Public Assessment Report

Trimethoprim 200mg Tablets

Trimethoprim

PL 18224/0057

Karib Kemi-Pharm Ltd

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Lay Summary

The MHRA granted a Marketing Authorisation (licence) to Karib Kemi-Pharma for the medicinal product Trimethoprim 200mg Tablets on 02/03/2009. The product was confirmed to be identical to the cross reference product, Trimethoprim 200 mg Tablets (PL 16363/0024), held by Milpharm Limited, London, UK.

Trimethoprim is an anti-bacterial drug used in the treatment of susceptible infections caused by Trimethoprim sensitive organisms including most gram-positive and gram-negative aerobic organisms and in for the prophylaxis of recurrent urinary tract infections.

The product contains the active ingredient trimethoprim, a bacteriostatic antibiotic that interferes with the action of dihydrofolate reductase, inhibiting the synthesis of tetrahydrofolic acid (and thus synthesis of DNA nucleosides thymidine and uridine).
Scientific Discussion

INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the UK granted marketing authorisations for the medicinal product Trimethoprim 200mg Tablets to Karib Kemi-Pharm Ltd on 02/03/2009.

The product contain the active ingredient trimethoprim, a bacteriostatic antibiotic that interferes with the action of dihydrofolate reductase, inhibiting the synthesis of tetrahydrofolic acid (and thus synthesis of DNA nucleosides thymidine and uridine). Bacteria are unable to take up folic acid from the environment and are thus dependant on their own de novo synthesis, so inhibition of this system starves the bacteria of two bases necessary for DNA replication and transcription.

Trimethoprim is used in the treatment of susceptible infections caused by Trimethoprim sensitive organisms including most gram-positive and gram-negative aerobic organisms and in for the prophylaxis of recurrent urinary tract infections.

This was a national simple abridged; ‘informed consent’ application submitted under article 10c (Directive 2001/83/EC as amended) for Trimethoprim 200 mg tablets by Karib Kemi-Pharm Limited. It is cross-referring to PL 16363/0024 for Trimethoprim 200 mg Tablets held by Milpharm Limited, London, UK, which was first authorised in March, 2001 as an abridged simple application.

The holder of the cross reference product has declared that the applicant does have access to the quality, pre-clinical and clinical dossiers and the applicant has provided a declaration that they have the quality dossier in their possession.

PHARMACEUTICAL ASSESSMENT

DRUG SUBSTANCE

Trimethoprim  (Ph. Eur.)  
Molecular formula: C_{14}H_{18}N_{4}O_{3};  Molecular weight: 290.3  
White or yellowish-white powder. Very slightly soluble in water, slightly soluble in alcohol.  
ATC code:  J01E A01

![Chemical Structure of Trimethoprim]

Physical form: White or yellowish white powder

Solubility: Very slightly soluble in water, slightly soluble in alcohol

The drug substance is made by the same manufacturer and by the same process as the reference product.
An appropriate specification based on the European Pharmacopoeia has been provided.

Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Active trimethoprim is stored in appropriate packaging. The specifications and typical analytical test reports are provided and are satisfactory.

Batch analysis data are provided and comply with the proposed specification.

Satisfactory certificates of analysis have been provided for working standards used by the active substance manufacturer and finished product manufacturer during validation studies.

Appropriate stability data have been generated.

**DRUG PRODUCT**

**Other Ingredients**

The other ingredients of the drug product are listed below

<table>
<thead>
<tr>
<th>Ingredient</th>
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<tr>
<td>Trimethoprim</td>
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<tr>
<td>Lactose Monohydrate</td>
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<tr>
<td>Povidone 25CPS</td>
<td></td>
</tr>
<tr>
<td>Crospovidone</td>
<td></td>
</tr>
<tr>
<td>Sodium starch glycollate (Type A)</td>
<td></td>
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<tr>
<td>Magnesium Stearate</td>
<td></td>
</tr>
<tr>
<td>Industrial Methylated spirit</td>
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<td>Water Purified</td>
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The composition is identical to the previously approved cross-referenced product. No excipients of human or animal origin are used.

**Manufacture**

The drug product will be manufactured by the same manufacturer using the same processes as the reference product. A statement from the finished product manufacturer indicating their willingness to manufacture the product for the applicant was provided.

**Finished product specification**

The finished product specification is satisfactory.

**Container Closure System**
Pack sizes of 50, 100, 500, 1000 and 5000 tablets for bulk packs and blister packs of 6, 14 and 28 tablets as patient packs are proposed. These are identical to previously approved product. (Pack sizes of 6 & 14 tablets were added as a variation (0008; 20/05/03) to the original application in the cross-referenced product).

The MAA and SPC indicate that the finished product will be packed in:
   a) High density polystyrene with polythene lids and/or polypropylene containers with polythene lids and polyurethane or polythene inserts for pack sizes of 50 tablets and above
   b) Blister pack - 25μ PVC glass-clear/bluish rigid PVC (pharmaceutical grade) 20 micron hard tempered aluminium foil coated on the pull side with 6-7 gsm heat seal lacquer and printed on the bright side.

These are identical to that of the cross-referenced products.

**Stability**
The proposed shelf life for 36 months has been previously approved for the cross-referenced product.

The recommended storage conditions are Do not store above 25ºC. Store in the original container.

**Summary of Product Characteristics**
The SPC for the product reflects the SPC of the cross-referenced product.

**Patient Information Leaflet**
Patient information leaflet is identical to that approved for the cross-reference product, and is therefore, acceptable.

**ASSESSOR'S OVERALL CONCLUSIONS ON QUALITY AND ADVICE**
A Marketing Authorisation was granted.
PRE-CLINICAL ASSESSMENT

No pre-clinical data were submitted for this application and none were required.
MEDICAL ASSESSMENT

No clinical data were submitted with this application and none were required.
Overall Conclusion and Risk/Benefit Analysis

Quality
The quality aspects of the product were confirmed to be identical to the cross-reference product.

Pre-Clinical
No new preclinical data were submitted and none are required for applications of this type.

Clinical
The clinical aspects of the product were confirmed to be identical to the cross-reference product.

Risk/Benefit Analysis
The product was demonstrated to be identical to the cross-reference product and which has already been found to have a positive risk/benefit ratio.
### Steps Taken During Assessment

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<tr>
<td>1</td>
<td>The MHRA received the application on 22/02/2006.</td>
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<td>2</td>
<td>Following standard checks and communication with the applicant the MHRA considered the application valid on 27/02/2006.</td>
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<tr>
<td>3</td>
<td>Following assessment of the application the MHRA requested further information from the applicant regarding the quality assessment on 16/06/2006, and 18/03/2008.</td>
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<td>4</td>
<td>The applicant provided further information in regard to the quality assessment on 08/08/2007, and 19/08/2008.</td>
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<tr>
<td>5</td>
<td>The application was determined on 02/03/2009</td>
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Steps Taken after Assessment

No non-confidential changes have been made to the market authorisation.
SUMMARY OF PRODUCT CHARACTERISTICS

1  NAME OF THE MEDICINAL PRODUCT
Trimethoprim 200mg Tablets.

2  QUALITATIVE AND QUANTITATIVE COMPOSITION
Trimethoprim  200.00mg
For a full list of all excipients, see section 6.1.

3  PHARMACEUTICAL FORM
Tablet; White coloured flat bevelled edged tablets engraved with 'MT200'.
Slight characteristics odour

4  CLINICAL PARTICULARS

4.1  Therapeutic indications
Treatment of susceptible infections caused by Trimethoprim sensitive organisms including most gram-positive and gram-negative aerobic organisms, including *Haemophilus influenzae*, *Streptococcus pneumoniae*, *Klebsiella pneumonia*, *Staphylococcus aureus*, *Eschersichia coli*, *Enterobacter*, *Proteus* and *Streptococcus faecalis*.

Exceptions include anaerobic bacteria. *Mycobacterium tuberculosis*, *Neisseria gonorrhoeae*, *pseudomonas aeruginosa* and *Treponema pallidum*.

Prophylaxis of recurrent urinary tract infections.

Route of administration: Oral

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

4.2  Posology and method of administration
*Adults*: treatment of urinary tract infections and all other susceptible infections: 200mg twice daily.
Long term prophylaxis of recurrent urinary tract infections: 100mg at night before bedtime.

Children: 4 months to 12 years of age: - treatment of urinary tract infection and all other susceptible infections: 60mg/kg bodyweight daily, sub-divided into 2 equal doses.

Long term prophylaxis of recurrent urinary tract infections: 2.5mg/kg bodyweight daily given as a single dose before bedtime.

Elderly: treat as for adults.

4.3 Contraindications
Hypersensitivity to Trimethoprim or to any other component of the formulation. Severe hepatic insufficiency. Severe renal insufficiency. Megaloblastic anaemia and other blood dyscrasias. Trimethoprim should not be administered to premature infants or children under 4 months of age.

Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galacactose malabsorption should not take this medicine.

4.4 Special warnings and precautions for use
Patients with marked impairment of renal function; care should be taken to avoid accumulation and resulting adverse hepatological effects. Regular haematological tests should be undertaken in patients receiving long-term treatment and those pre-disposed to folate deficiency. Particular care should be exercised in the haematological monitoring of children on long-term therapy.

4.5 Interaction with other medicinal products and other forms of interaction
Trimethoprim may potentiate the anticoagulant effects of warfarin.

4.6 Pregnancy and lactation
Trimethoprim should not be administered to pregnant women. Trimethoprim is not contraindicated for short-term use in lactating mothers, although the drug is excreted in breast milk.

4.7 Effects on ability to drive and use machines
None known.
4.8 Undesirable effects
Nausea, vomiting, gastro-intestinal disturbances, headache are rare. Skin rash, pruritis and urticaria have been reported occasionally. Cases of megaloblastic anaemia during prolonged therapy with trimethoprim in doses higher than those recommended rarely occur but are reversible with discontinuation of therapy and administration of folinic acid. More severe skin sensitivity reactions like erythema multiforme, Stevens Johnson syndrome and epidermal necrolysis have been reported rarely. Aseptic meningitis has been reported.

Anaphylactic reactions, anaphylactoid reactions and angioedema have been reported rarely.

4.9 Overdose
Treat symptomatically, gastric lavage and forced diuresis can be used. Depression of haematopoiesis by trimethoprim can be counteracted by intramuscular injections of calcium folinate.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties
Trimethoprim has a potent anti-microbial activity through its selective inhibition of bacterial dihydrofolate reductase. It is effective against most gram-positive and gram-negative aerobic organisms.

5.2 Pharmacokinetic properties
Absorption is by the oral route. Peak plasma levels are reached in about one hour but significant plasma levels are obtained within half-an-hour.

Excretion is mainly in the urine in the form of the unchanged drug.

Trimethoprim may cause an apparent rise in serum creatinine levels due to competition in the tubular secretory mechanisms.

5.3 Preclinical safety data
There are no preclinical data of relevance to the prescriber additional to that included in other sections of SmPC.
6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

- Lactose monohydrate
- Povidone 25cps
- Crospovidone
- Sodium starch glycollate
- Magnesium stearate E572
- Industrial methylated spirit
- Purified water

6.2 Incompatibilities
None known

6.3 Shelf life
36 months

6.4 Special precautions for storage
Do not store above 25°C. Store in the original container.

6.5 Nature and contents of container
High density polystyrene with polythene lids and/or polypropylene containers with polythene lids and polyurethane or polythene inserts.

Blister pack - 25 micron PVC glass-clear/bluish rigid PVC (pharmaceutical grade) 20 micron hard tempered aluminium foil coated on the pull side with 6-7 gsm heat seal lacquer and printed on the bright side.

Pack sizes: 50, 100, 500, 1000, 5000 (Bulk pack), 6, 14 & 28 (blister pack)

6.6 Special precautions for disposal
No special instruction

7 MARKETING AUTHORISATION HOLDER
Karib Kemi Pharm Limited
Karib House
63-65 Imperial Way
Croydon
Surrey CR0 4RR
U. K.

8 MARKETING AUTHORISATION NUMBER(S)
PL 18224/0057

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
02/03/2009

10 DATE OF REVISION OF THE TEXT
02/03/2009
Read all of this leaflet carefully before you start taking this medicine.
• Keep this leaflet. You may need to read it again.
• If you have any further questions, ask your doctor or pharmacist.
• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.
• If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

In this leaflet:
1. WHAT TRIMETHOPRIM 200mg TABLETS ARE AND WHAT THEY ARE USED FOR
2. BEFORE YOU TAKE TRIMETHOPRIM 200mg TABLETS
3. HOW TO TAKE TRIMETHOPRIM 200mg TABLETS
4. POSSIBLE SIDE EFFECTS
5. HOW TO STORE TRIMETHOPRIM 200mg TABLETS
6. FURTHER INFORMATION

1. WHAT TRIMETHOPRIM 200mg TABLETS ARE AND WHAT THEY ARE USED FOR

Trimethoprim belongs to a group of medicines called anti-infectives; it is a broad-spectrum agent which kills a wide range of bacteria causing your symptoms.

Trimethoprim is used for the treatment of infections caused by organisms that are susceptible to Trimethoprim and particularly for the prevention of recurring urinary tract infection.

2. BEFORE YOU TAKE TRIMETHOPRIM 200mg TABLETS

Do not take Trimethoprim 200mg Tablets
• If you are allergic (hypersensitive) to trimethoprim or any of the other ingredients of Trimethoprim 200mg Tablets.

Take special care with TRIMETHOPRIM 200mg TABLETS
• If you are allergic to any other substances such as food, preservatives or dyes.
• If you have had liver disease, renal (kidney) problems and any form of anaemia.
• If you are pregnant or likely to become pregnant.
• If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.
Taking other medicines
Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Although certain medicines should not be used together at all, in other cases two different medicines may be used together even if an interaction might occur. In these cases, your doctor may want to change the dose, or other precautions may be necessary. Tell your doctor if you are taking any of the following:

Warfarin: Trimethoprim may potentiate the anticoagulant effect of Warfarin. Check with your doctor before taking any such medicine while you are taking trimethoprim.

Taking TRIMETHOPRIM 200mg TABLETS with food and drink
There are no special instructions for taking Trimethoprim 200mg Tablets with food and drink.

Pregnancy and breast-feeding
Ask your doctor or pharmacist for advice before taking any medicine. Do not use Trimethoprim 200mg Tablets during pregnancy unless your doctor considers it absolutely essential. Trimethoprim 200mg Tablets can be used by breast-feeding mothers, although trimethoprim is passed into breast milk.

Driving and using machines
There are no known effects on driving ability or using machines.

Important information about some of the ingredients of TRIMETHOPRIM 200mg TABLETS
Patients who are intolerant to lactose should note that each Trimethoprim 200mg Tablet contains a small amount of lactose.

3. HOW TO TAKE TRIMETHOPRIM 200mg TABLETS

Always take Trimethoprim 200mg Tablets exactly as your doctor has told you. You should check with your doctor or pharmacist if you are not sure. Take this medicine by mouth and only in the doses prescribed by your doctor.

The usual dose is:

Adults and the elderly
Treatment of urinary tract infections and all other susceptible infections: 200mg twice daily
Long-term preventive treatment of recurrent urinary tract infections: 100mg at night before bedtime.

Children
Trimethoprim 200mg Tablets must not be given to children under 4 months of age.
4 months to 12 years of age
Treatment of urinary tract infections and all other susceptible infections: 60mg/kg body weight daily, sub-divided into 2 equal doses.
Long term preventive treatment of recurring urinary tract infections: 2.5mg/kg body weight daily given as single dose before bedtime.
If you feel that this medicine is not working as well after you have taken it for a short time (1-2 weeks) do not increase the dose, instead check with your doctor.

If you take more TRIMETHOPRIM 200mg TABLETS than you should
If you should accidently swallow a greater quantity of Trimethoprim 200mg Tablets that have been prescribed for you, contact your doctor or the Accident & Emergency Department of your nearest hospital at once. Always keep any remaining tablets in the labelled container in which they were given to you so that the medicine can be identified by the doctor or the pharmacist at the hospital.

If you forget to take TRIMETHOPRIM 200mg TABLETS
If you forget to take your medicine, just carry on with the next dose as normal. Do not take a double dose to make up for a forgotten dose. If you are not sure, ask your doctor or pharmacist for advice. If you stop taking TRIMETHOPRIM 200mg TABLETS
Do not stop the treatment without talking to your doctor first. You may feel well but the tablets are helping to prevent another attack of your disease. If you have any further questions on the use of this product, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS
Like all medicines, Trimethoprim 200mg Tablets can cause side effects, although not everybody gets them.

Occasional: Trimethoprim 200mg Tablets may cause skin rashes, itching and redness of the skin.

The following need quick medical attention:

Rare: nausea, vomiting, gastro-intestinal disturbances, headache, severe skin lesions, severe rashes, blistering and peeling of the skin and ulceration of mouth which may be accompanied by generalised symptoms such as fever.

Allergic reactions: a puffy, swollen face, tongue or body have been reported rarely. Very occasionally, these reactions may be severe causing shortness of breath, swelling, shock and collapse. If you develop any allergic symptoms, stop taking the medicine and contact your doctor immediately.

There is a possibility of the patient developing anaemia, mostly megaloblastic anaemia on prolonged treatment. This is more probable in patients who are prone to low levels of folate (a substance in the body which comes from several foods). Blood test should be done at regular intervals during long term therapy.
If any of the side effects gets serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.

5. HOW TO STORE TRIMETHOPRIM 200mg TABLETS

Do not store above 25°C. Store in the original container.
Keep out of the reach and sight of children.

Do not use Trimethoprim 200mg Tablets after the expiry date which is stated on the carton after EXPIRY DATE. The expiry date refers to the last day of that month.

Medicines should not be disposed of via wastewater or household waste. Ask your pharmacist how to dispose of medicines no longer required. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Trimethoprim 200mg Tablets contains

The active substance is (Trimethoprim.
The other ingredients are Lactose monohydrate, Povidone, Cross povidone, Sodium starchglycollate and Magnesium stearate.

What Trimethoprim 200mg Tablets looks like and contents of the pack

Trimethoprim 200mg Tablets are white, flat beveled edged tablets engraved with ‘MT200’.

The tablets are available in container pack sizes of 50, 100, 500, 1000 and 5000. The tablets are also available in blister packs of 6, 14 and 28 tablets.

Marketing Authorisation Holder and Manufacturer

The Product Licence Holder and Manufacturer of Trimethoprim 200mg Tablets is:
Karib Kemi Pharm Ltd., Karib House, 63-65 Imperial Way, Croydon, Surrey CR0 RR, UK.

This leaflet was last approved in May 2007.