

**CHLORAMPHENICOL 1.0% W/W EYE OINTMENT
PL 17918/0004**

UKPAR

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**CHLORAMPHENICOL 1.0% W/W EYE OINTMENT
PL 17918/0004**

LAY SUMMARY

The MHRA granted Tubilux Pharma SpA Marketing Authorisations (licences) for the medicinal product Chloramphenicol 1.0% w/w Eye Ointment (PL 17918/0004) on 1st March 2007. This is a prescription-only medicine (POM) for the treatment of bacterial conjunctivitis, which is an infection that causes redness, discomfort and discharge from the affected eye.

This product contains the active substance chloramphenicol, an antibiotic that helps kill the bacteria (germs).

No new or unexpected safety concerns arose from this application and it was therefore judged that the benefits of taking Chloramphenicol 1.0% w/w Eye Ointment outweigh the risks, hence a Marketing Authorisation has been granted.

**CHLORAMPHENICOL 1.0% W/W EYE OINTMENT
PL 17918/0004**

SCIENTIFIC DISCUSSION

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INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted a marketing authorisation for the medicinal product Chloramphenicol 1.0% w/w Eye Ointment (PL 17918/0004) on 1st March 2007 to Tubilux Pharma SpA. The product is a prescription-only medicine.

The application was submitted as an abridged application according to Article 10.1 of Directive 2001/83/EC, as amended, claiming essential similarity to the original product Chloromyecetin 1% Ointment (Parke-Davis and Co, Limited) which has been authorised in the EU for more than 10 years.

The product contains the active ingredient chloramphenicol, widely used as an ocular antibiotic with a broad spectrum of activity against both gram-positive and gram-negative bacteria. It exerts its antibacterial effect by binding to bacterial ribosomes and inhibiting bacterial protein synthesis at an early stage.

Chloramphenicol is indicated for the treatment of bacterial conjunctivitis caused by chloramphenicol-susceptible organisms.

PHARMACEUTICAL ASSESSMENT

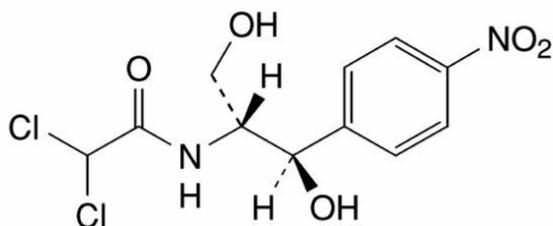
DRUG SUBSTANCE

Chloramphenicol

INN: Chloramphenicol

Chemical Name: 2,2-dichlor-*N*- [(*aR*,*bR*)-*b*-hydroxy-*a*-hydroxymethyl- 4-nitrophenethyl] acetamide

Structure:



Molecular Formula: C₁₁H₁₂Cl₂N₂O₅

Molecular Weight: 323.13

Appearance: White to greyish-white or yellowish-white, fine crystalline powder or fine crystals

Synthesis of the drug substance from the designated starting materials has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory specification tests are in place for all starting materials and reagents, and these are supported by relevant certificates of analysis.

An appropriate specification is provided for the active substance chloramphenicol. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications. Batch analysis data are provided that comply with the proposed specification.

The active substance is packed in double polyethylene bags (the inner bag colourless and outer bag black), which are tied with a flexible plastic band. These are placed into fibre drums and sealed with galvanised steel clamping rings. Specifications have been provided for all packaging and all primary packaging has been shown to comply with Directive 2002/72/EC concerning contact of materials with food.

Appropriate stability data have been generated and support a shelf-life of 5 years, which is acceptable.

Other ingredients

Other ingredients consist of the pharmaceutical excipients liquid paraffin and white petroleum. Liquid paraffin complies with its European Pharmacopoeia monograph and white petroleum complies with its British Pharmacopoeia monograph. Satisfactory certificates of analysis have been provided for all excipients.

None of the excipients used contain materials of animal or human origin.

Product development

A satisfactory pharmaceutical development section has been provided. The rationale and function of each excipient is discussed. The excipients used are typical in the manufacturing of ointments.

Manufacture

A satisfactory batch formula has been provided for the manufacture of the product along with an appropriate account of the manufacturing process. In-process controls are satisfactory based on process validation data and controls on the finished product. The manufacturing process has been validated and has shown satisfactory results.

Finished product specification

The finished product specification is satisfactory. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificate of analysis have been provided for all working standards used.

Container-closure system

The product is packaged in an aluminium tube with a nozzle and a screw cap closure made from polyethylene. Pack size is 4 grams. Suitable specifications and certificates of analysis have been provided for the finished packaging. All primary packaging has been shown to comply with Directive 2002/72/EC concerning contact of materials with food.

Stability of the product

Finished product stability studies have been conducted in accordance with current guidelines. Based on the results, a shelf-life of 24 months has been set (which reduces to 28 days after opening), with the storage instructions "Protect from light" and "Do not store above 25 degrees".

The applicant has provided suitable post approval stability commitments to follow-up the current batches on stability and to add the first three commercial batches as they become available.

Bioequivalence

No bioequivalence studies were submitted and none are required for an application of this type.

ADMINISTRATIVE**Expert Report**

A pharmaceutical expert report has been written by a suitably qualified person and is satisfactory.

Summary of Product Characteristics (SPC)

This is consistent with that for the reference product and is satisfactory.

Labelling

These are satisfactory

Patient Information Leaflet

This is consistent with the SPC and is satisfactory. The marketing authorisation holder has provided a commitment to update the marketing authorisation no later than 1st July 2008 with a package leaflet in compliance with Article 59 of Council Directive 2001/83/EC and that the leaflet shall reflect the results of consultation with target patient groups.

MAA Form

This is satisfactory.

Conclusion

It is recommended that a Marketing Authorisation is granted for this application.

The requirements for a generic medicinal product have been met with respect to qualitative and quantitative content of the active substance used in the proposed and reference products.

PRECLINICAL ASSESSMENT

This application claims to be a generic medicinal product of Chloromycetin 1% Ointment (Parke-Davis and Co Limited), which has been licensed within the EEA for over 10 years.

No new preclinical data have been supplied with this application and none are required for an application of this type.

CLINICAL ASSESSMENT

CLINICAL PHARMACOLOGY

No new data have been provided.

No new bioequivalence studies were undertaken as bioequivalence can be surmised from the quantitative and qualitative similarity of the applicant's and the reference product.

EFFICACY

No new data have been provided.

SAFETY

No new data have been provided.

EXPERT REPORTS

A clinical expert report has been written by a suitably qualified person and is satisfactory.

SUMMARY OF PRODUCT CHARACTERISTICS (SPC)

These are consistent with those for the reference products and are satisfactory.

PATIENT INFORMATION LEAFLET (PIL)

These are consistent with the SPC and are satisfactory.

LABELLING

These are satisfactory

APPLICATION FORMS (MAA)

These are satisfactory.

DISCUSSION

Bioequivalence has been shown from the quantitative and qualitative similarity of the applicant's and the reference product.

MEDICAL CONCLUSION

A marketing authorisation is recommended for this application.

OVERALL CONCLUSION AND RISK BENEFIT ASSESSMENT

QUALITY

The important quality characteristics of Chloramphenicol 1.0% w/w Eye Ointment 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.

PRECLINICAL

No new preclinical data were submitted and none are required for an application of this type.

EFFICACY

As the product is a simple ointment, quantitatively and qualitatively similar to the reference product, no bioequivalence data are required and the proposed products can be considered as generic medicinal products to the reference product.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory.

RISK BENEFIT ASSESSMENT

The quality of the product is acceptable and no new preclinical or clinical safety concerns have been identified. Extensive clinical experience with chloramphenicol is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

CHLORAMPHENICOL 1.0% W/W EYE OINTMENT
PL 17918/0004

STEPS TAKEN FOR ASSESMENT

1	The MHRA received the marketing authorisation applications on 21 st June 2002
2	Following standard checks and communication with the applicant the MHRA considered the applications valid on 21 st August 2002
3	Following assessment of the applications the MHRA requested further information relating to the clinical dossiers on 18 th September 2002, 7 th February 2003 and 19 th December 2003, and further information relating to the quality dossiers on 23 rd January 2003, 7 th February 2003 and 6 th February 2006
4	The applicant responded to the MHRA's requests, providing further information on 20 th November 2003 and 9 th December 2005 for the clinical sections, and on 20 th November 2003, 9 th December 2005 and 13 th December 2006 for the quality sections.
5	The applications were determined on 1 st March 2007

**CHLORAMPHENICOL 1.0% W/W EYE OINTMENT
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STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Chloramphenicol 1% w/w Eye Ointment

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of ointment contains Chloramphenicol 1.0% w/w

For full list of excipients, see Section 6.1

3 PHARMACEUTICAL FORM

Eye ointment

A yellowish-white ointment

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Chloramphenicol is a broad spectrum antibiotic for the treatment of bacterial conjunctivitis caused by chloramphenicol susceptible organisms.

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Topical administration to the eye only.

Adults, children and infants: The recommended dosage for adults, children and infants of all age groups is a small amount of the ointment to be applied to the affected eye every 3 hours or more frequently if required. Treatment should be continued for 48 hours after the eye appears normal.

Elderly: As for adults. Chloramphenicol has been used successfully at normal dosages in elderly patients. The pattern and incidence of adverse effects does not appear to differ from younger adults.

4.3 Contraindications

Chloramphenicol ointment must not be administered to:

- Patients who have a history of hypersensitivity to chloramphenicol or to any other ingredient of the ointment
- Patients who have experienced bone marrow suppression during previous exposure to chloramphenicol.

4.4 Special warnings and precautions for use

Chloramphenicol is absorbed systemically from the eye and systemic toxicity has been reported (see section 4.8).

Bone marrow hypoplasia, including aplastic anaemia and death, has been reported following topical use of chloramphenicol. Whilst the hazard is a rare one, it should be borne in mind when assessing the benefits expected from the use of the compound.

If chloramphenicol eye ointment is to be used on a long-term or intermittent basis, it may be advisable to perform a routine blood profile before therapy and at appropriate intervals thereafter to detect any haemopoietic abnormalities.

In severe bacterial conjunctivitis and in cases where infection is not confined to the conjunctivae, the topical use of chloramphenicol should be supplemented by appropriate systemic treatment.

Chloramphenicol does not provide coverage against *Pseudomonas* spp. or *Serratia marcescens*.

The use of topical chloramphenicol may occasionally result in overgrowth of non-susceptible organisms including fungi. If any new infection appears during treatment, the antibiotic should be discontinued and appropriate treatment given.

It is recommended that all types of contact lenses be avoided during ocular infections.

4.5 Interaction with other medicinal products and other forms of interaction

None Known

If a concomitant topical treatment to the eye is required, the administration of the different products should be separated by an adequate period of time.

4.6 Pregnancy and lactation

The safety of topical chloramphenicol in pregnancy and lactation has not been established. It should therefore only be used when considered essential by the physician and only if it is considered that the anticipated benefit outweighs the potential risk.

4.7 Effects on ability to drive and use machines

Blurring of vision can occur with the ointment and patients should be warned not to drive or operate machinery unless their vision is clear.

4.8 Undesirable effects

Transient burning or stinging sensations may occur with the use of chloramphenicol eye drops. Serious side effects include hypersensitivity reactions that may manifest as angioneurotic oedema, anaphylaxis, urticaria, fever, and vesicular and maculopapular dermatitis. Treatment must be discontinued immediately in such cases.

Bone marrow suppression, including the idiosyncratic type of irreversible and fatal aplastic anaemia that is recognized to occur with systemic therapy, has been reported in association with topical administration of chloramphenicol.

4.9 Overdose

Accidental overdose or accidental ingestion of chloramphenicol eye ointment is unlikely to cause systemic toxicity due to low content of chloramphenicol in the product.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

ATC Code: S01AA01

Mechanism of Action:

Chloramphenicol exerts its antibacterial effect by binding to bacterial ribosomes and inhibiting bacterial protein synthesis at an early stage.

Susceptibility:

The following bacterial species are recognised conjunctival pathogens and may be susceptible to chloramphenicol. However due to the prevalence of acquired resistance to chloramphenicol in these species, the results of susceptibility testing should be taken into account as soon as these are available. If no susceptibility test result is available, the choice of antibacterial agent should be influenced by local information on the likely prevalence of resistance to chloramphenicol in species that are commonly pathogenic in the eye.

Staphylococcus aureus

Streptococcus pyogenes

Streptococcus pneumoniae

Other beta-haemolytic streptococci

Haemophilus influenzae

Moraxella catarrhalis

Neisseria gonorrhoeae

Resistance:

Acquired resistance to chloramphenicol has been described in all the above species. Most commonly this is mediated by bacterial production of a chloramphenicol acetyl transferase that inactivates the drug. Chloramphenicol is not generally active against the enterobacteriaceae and is not active against non-fermenters such as *Pseudomonas aeruginosa*.

5.2 Pharmacokinetic properties

Chloramphenicol is found in measurable amounts in the aqueous humour following local application to the eye.
Systemic exposure to chloramphenicol occurs at a very low level after topical ophthalmic use.

5.3 Preclinical safety data

Pre-clinical safety data does not add anything of further significance to the prescriber.

6 PHARMACEUTICAL PARTICULARS**6.1 List of excipients**

Liquid paraffin
White soft paraffin

6.2 Incompatibilities

Not Applicable

6.3 Shelf life

2 years unopened
28 days opened

6.4 Special precautions for storage

Do not store above 25°C. Protect from light.

6.5 Nature and contents of container

Aluminium tube with epoxy-phenolic-ureic resin internal coating.
Polyethylene screw cap and nozzle.
Pack size 4g tube

6.6 Special precautions for disposal

Dispose of any unused ointment 28 days after opening the pack. Do not use if the pack is open when supplied.

7 MARKETING AUTHORISATION HOLDER

Tubilux Pharma SpA
Via Costarica,
20/22 – 00040 Pomezia
Rome, Italy

8 MARKETING AUTHORISATION NUMBER(S)

PL 17918/0004

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

01/03/2007

10 DATE OF REVISION OF THE TEXT

01/03/2007

CHLORAMPHENICOL 1% W/W EYE OINTMENT



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PATIENT INFORMATION LEAFLET

Please read this leaflet before you use this medicine, because it contains important information. If you do not understand it or have questions, ask your doctor or pharmacist.

WHAT IS IN THE TUBE?

The name of your medicine is Chloramphenicol Eye Ointment. It contains 1% Chloramphenicol which is equivalent to 1 mg of chloramphenicol per ml. It also contains liquid paraffin and white petroleum.

The active ingredient of your ointment is Chloramphenicol. Chloramphenicol Eye Ointment is an antibiotic ointment used to treat bacterial conjunctivitis, which is an infection that causes redness, discomfort and discharge from the affected eye.

Each tube of Chloramphenicol 1% Eye Ointment contains 4 grams of ointment.

WHO HAS MADE YOUR OINTMENT?

The product licence holder and manufacturer of Chloramphenicol 1% Eye Ointment is Tubilux Pharma S.p.A. Via Costarica 20/22, 00040 Pomezia, Italy

WHY DOES YOUR DOCTOR WANT YOU TO USE CHLORAMPHENICOL OINTMENT?

Your doctor has prescribed this medicine for you for the management of conjunctivitis, which is a bacterial infection of the eye. The antibiotic, chloramphenicol, will help to kill the bacteria (germs).

BEFORE YOU USE YOUR OINTMENT

You should only use Chloramphenicol Eye Ointment if your doctor has asked you to. Some people should not use Chloramphenicol Eye Ointment. Please read the following. If the answer is **yes** to **any** of these questions, you must tell your doctor before using this medicine.

- Are you sensitive/allergic to any of the ingredients in this product?
- Are you pregnant or intending to become pregnant?
- Are you breast-feeding?
- Are you taking other medicines?
- Have you experienced myelosuppression from previous use of Chloramphenicol?

WARNING

- If you are using this medicine and develop signs of irritation or sensitivity, please consult your doctor.

CAN YOU USE CHLORAMPHENICOL EYE OINTMENT WITH OTHER MEDICINES?

Your medicine may affect the action of other eye drops/ointments that you are using and could alter their effect. Therefore if you have to use other medicines with Chloramphenicol Eye Ointment you should discuss these with your doctor.

WHEN SHOULD CHLORAMPHENICOL EYE OINTMENT BE USED WITH CARE?

It is not advisable to wear any type of contact lenses during treatment with Chloramphenicol Eye Ointment.

Avoid driving or operating machinery if your vision becomes blurred immediately after using the eye ointment.

WHEN AND HOW TO USE CHLORAMPHENICOL EYE OINTMENT?

Following your doctor's directions about when and how to use Chloramphenicol Eye Ointment and look at the label. Your pharmacist may also help if you are not sure.

You should use the ointment exactly as your doctor has directed.

The usual dose for adults, children and infants of all age groups is as follows:

A small amount of ointment to be applied into the affected eye every three hours or more frequently if required, as directed by your doctor.

Treatment is normally continued for 48 hours after the eye appears normal.

If you have a severe infection you may also be given antibiotics to take by mouth.

Chloramphenicol may not work against certain types of infections. If your symptoms are not getting better you should tell your doctor at once.

If you use Chloramphenicol Eye Ointment for a long time, your doctor may want to take blood samples to make sure the chloramphenicol has not affected your blood in any way.

The contents are sterile until the seal is broken. Do not use if the seal is broken before first opening.

Before using the eye ointment wash your hands.

Unscrew the cap and tilt your head backwards.

Gently squeeze the tube and measure about 1 cm of ointment onto the forefinger.

Pull the lower eyelid gently downward with the other hand to form a pocket between your eyelid and your eye.

Apply the ointment to the lower eyelid having used the other hand.

Avoid touching the eye with the tip of the tube.

Put the cap on the tube and wash your hands.

WHAT IF I MISS A DOSE?

If you miss a dose of Chloramphenicol Eye Ointment you should put the ointment into the eye as soon as possible, but if it is almost time for the next dose then miss the skipped dose and return to your normal dosing schedule.

WHAT IF I USE TOO MUCH?

If you accidentally use too much or swallow your ointment, contact your doctor straight away or go to the nearest hospital casualty department. Always take the remaining ointment in the tube with the label, to enable the doctor or the hospital to identify the medicine.

CAN CHLORAMPHENICOL EYE OINTMENT CAUSE PROBLEMS?

Chloramphenicol 1% Eye Ointment is usually well tolerated.

However as with other eye preparations, you may occasionally experience eye irritation or visual blurring after initial insertion. If this persists, increases, or if you notice any other changes, stop using your medicine and consult your doctor or pharmacist. Do not drive or operate hazardous machinery while this persists.

Sometimes, when an antibiotic is used for a long time, other types of bacteria or fungi, which are not killed, take over from the original infection. This may seem as if the original infection has not cleared up or has got worse. Therefore, if you do not get better, tell your doctor at once, he/she may need to change your treatment.

If you develop any of the following, stop using the ointment and tell your doctor at once: wheezing, fever, swelling of your face, lips or tongue, rash with swelling of the skin. On very rare occasions, patients using chloramphenicol have developed changes in the make up of their blood. This might lead to bruising, bleeding, infections and weakness. If you get these or any other unusual effects you should tell your doctor immediately.

STORING YOUR CHLORAMPHENICOL EYE OINTMENT CONTAINER

Keep this medicine in its original container, store below 25°C and protect from light.

- Do not give your medicine to someone else, even if they have the same symptoms.
- Keep this medicine away from children.
- Do not use this medicine after the expiry date shown on the label.
- The medicine should not be used for longer than 28 days after first opening the tube; any eye ointment left in the tube after this time should be returned to your pharmacist.

A REMINDER

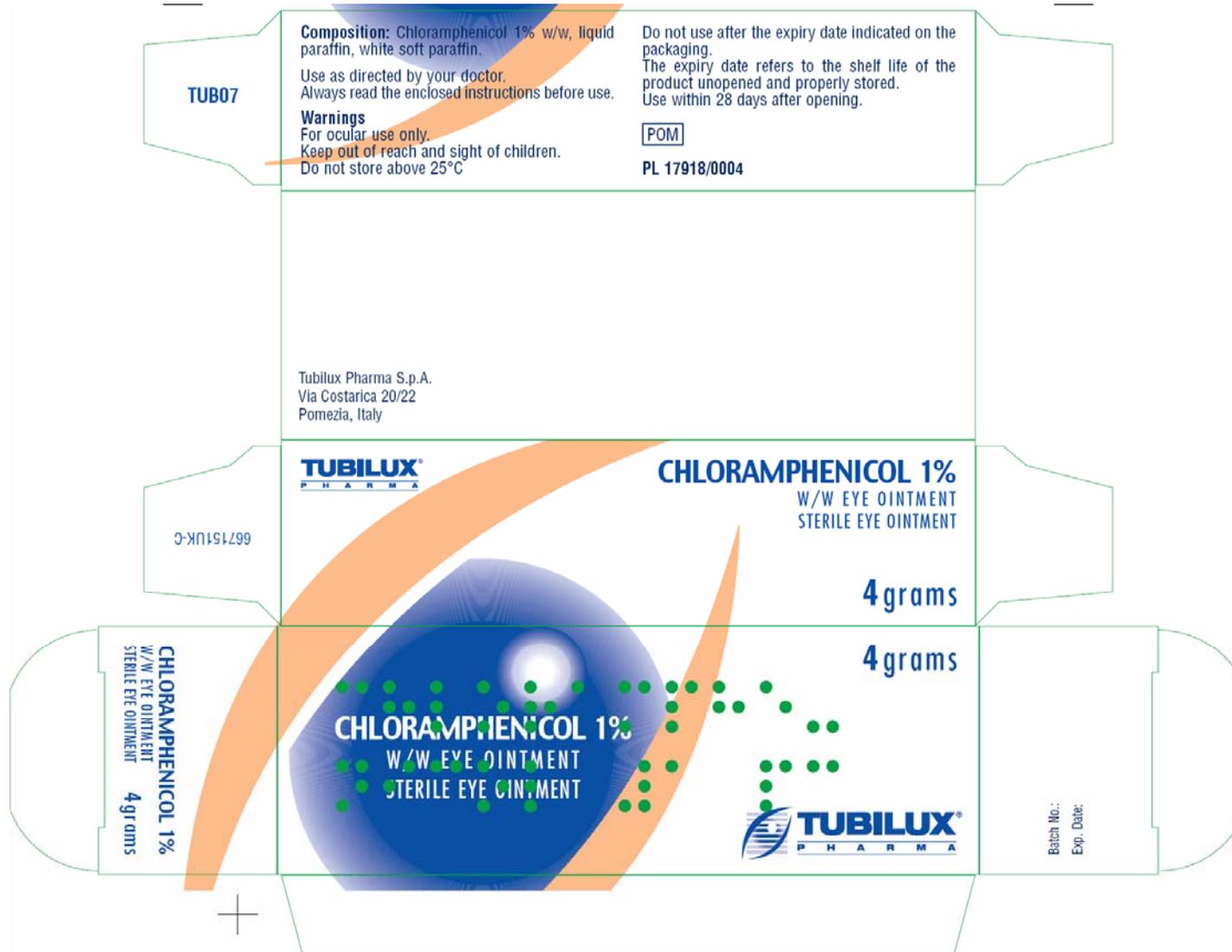
Remember this medicine is for you. Never give it to someone else, even if his or her symptoms are the same as yours.

The leaflet does not contain the complete information about Chloramphenicol 1% Eye Ointment. If you have any questions or are not sure about anything ask your doctor or pharmacist who has access to additional information.

The information in this leaflet applies only to Chloramphenicol 1% Eye Ointment.

The leaflet was prepared in March 2006

Chloramphenicol 1% w/w Eye Ointment PL No. 17918/0004





227151UK-C
TUBILUX®
P H A R M A

4 grams



Composition: Chloramphenicol 1% w/w, liquid paraffin, white soft paraffin

Use as directed by your doctor.

Always read the enclosed instructions before use

Warnings

For ocular use only.

Keep out of reach and sight of children.

Do not store above 25°C

Do not use after the expiry date indicated on the packaging.

Use within 28 days after opening.

Tubilux Pharma S.p.A.
Via Costarica, 20/22,
Pomezia, Italy



POM

PL 17918/0004