layer at the front of the eye (the cornea) have developed cloudy patches on the cornea due to calcium build-up during treatment.

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Zoftacot

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton, sachet and single-dose container after EXP. The expiry date refers to the last day of that month.

Do not store above 25°C.

After first opening of the sachet: use the single-dose containers within one month.
Keep the single-dose containers in the sachet to protect them from light.
Write down the date of first opening on the sachet.

After first opening of the single-dose container: use immediately and discard the single-dose container after use.

Since sterility cannot be maintained after the individual single-dose container is opened, any remaining contents must be discarded immediately after administration.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Zoftacot contains

- The active substance is hydrocortisone sodium phosphate.
  1 ml eye drops, solution contains 3.35 mg of hydrocortisone sodium phosphate.
- The other ingredients are disodium phosphate dodecahydrate, sodium dihydrogen phosphate monohydrate, sodium chloride, disodium edetate, hydrochloric acid (for pH adjustment),water for injections.

What Zoftacot looks like and contents of the pack

This medicinal product is presented as an eye drops solution in single-dose container.
The solution is a practically clear, colourless to slightly yellow, practically free from particles, packed in a sachet of 10 units, each single-dose container holding 0.4 ml of product.
The pack size contains 10 (1 x 10), 20 (2 x 10), 30 (3 x 10) or 60 (6 x 10) single-dose containers.
Not all pack sizes may be marketed.

Marketing Authorisation Holder
LABORATOIRES THEA
12, rue Louis Blériot
63017 CLERMONT-FERRAND Cedex 2
FRANCE

Manufacturer
LABORATOIRES UNITHER
ZI de la Guérie
50 211 COUTANCES CEDEX
FRANCE

or

LABORATOIRES THEA
12, rue Louis Blériot
63017 CLERMONT-FERRAND Cedex 2
FRANCE

This medicinal product is authorised in the Member States of the EEA under the following names:

[To be completed nationally]

This leaflet was last revised in

Detailed information on this medicine is available on the website of {MS/Agency}

Module 4

Labelling

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

I OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

ZOFTACOT 3.35 mg/ml eye drops, solution in single-dose container
hydrocortisone sodium phosphate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

1 ml contains 3.35 mg of hydrocortisone sodium phosphate.
One drop contains approximately 0.12 mg of hydrocortisone sodium phosphate.

3. LIST OF EXCIPIENTS

Disodium phosphate dodecahydrate, sodium dihydrogen phosphate monohydrate, sodium chloride, disodium edetate, hydrochloric acid, water for injections.

4. PHARMACEUTICAL FORM AND CONTENTS

Eye drops, solution in single-dose container.
10 x 0.4 ml
20 x 0.4 ml
30 x 0.4 ml
60 x 0.4 ml

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Ocular use.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP {MM/YYYY}
After first opening of the sachet: use the single-dose containers within one month.
After first opening of the single-dose container: use immediately and discard the single-dose container after use.

9. SPECIAL STORAGE CONDITIONS

Do not store above 25°C.
Keep the single-dose containers in the sachet, in order to protect from light.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Laboratoires THEA
12, rue Louis Blériot
63017 Clermont-Ferrand Cedex 2
France

12. MARKETING AUTHORISATION NUMBER(S)

<[To be completed nationally]>

13. BATCH NUMBER

Lot {number}

14. GENERAL CLASSIFICATION FOR SUPPLY

<[To be completed nationally]>

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

zoftacot

17. UNIQUE IDENTIFIER – 2D BARCODE

<2D barcode carrying the unique identifier included.>

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

<PC: {number}
SN: {number}
NN: {number}>

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

II SACHET

1. NAME OF THE MEDICINAL PRODUCT

ZOFTACOT 3.35 mg/ml eye drops, solution in single-dose container

hydrocortisone sodium phosphate

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Laboratoires THEA

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot {number}

5. OTHER

10 x 0.4 ml
Ocular use
After first opening of the sachet: use the single-dose containers within one month.
Keep the single-dose containers in the sachet, in order to protect from light.
After opening of the single-dose container: use immediately and discard after use.
Date of first opening:

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

III SINGLE-DOSE CONTAINER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

ZOFTACOT 3.35 mg/ml
Ocular use

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP {MM/YYYY}

4. BATCH NUMBER

Lot {number}

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.4 ml

6. OTHER

Module 5

Scientific discussion during the initial procedure

I. Introduction

Based on the review of the data on quality, safety and efficacy, the member states involved in the procedure considered that the application for ZOFTACOT (Hydrocortisone sodium phosphate, 3.35 mg/ml, Eye drops, solution in single-dose container - MA No 044061; Procedure No IT/H/0413/001/DC) could be approved. This product is a prescription-only medicine indicated for the treatment of mild non-infectious allergic or inflammatory conjunctival diseases.

This application was submitted using the Decentralised Procedure (DCP), with Italy (IT) as Reference Member State (RMS) and AT BE BG CY CZ DE DK EL ES FI FR HR IE IS LU NL NO PL PT RO SE SI SK UK as Concerned Member States (CMS). This application was submitted under Article 10(3) of Directive 2001/83/EC, as amended. The reference product is authorized in Italy since 1958 under the trade name Idracemi 0,335% Eye drops, solution (Bottle of 10 ml - AIC 014438016), whose MAH is the same of the present application.

Zoftacot is an anti-inflammatory agent for local use (ATC-code: S01BA02) and is a low potent corticosteroid. Inflammation of the ocular surface may involve the conjunctiva and the cornea and may be caused by allergy, post-infectious inflammation, trauma, surgery, specific immune activation.

Corticosteroids exert their effects by binding to cytoplasmic glucocorticoids receptors within target cells. Following ligand binding, proteins associated with glucocorticoids receptor complex dissociate, glucocorticoids receptor complex is directed into the nucleus where it can interact with specific DNA sequences, and glucocorticoid responses are generated.
Hydrocortisone has a low binding affinity for glucocorticoids receptors, especially in presence of a phosphate group.
Corticosteroids affect the release of substances that module inflammation: they inhibit the synthesis and release of pro-inflammatory chemical mediators (such as eicosanoids, PAF, TNF, and others), and through lipocortin. They inhibit the anzyme phospolipase A2 and thus the conversion of phospholipids to arachidonic acid: synthesis of prostaglandins, thromboxanes A and prostacyclins is therefore prevented.
Due to its pharmacokinetic properties, hydrocortisone exerts its anti-inflammatory effect on the ocular surface, in the subconjunctival tissues and corneal stroma. Hydrocortisone penetrates into the eye as well as the intraocular structures of the anterior segment of the eye. Systemic passage of hydrocortisone is low (<3% of applied dose). Due to low potency, hydrocrtisone is indicated in mild non-infectious clinical conditions.

ZOFTACOT has the same qualitative and quantitative composition of a medicinal product already approved in Italy, IDRACEMI, except for the absence of parabens in the new formulation.
Initial claimed indication was “Treatment of inflammatory and allergic disorders of the anterior segment of the eye”.

A new PK animal study has been provided in order to demonstrate that the formulation test (without parabens) shows similar kinetic profiles compared with the reference formulation (with parabens) and that absence of parabens does not impact on availability.
Moreover, MAH presented literature data on pharmacokinetics, pharmacodinamic, clinical efficacy and safety of ocular hydrocortisone and of topic ocular corticosteroids in general.

In adding to literature data and to the PK preclinical study, two tolerability studies in rabbit showing that Hydrocortisone sodium phosphate was well tolerated after repeated administrations, have been submitted.

The RMS has been assured that acceptable standards of GMP are in place for these product types at all sites responsible for the manufacture and assembly of this product. For manufacturing sites within the Community, the RMS has accepted copies of current manufacturer authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites. For manufacturers of the active substance, QP declarations for GMP compliance have been submitted.

II. About the product

Proposed name of the medicinal product in the RMS	ZOFTACOT
Name of the drug substances (INN name):	Hydrocortisone sodium phosphate
Pharmaco-therapeutic group (ATC Code):	S01BA02
Pharmaceutical form(s) and strength(s):	Eye drops, solution in single-dose container, 3.35 mg/ml
Reference Number(s) for the Decentralised Procedure	IT/H/0413/001/DC
Reference Member State:	Italy
Concerned Member States:	AT BE BG CY CZ DE DK EL ES FI FR HR IE IS LU NL NO PL PT RO SE SI SK UK
Marketing Authorisation Numbers	AIC No: 044061
Name and address of the Authorization Holder	Laboratoires Théa 12, rue Louis Blériot 63017 Clermont-Ferrand Cedex 2 - FRANCE

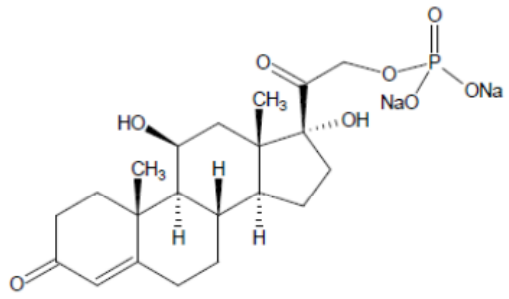
III. Scientific Overview and discussion

III.1 Quality aspects

ACTIVE SUBBSTANCE – Hydrocortisone sodium phosphate

Chemical name: 11β,17α-dihydroxy-3,20-dioxopregn-4-en-21-yl orthophosphate disodium

Structural formula:



Molecular formula: $C_{21}H_{29}Na_2O_8P$
Molecular weight: 486.40 g/mol

Appearance:	White or practically white powder
Solubility:	Freely soluble in water, practically insoluble in absolute alcohol
Specific optical rotation:	+121° to +129° as 1% w/v solution in water at 20°C

Hydrocortisone sodium phosphate is produced as a single enantiomer with absolute configuration of the chiral centres as follows: 8*S*, 9*S*, 10*R*, 11*S*, 13*S*, 14*S*, 17*R.*

Hydrocortisone sodium phosphate is not specifically present in the European Pharmacopeia, but quality requirements are considered in BP and USP monographs.

Results on three production batches show compliance with the specification proposed, which are acceptable. Container closure system has been adequately described. Appropriate stability data have been generated, supporting a suitable retest period .

DRUG PRODUCT

Other Ingredients
The finished product is a practically clear, colourless to slightly yellow solution, practically free from particles presented in single dose units. The pharmaceutical form consists of eye drop containing: Hydrocortisone sodium phosphate (3.35 mg/ml) and the following excipients: Disodium phosphate dodecahydrate, Sodium dihydrogen phosphate monohydrate, Sodium chloride, Disodium edetate, Hydrochloric acid concentrated, water for injections. ZOFTACOT has the same composition than reference product Idracemi® presented in multidose container but without preservative agents (methylparaben and propylparaben).

All the excipients are free from any risk of TSE.

Pharmaceutical Development
The establishment of the pharmaceutical equivalence was achieved by comparative studies (batches analysis and drop size study) between batches of ZOFTACOT and the reference product Idracemi®.

Suitable pharmaceutical development data have been provided for this application.

Manufacturing Process
Satisfactory batch formula has been provided for the manufacture of the medicinal product, along with an appropriate description of the manufacturing process. The manufacturing process has been validated on three industrial batches.

Control of Finished Product

The finished product specifications are satisfactory. Test methods have been described and adequately validated, as appropriate. Batch data have been provided and comply with the release specifications.

Container Closure System
The chosen container consists in single dose units made of low-density polyethylene without additives complying with the current European Pharmacopoeia 3.1.4.

Stability
Finished product stability studies were performed in accordance to current guidelines on batches of finished product packed in the packaging proposed for marketing. Based on the results, the following shelf-life and in-use periods have been proposed:
2 years in the outer packaging;
after first opening of the sachet: use the single-dose containers within 1 month;
after first opening of the single-dose container: use immediately and discard the single-dose container after use;
with the following special precautions for storage:
do not store above 25°C;
keep the single-dose containers in the sachet, in order to protect from light.

III.2 Non-clinical aspects

Zoftacot is a generic application for Idracemi® for ophthalmic use.
Pharmacodynamic, pharmacokinetic and toxicological properties of hydrocortisone are well known.

However taking into account that, for this product the quali-quantitative formula in excipients is different from the current Idracemi formula for the absence of the preservatives, the applicant has performed, in adding to literature data, one PK study (please refer to P*harmacokinetics*) and two tolerability studies in order to compare the ocular penetration and tolerance of the proposed medicinal product and the reference product Idracemi® . A ocular tolerance study has been conducted to compared the safety between eye drop containing hydrocortisone without preservatives and the reference product Idracemi® with preservatives. The results of the study showed that Zoftacot is well tolerated, as Idracemi.

Also the ocular tolerability study conducted in order to investigate the toxicity of the potential impurities, showed that Zoftacot was very well tolerated .

Ecotoxicity/environmental risk assessment (ERA)

Under the proposed conditions of use, data submitted by the MHA for ERA showed that Zoftacot will not lead to an increased exposure to the environment.

III.3 Clinical aspects

Introduction
Based on the review of the quality, safety and efficacy data, the Member States involved in the procedure have granted a marketing authorisation for ZOFTACOT for the following therapeutic indication:
Treatment of mild non-infectious allergic or inflammatory conjunctival diseases.

The application was made in accordance with Article 10(3) of Directive 2001/83/EC because “ZOFTACOT”, is the hybrid form of the reference product “IDRACEMI”, a locally applied and locally acting medicinal product. IDRACEMI has been marketed by LABORATOIRES THÉA in Italy since November 1958.

ZOFTACOT 3.35 mg/mL eye drops is a sterile, preservative-free solution containing 0.335% hydrocortisone sodium phosphate, in single use containers; it has the same qualitative and quantitative composition in terms of active ingredient as IDRACEMI eye drops. ZOFTACOT differs from IDRACEMI only in the absence of the preservatives. The removal of parabens is indented to avoid potential toxicities.

Pharmacokinetics

No new pharmacokinetics studies were performed in humans.
Data from the literature of the active compound of SOFTACORT with particular attention to its ocular use were presented. Hydrocortisone penetrates into the eye as well as the intraocular structures of the anterior segment of the eye, even if ocular penetration of hydrocortisone, as measured in animal models, is less than 3%, with the majority present in the conjunctiva and cornea (80% to 86%)
A new PK study was conducted in order to assess the ocular penetration of hydrocortisone in cornea (C), conjunctivae (bulbar and palpebral) (CJ), aqueous humor (AH) and plasma (PL) after a single instillation in right eyes of 84 pigmented rabbits.
Content of hydrocortisone was determined in ocular samples (C, CJ, AH) and plasma (PL) following the RRLC-MS/MS validated method and in plasma following a non-GLP method.

The results of the analysis indicated that penetration of hydrocortisone was the highest in the cornea, followed by the conjunctivae, and the aqueous humor, regardless of the formulation. A weak systemic passage of hydrocortisone was observed (< 2% of applied dose).
Any difference of the hydrocortisone concentrations was observed after ZOFTACOT and Idracemi in Aqueous humor and conjunctiva, with the exception of 4 and 8 hours post dose were ZOFTACOT had concentrations significantly lower than Idracemi in the Cornea and with the exception of 2 and 8 hours post dose were ZOFTACOT had concentrations significantly higher than Idracemi in plasma.

A strict PK equivalence has been demonstrated in the conjunctiva.

Pharmacodynamics

Hydrocortisone or cortisol is a glucocorticoid secreted from the adrenal gland and equipped with anti-inflammatory activity capable of releasing and inducing the synthesis of the specific PLA2 inhibitor (lipocortin) therefore blocking the arachidonate cascade and the formation of flogogen factors, like prostaglandins, thromboxanes, leukotrienes. Such a mechanism of action explains the anti-inflammatory and anti-allergic activity of hydrocortisone. Hydrocortisone in classified as a short acting corticosteroid.

Clinical efficacy

Literature data are available on clinical efficacy and safety of ocular hydrocortisone and of topic ocular corticosteroids in general. Clinical data are obtained with different formulations and concentrations of hydrocortisone ocular preparations. A few well-designed clinical trials evaluating the efficacy of hydrocortisone in ocular inflammation are described in literature. In these publications, hydrocortisone has been used with concentrations ranging from 0.1% to 2.5% in a variety of ophthalmologic diseases; none of them used the concentration 3.35 mg/mL (0.335%) of hydrocortisone sodium phosphate.
There is no scientific data in the literature to guide the choice of concentration in hydrocortisone eye drops.

No new efficacy data have been submitted. The MAH taking into account both the minor differences in the excipient composition between the generic and the reference medicinal product and the results from pre-clinical studies, considered a clinical trial showing therapeutic equivalence not necessary.
According to the EMA Guideline on the Investigation of Bioequivalence (CPMP/EWP/QWP/1401/98 Rev.1 Corr**, paragraph “locally acting locally applied products”) in case of solutions as eye drops, the waiver of the need to provide equivalence data may be acceptable if any qualitative or quantitative differences in excipients is adequately justified in relation to their influence on therapeutic equivalence. The MAH has submitted the PK study T02F14412 performed in animal model (please refer to *Non clinical aspects*) in order to demonstrate that the formulation test (without parabens) show similar kinetic profiles compared

with the reference formulation (with parabens). The PK study demonstrated a similar PK profiles between ZOFTACOT and the reference in the conjunctiva and in the aqueous humour. Considering that a comparable bioavailability of hydrocortisone between the proposed product ZOFTACOT and the reference product IDRACEMI has been strictly demonstrated in the conjunctiva in animals with no statistical nor clinical differences at any point, the therapeutic indication proposed by the MAH limited to focus on the conjunctival inflammation is endorsed. Claimed therapeutic indication had been amended during procedure and restricted to "*Treatment of non-infectious allergic or inflammatory conjunctival diseases*. Following assessor's opinion that considering the low potency of hydrocortisone and the low concentration of this preparation, the use of medicinal product should be reserved only to mild conditions, therapeutic indication has been further restricted to "*Treatment of mild non-infectious allergic or inflammatory conjunctival diseases*". Therefore, based on all available data the waiver to therapeutic equivalence trial was considered accepted.

Clinical safety

Non new safety study in humans was performed. No specific literature data are available with hydrocortisone 0.335%; data on other concentrations show the well known safety profile of topical corticosteroids. Ocular hydrocortisone has been used for several decades in a range of ocular indications.
As hydrocortisone is considered characterized by a low potency and considering the low fraction of drug absorbed, local and systemic toxicity is therefore considered limited.
The removal of parabens would favorably impact on local tolerance of medicinal product. Non clinical studies conducted on animal models showed a similar local tolerability with respect to reference medicinal products (please refer to *Non clinical aspects*). No new safety issues are expected.

RISK MANAGEMENT PLAN
The Applicant has submitted a risk management plan, in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Zoftacot. The authorized RMP version is 1.4.

- Summary table of safety concerns as approved in RMP:

Summary of safety concerns	
Important identified risks	- Herpes simplex infection reactivation - Ocular infections (Bacterial and Fungal) - Prolonged use or overdose: Ocular hypertension and glaucoma - Corneal calcification (phosphate-related risk)
Important potential risks	- Prolonged use: posterior subcapsular cataract - Delayed healing - Perforations in case of thinning of the cornea and sclera - Inhibition of fetal adrenal cortex, intrauterine growth delay in case of use during pregnancy - Adrenal suppression, ocular hypertensive response, glaucoma or cataract in case of use in paediatric population -Ocular hypertensive response, glaucoma and cataract in case of use in Elderly - Inhibition of the function of the adrenal cortex in breastfed infant
Missing information	-

- Summary of Planned Risk Minimisation Activities as approved in RMP:

Concerning the current RMP version, the proposed routine risk minimisation measures are evaluated as sufficient; as a consequence, no additional risk minimisation measures have been set in this RMP.

SUMMARIES OF PRODUCT CHARACTERISTICS (Sm.PCs), PATIENT INFORMATION LEAFLETS (PILs) AND LABELLING

The SmPCs, PILs and labelling are acceptable from a clinical perspective. The SmPCs are consistent with those for the originator product. A more precise posology, specifically indicating the frequency of administration and the maximum daily dose, and a duration of treatment have been specified respect to what authorized for IDRACEMI, this will allow a more appropriate and safer use of medicinal product. The PILs are consistent with the details in the SmPCs and in-line with the current guidelines. The labelling is in-line with current guidance.

The packed leaflet has been evaluated via user consultation study in accordance with the requirements of articles 59(3) and 61(1) of directive 2001/83/EC. The language used for the purpose of the user testing PIL was English.

IV Overall conclusions and benefit-risk assessment

This Application is related to the request of the Applicant LABORATOIRES THÉA for the Marketing Authorisation of a medicinal product containing hydrocortisone in eye drop solution. The application was made in accordance with Article 10(3) of Directive 2001/83/EC because "ZOFTACOT 3.35 mg/ml, Eye drops, solution in single-dose container", is the hybrid form of the reference product "IDRACEMI", a locally applied and locally acting medicinal product.
IDRACEMI has been marketed by LABORATOIRES THÉA in Italy since November 1958.

The quality characteristics of ZOFTACOT 3.35 mg/ml, Eye drops, solution in single-dose container are well-defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

Based on the legislation requirements related to these kind of application ("Hybrid application") data from a clinical equivalence study were provided.

The efficacy and safety profiles of hydrocortisone are well known; two new preclinical studies and the pk study were submitted in accordance to the legislation requirements. No new safety concerns are unexpected.

In addition to the pk preclinical study the MHA has submitted two tolerability studies in order to investigate the local tolerance of Zoftacort. A ocular tolerance study has been conducted to compared the safety between eye drop containing hydrocortisone without preservatives and the reference product Idracemi® with preservatives. The results of the study showed that Zoftacot is well tolerated, as Idracemi.

Also the ocular tolerability study conducted in order to investigate the toxicity of the potential impurities, showed that Zoftacot was very well tolerated .
No new or unexpected safety concerns arose from the clinical equivalence study.

The SmPCs, PILs and labelling are satisfactory, and consistent with those for the reference products, where appropriate, along with current guidelines.

BENEFITI RISK ASSESSMENT
The quality of the product ZOFTACOT 3.35 mg/ml, Eye drops, solution in single-dose container is acceptable, and no new non-clinical or clinical safety concerns have been identified.

Hydrocortisone sodium phosphate was introduced in oftalmology several decades ago and it is used in several ocular inflammatory diseases. Efficacy and tolerability of topical corticosteroids in ocular disease are well known.
ZOFTACOT, a solution in single-dose container, differs from the reference medicinal product, IDRACEMI, for the only absence of parabens as preservative; the removal of parabens would translate in a better local tolerability.
The MAH taking into account both the minor differences in the excipient composition between the generic and the reference medicinal product and the results from pre-clinical studies, considered a clinical trial showing therapeutic equivalence not necessary.
A PK study was submitted to demonstrate that the formulation test (without parabens) show similar kinetic profiles compared with the reference formulation (with parabens). The PK study demonstrated a similar PK profiles between ZOFTACOT and the reference in the conjunctiva and in the aqueous humour. Considering that a comparable bioavailability of hydrocortisone between the proposed product ZOFTACOT and the

reference product IDRACEMI has been strictly demonstrated in the conjunctiva in animals with no statistical nor clinical differences at any point, and taking into account the low potency of hydrocortisone and the low concentration of this preparation, therapeutic indication has been further restricted to “Treatment of mild non-infectious allergic or inflammatory conjunctival diseases”.
Therefore, based on all available data the waiver to therapeutic equivalence trial was accepted.

The benefit/risk balance is, therefore, considered to be positive.