Public Assessment Report

Decentralised Procedure

CLINDAMYCIN 300 MG CAPSULES, HARD

UK/H/4176/002/DC
UK Licence No: PL 33155/0012

RIVOPHARM (UK) LIMITED
LAY SUMMARY

On 10th July 2012, the UK granted Rivopharm (UK) Limited a Marketing Authorisation (licence) for Clindamycin 300 mg capsules, hard.

Clindamycin 300 mg capsules, hard contain clindamycin hydrochloride and belongs to a group of medicines called antibiotics. Antibiotics are used to treat infections. Clindamycin capsules are used to kill certain serious bacterial infections.

No new or unexpected safety concerns arose from this application and it was, therefore, judged that the benefits of taking Clindamycin 300 mg capsules, hard outweigh the risks; hence a Marketing Authorisation has been granted.
# TABLE OF CONTENTS

Module 1: Information about initial procedure .................................................. Page 4
Module 2: Summary of Product Characteristics .............................................. Page 5
Module 3: Product Information Leaflets ......................................................... Page 10
Module 4: Labelling ......................................................................................... Page 14
Module 5: Scientific Discussion ....................................................................... Page 16  
  1 Introduction
  2 Quality aspects
  3 Non-clinical aspects
  4 Clinical aspects
  5 Overall conclusions
Module 6: Steps taken after initial procedure .................................................. Page 25
# Module 1

<table>
<thead>
<tr>
<th><strong>Product Name</strong></th>
<th>Clindamycin 300 mg Capsules, Hard</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Type of Application</strong></td>
<td>Generic hybrid, Article 10.3</td>
</tr>
<tr>
<td><strong>Active Substance</strong></td>
<td>Clindamycin hydrochloride</td>
</tr>
<tr>
<td><strong>Form</strong></td>
<td>Capsule, hard</td>
</tr>
<tr>
<td><strong>Strength</strong></td>
<td>300 mg</td>
</tr>
</tbody>
</table>
| **Marketing Authorisation Holder (MAH)** | Rivopharm UK Limited  
6th floor, 28 Kingsway  
London  
WC2B 6JR  
United Kingdom |
| **Reference Member State (RMS)** | UK |
| **Concerned Member State (CMS)** | Norway (NO) and Sweden (SE) |
| **Procedure Number**   | UK/H/4176/002/DC                  |
| **End of Procedure**   | Day 205 – 8th June 2012           |
Module 2
Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT
Clindamycin 300 mg capsules, hard.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION
Each capsule contains:
clindamycin hydrochloride equivalent to 300 mg clindamycin.
Exciipient: 283 mg lactose/ Clindamycin 300 mg capsules
For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM
Capsule.
Clindamycin capsules are white/white hard capsules with a marking of 'CLIN 300' on the capsule body.

4 CLINICAL PARTICULARS
4.1 Therapeutic indications
Clindamycin is indicated for the treatment of:
Serious infections caused by anaerobic bacteria, including intra-abdominal infections, skin and soft tissue infections. As needed, clindamycin should be administered in conjunction with another antibacterial agent that is active against gram negative aerobic bacteria.
- Tonsillitis
- Dental infection

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

4.2 Posology and method of administration
Clindamycin capsules are given orally. The product should always be taken with a full glass of water in an upright position.
Absorption of Clindamycin capsules is not appreciably modified by the presence of food.

Adults,
The usual dose is 150-450 mg every six hours, depending on the severity of the infection.

Elderly patients
Dosage requirements in elderly patients should not be influenced by age alone

Children
The usual dose is 3-6 mg/kg every six hours depending on the severity of the infection (not to exceed the adult dose).

Clindamycin capsules are not suitable for children who are unable to swallow them whole. The capsules do not provide exact mg/kg doses therefore it may be necessary to use an alternative formulation in some cases.

Renal impairment
No dose adjustment is necessary in patients with mild to moderate impairment of renal function. In patients with severe renal impairment or anuria, plasma concentration should be monitored. Depending on the results, this measure can make a reduction in dosage or an increase in the dose interval of 8 or even 12 hours necessary.

Hepatic impairment
In patients with moderate to severe hepatic impairment, elimination half-life of clindamycin is prolonged. A reduction in dosage is generally not necessary if clindamycin is administered every 8 hours. However, the plasma concentration of clindamycin should be monitored in patients with severe hepatic impairment. Depending on the results, this measure can make a reduction in dosage or an increase in the dose intervals necessary.
4.3 Contraindications
Clindamycin capsules are contraindicated in patients previously found to be sensitive to clindamycin, lincomycin or to any of the excipients.

4.4 Special warnings and precautions for use
Clindamycin should only be used in the treatment of serious infections and when the possible benefit of using clindamycin is considered to outweigh the risk of antibiotic-associated diarrhoea or colitis, which may progress to pseudomembranous colitis, toxic megacolon and death. These intestinal complications are more likely to be severe and to become life-threatening in older patients or patients who are debilitated. Caution should also be used when prescribing clindamycin for individuals with a history of gastrointestinal disease, especially colitis.

If marked diarrhoea occurs during therapy, clindamycin should be discontinued immediately and appropriate diagnostic and therapeutic measures should be instituted. It should be noted that the onset of these intestinal complications of clindamycin treatment may be delayed until several weeks following the cessation of therapy. The most commonly implicated cause is an overgrowth of toxin-producing Clostridium difficile as a result of disruption of the bowel flora by clindamycin.

Laboratory tests for renal and hepatic function should be carried out during prolonged therapy. Close monitoring is also recommended in patients with renal or hepatic insufficiency and in neonates and infants, all of whom may require dose reduction and/or an extended interval between doses. Prolonged administration of Clindamycin capsules, as with any anti-infective, may result in super – infection due to organism resistant to clindamycin.

Care should be observed in the use of Clindamycin capsules in atopic individuals.

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

The choice of clindamycin should be based on factors such as severity of the infection, the prevalence of resistance to other suitable agents and the risk of selecting clindamycin-resistance bacteria

4.5 Interaction with other medicinal products and other forms of interaction
Clindamycin has been shown to have neuromuscular blocking properties that may enhance the action of other neuromuscular blocking agents. It should be used with caution, therefore, in patients receiving such agents.

Antagonism has been demonstrated between clindamycin and erythromycin in vitro. Because of possible clinical significance the two drugs should not be administered concurrently.

4.6 Fertility, pregnancy and lactation

Fertility
In animal studies, clindamycin had no effect on male or female fertility (see Section 5.3).

Pregnancy
Safety for use in pregnancy has not yet been established. In animal studies, no effect of Clindamycin on embryofetal and postnatal development was observed (see section 5.3). The use of Clindamycin capsules may be considered during pregnancy, if necessary.

Lactation
Clindamycin is excreted in human milk. Caution should be exercised when Clindamycin capsules are administered to a nursing mother.

4.7 Effects on ability to drive and use machines
Clindamycin is not known to interfere with the ability to drive or operate machinery.

4.8 Undesirable effects

Blood and the lymphatic system disorders
Transient neutropenia (leucopenia), eosinophilia, agranulocytosis and thrombocytopenia have been reported. No direct aetiological relationship to concurrent clindamycin therapy could be made in any of the foregoing.
Immune system disorders
A few cases of anaphylactoid reactions have been reported.

Gastro-intestinal disorders
Oesophageal ulcers have been reported as serious adverse events: oesophagitis with oral preparations, nausea, vomiting abdominal pain and diarrhoea (see Section 4.4 Special Warnings and Special Precautions for Use, Warning)

Hepato-biliary disorders
Jaundice and abnormalities in liver function tests have been observed during clindamycin therapy.

Skin and subcutaneous tissue disorders
Maculopapular rash and urticaria have been observed during drug therapy. Generalised mild to moderate morbilliform-like skin rashes are the most frequently reported reactions. Rare instances of erythema multiforme, some resembling Stevens-Johnson syndrome, have been associated with clindamycin. Pruritus, vaginitis and rare instances of exfoliative and vesiculobullous dermatitis have been reported. Serious cutaneous adverse reaction (SCAR) and rare cases of toxic epidermal necrolysis have been reported during post-marketing surveillance.

Nervous system disorders
Frequent cases of Dysgeusia have been observed upon systemic administration of clindamycin using injectables (IM or IV), capsules, or oral granulate solutions, which include a few (non-frequent) serious adverse events.

4.9 Overdose
In cases of overdosage no specific treatment is indicated. The serum biological half-life of clindamycin is 2.4 hours. Clindamycin cannot readily be removed from the blood by dialysis or peritoneal dialysis.

If an allergic adverse reaction occurs, therapy should be with the usual emergency treatments, including corticosteroids, adrenaline and antihistamines.

5 PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antimicrobial, systemic
ATC classification: J01FF

Mode of action
Clindamycin is a lincosamide antibiotic with a primarily bacteriostatic action against Gram-positive aerobes and a wide range of anaerobic bacteria. Lincosamides such as clindamycin bind to the 50S subunit of the bacterial ribosome similarly to macrolides such as erythromycin and inhibit the early stages of protein synthesis. The action of clindamycin is predominantly bacteriostatic although high concentrations may be slowly bactericidal against sensitive strains.

Mechanism of resistance
Resistance to clindamycin usually occurs via macrolide-lincosamide-streptogramin B (MLS\textsubscript{B}) type of resistance, which may be constitutive or inducible.

Breakpoints
The minimum inhibitory concentrations (MIC) breakpoints are as follows:

- Eucast
  - Staphylococci: sensitive ≤ 0.5 resistant > 0.5
  - Streptococci ABCG and pneumoniae: sensitive ≤ 0.5 resistant > 0.5
  - Gram positive anaerobes: sensitive ≤ 4 resistant > 4
  - Gram negative anaerobes: ≤ 4 resistant > 4

Susceptibility
The prevalence of acquired resistance may vary geographically and with time for selected species and local information on resistance is desirable, particularly when treating severe infections. As necessary, expert advice should be sought when local prevalence of resistance is such that the utility of the agent in at least some types of infections is questionable.
Species

<table>
<thead>
<tr>
<th>Susceptible Gram-positive aerobes</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Staphylococcus aureus</em></td>
</tr>
<tr>
<td><em>Staphylococcus epidermidis</em></td>
</tr>
<tr>
<td><em>Streptococcus pneumonia</em></td>
</tr>
<tr>
<td><em>Streptococcus pyogenes</em></td>
</tr>
<tr>
<td><em>Streptococcus viridans</em></td>
</tr>
</tbody>
</table>

Anaerobes

<table>
<thead>
<tr>
<th>Bacteroides fragilis group</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Bacteroides melaninogenicus</em></td>
</tr>
<tr>
<td><em>Bifidobacterium</em></td>
</tr>
<tr>
<td><em>Clostridium perfringens</em></td>
</tr>
<tr>
<td><em>Eubacterium</em></td>
</tr>
<tr>
<td><em>Fusobacterium</em></td>
</tr>
<tr>
<td><em>Peptococcus</em></td>
</tr>
<tr>
<td><em>Peptostreptococcus</em></td>
</tr>
<tr>
<td><em>Propionibacterium</em></td>
</tr>
<tr>
<td><em>Veillonella</em></td>
</tr>
</tbody>
</table>

Resistant

<table>
<thead>
<tr>
<th>Clostridia spp.</th>
</tr>
</thead>
<tbody>
<tr>
<td>Enterococci</td>
</tr>
<tr>
<td>Enterobacteriaceae</td>
</tr>
</tbody>
</table>

*Up to 50% of methicillin-resistant *S. aureus* have been reported to be resistant to clindamycin in some areas. More than 90% of methicillin-resistant *S. aureus* (MRSA) are resistant to clindamycin and it should not be used while awaiting susceptibility test results if there is any suspicion of MRSA.

5.2 Pharmacokinetic properties

General characteristics of active substance

Absorption

After oral administration clindamycin is absorbed quickly and almost completely (>90%). The absorption is not affected by food. The peak plasma concentration is achieved within approximately 45 minutes after oral administration. The bioavailability is non-linear and decreases with increasing doses. Following a 600 mg dose the absolute bioavailability is 53±14%.

Distribution

Clindamycin is widely distributed in body fluids and tissues. It diffuses across the placenta but not the healthy blood-brain barrier. 68 – 93 % of clindamycin in the circulation is bound to plasma proteins. Clindamycin is distributed very highly intracellular due to the lipophilic properties. The intracellular concentrations are 10-50 times higher than the extracellular concentrations.

Metabolism

Clindamycin undergoes metabolism, presumably in the liver, to the active N-demethyl and sulphoxide metabolites, and also some inactive metabolites and about 4% in the faeces: the remainder is excreted as inactive metabolites.

Excretion

Half-life is approximately two and a half hour in children and approximately 3 hours in adults. Clindamycin is excreted as biological active and biological inactive metabolites in faeces, urine and bile. Faecal excretion is predominant. About 10% of the drug is excreted in the urine as active drug and about 4% in the faeces; the remainder is excreted as inactive metabolites.

Characteristics in patients

**Elderly:**

The half-life, volume of distribution and clearance, and extent of absorption after administration of clindamycin phosphate are not altered by increased age.

**Patients with renal impairment:**
In the presence of renal impairment, elimination half-life is prolonged; however, a dosage reduction is unnecessary in the event of mild to moderate impairment of renal function.

*Patients with hepatic impairment:*
In patients with moderate to severe hepatic impairment the half life is prolonged, but when giving the dose every 8 hour accumulation is rarely seen. Dose reduction is normally not necessary in patients with hepatic impairment.

5.3 Preclinical safety data
In dogs, repeated high oral doses produced ulceration of the mucosa of the stomach and gall bladder. However preclinical data reveal no special hazard for humans based on studies of repeat dose toxicity, or effects on male and female fertility as well as embryofoetal and postnatal development, genotoxicity.

Carcinogenicity studies have not been conducted.

6 PHARMACEUTICAL PARTICULARS
6.1 List of excipients
Lactose monohydrate
Maize starch
Talc
Magnesium Stearate

Capsule shell
Gelatin
Titanium dioxide (E 171)

Printing ink
Shellac
Iron oxide black (E172)
Propylene glycol (E1520)

6.2 Incompatibilities
Not applicable.

6.3 Shelf life
15 months

6.4 Special precautions for storage
Do not store above 30°C.
Store in the original package in order to protect from light.

6.5 Nature and contents of container
The blister pack (PVC/aluminium) contains 20, 32 or 100 capsules, respectively. Not all pack sizes may be marketed.

6.6 Special precautions for disposal
No special requirements.

7 MARKETING AUTHORISATION HOLDER
Rivopharm UK Ltd.
6th floor, 28 Kingsway
London WC2B 6JR
UK

8 MARKETING AUTHORISATION NUMBER(S)
PL 33155/0012

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION
10/07/2012

10 DATE OF REVISION OF THE TEXT
10/07/2012
Module 3
Patient Information Leaflet

Please note that there is no mock-up available. The marketing authorisation holder has stated that it is not intending to market the product and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK PIL for review to the regulatory authority before marketing the product.

PACKAGE LEAFLET: INFORMATION FOR THE USER

Clindamycin
300 mg capsules, hard

clindamycin

Read all of this leaflet carefully before you start using 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 Clindamycin capsules are and what they are used for
2. Before you use Clindamycin capsules
3. How to use Clindamycin capsules
4. Possible side effects
5. How to store Clindamycin capsules
6. Further information

1. WHAT CLINDAMYCIN CAPSULES ARE AND WHAT THEY ARE USED FOR

Clindamycin 300 mg capsules, hard (called Clindamycin capsules in the rest of this leaflet) belong to a group of medicines called antibiotics. Antibiotics are used to treat infections. Clindamycin capsules are used to kill certain serious bacterial infections.

2. BEFORE YOU USE CLINDAMYCIN CAPSULES

Do not use Clindamycin capsules:

If you have been told you are allergic (hypersensitive) to clindamycin (the active ingredient in Clindamycin capsules), lincomycin (another antibiotic) or to any of the ingredients of Clindamycin capsules (found in section 6).

Take special care with Clindamycin capsules:

Check with your doctor or pharmacist before taking your medicine

– If you have diarrhoea or usually get diarrhoea when you take antibiotics or have ever suffered from problems with your stomach or intestines. If you develop severe or prolonged or bloody diarrhoea during or after using Clindamycin capsules tell your doctor immediately since it may be necessary to interrupt the treatment. This may be a sign of bowel inflammation (pseudomembranous colitis) which can occur following treatment with antibiotics.

– If you suffer from problems with your kidneys or liver.

– If you suffer from asthma, eczema or hayfever.

– If you have been told by your doctor that you have an intolerance to some sugars.
Taking other medicines

Some medicines can affect the way Clindamycin works, or Clindamycin itself can reduce the effectiveness of other medicines taken at the same time. Make sure your doctor knows if you are taking any medicines listed here:

- Erythromycin, an antibiotic used to treat infections.
- Muscle relaxants used for operations or hospital procedures.
- Oral contraceptive pills. You should use extra contraception such as condoms whilst taking Clindamycin capsules and for seven days after your last dose of Clindamycin capsules.

Please tell your doctor or pharmacist if you are taking or have recently taken any other medicines including medicines obtained without a prescription.

Using Clindamycin capsules with food and drink

The capsules may be taken either before or after a meal.

Pregnancy

If you are pregnant or planning to become pregnant you should contact your doctor before taking Clindamycin capsules.
The effects of Clindamycin capsules on the unborn child are not known.

Breast-feeding

Tell your doctor if you will be breast feeding while taking Clindamycin capsules as the active substance in this medicine may be passed into breast milk. Your doctor will decide if Clindamycin capsules are appropriate for you. It is not likely that a nursing infant will take in very much of the active substance from the milk it drinks. However, if your baby gets bloodstained diarrhoea or shows any signs of illness, tell your doctor at once. You should stop breast-feeding if this happens.

Driving and using machines

No effects have been reported on the ability to drive or use machines after taking Clindamycin capsules.

Important information about some of the ingredients of Clindamycin

Clindamycin capsules contain lactose, a type of sugar. If you have been told by your doctor that you have an intolerance to some sugars, contact your doctor before taking this medicine.

3. HOW TO USE CLINDAMYCIN CAPSULES

Always use Clindamycin capsules exactly as your doctor has told you. You should check with your doctor if you are not sure.

Adults and the elderly:
One capsule every six hours.

Children:
The usual dose in children is between 3 and 6 mg per kg of body weight every six hours, depending on the severity of the infection. Your doctor will work out the number of capsules that your child should have.
Long Term use of Clindamycin capsules

Your doctor will decide if you are taking Clindamycin capsules for a long time and may arrange regular liver, kidney and blood tests. Do not miss these check-ups with your doctor.

Long term use can also make you more likely to get other infections which do not respond to Clindamycin capsules treatment.

If you take more Clindamycin capsules than you should

If you accidentally take too many Clindamycin capsules contact your doctor at once or go to the nearest hospital casualty department.
Take the labelled medicine package with you, whether there are any Clindamycin capsules left or not.
Do not take any more capsules until your doctor tells you to.

If you forget to take Clindamycin capsules

If you forget the dose just a few hours late, take it straight away. If it is nearly time for your next dose miss out the forgotten one. Do not take a double dose to make up for a forgotten dose.

If you stop taking Clindamycin capsules

If you stop taking the medicine too soon your infection may come back again or get worse. Do not stop taking Clindamycin capsules unless your doctor tells you to.
If you have any further questions on the use of this product, speak to your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Clindamycin capsules can cause side effects, although not everybody gets them.

Tell your doctor immediately if you have any of the following side effects:

- severe, persistent or bloody diarrhoea (which may be associated with stomach pain or fever). This is an uncommon side effect which may occur after treatment with antibiotics and can be a sign of serious bowel inflammation.
- signs of a severe allergic reaction such as sudden wheeziness, difficulty in breathing, swelling of eyelids, face or lips, rash or itching (especially affecting the whole body).
- blisters and peeling of large areas of skin, fever, cough, feeling unwell and swelling of the gums, tongue or lips.
- yellowing of the skin and whites of the eyes (jaundice).

Other possible side effects may include effects on your:

- Nervous system: impaired sense of taste
- Skin: reddening of the skin, skin rash, itching (hives)
- Stomach and intestines: throat ulcers, sore throat, feeling sick, being sick, stomach pain and diarrhoea
- Blood system: reduced numbers of blood cells (shown on blood tests) which may cause bruising or bleeding or weaken the immune system
- Liver function: shown by blood tests
- Genital area: inflammation of the vagina

If any of the side effects get serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist.
5. HOW TO STORE CLINDAMYCIN CAPSULES

Keep out of the reach and sight of children.

Do not use Clindamycin capsules after the expiry date which is stated on the carton and the blister foil. The expiry date refers to the last day of that month.

Do not store above 30°C.
Store in the original package in order to protect from light.

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 Clindamycin capsules contain

Each capsule contains clindamycin hydrochloride equivalent to 300 mg of the active substance clindamycin.
The other ingredients are:
Capsule contents: lactose monohydrate, maize starch, talc, magnesium stearate.
Shell: gelatine and titanium dioxide (E171)
Printing ink: Shellac, iron oxide black (E172), propylene glycol.

What Clindamycin capsules look like and contents of the pack

Clindamycin capsules are white/white hard capsules with markings of ‘CLIN 300’ on the capsule body. They are available in blister packs of 20, 32 or 100 capsules.
Not all pack sizes may be marketed

Marketing authorisation holder and Manufacturer

Marketing Authorisation Holder

Rivopharm UK Ltd
6th floor, 28 Kingsway
London WC2B 6JR, UK

Manufacturer

Laboratories BTT
ZI de Krafft
67150 Erstein
France

Distributed by

Creo Pharma Ltd
Felsted Business Centre,
Felsted, Essex CM6 3LY

This leaflet was last revised in (06/2012)
Module 4
Labelling

Please note that there is no mock-up available. The marketing authorisation holder has stated that it is not intending to market the product and, thus, no UK-specific documents have been submitted. The marketing authorisation holder has committed to submit the UK labelling for review to the regulatory authority before marketing the product.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

1. **NAME OF THE MEDICINAL PRODUCT**

   Clindamycin 300 mg capsules, hard clindamycin

2. **STATEMENT OF ACTIVE SUBSTANCE(S)**

   Each hard capsule contains clindamycin hydrochloride equivalent to 300 mg clindamycin

3. **LIST OF EXCIPIENTS**

   Contains lactose

4. **PHARMACEUTICAL FORM AND CONTENTS**

   20 hard capsules
   32 hard capsules
   100 hard capsules

5. **METHOD AND ROUTE(S) OF ADMINISTRATION**

   Read the package leaflet before use
   For oral use

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

   Keep out of the reach and sight of children.

7. **OTHER SPECIAL WARNING(S), IF NECESSARY**

8. **EXPIRY DATE**

   EXP: {MM/YYYY}

9. **SPECIAL STORAGE CONDITIONS**

   Do not store above 30℃
   Store in the original package 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

Rivopharm UK Ltd.
6th floor 28 Kingsway
London WC2B 6JR
UK

12. MARKETING AUTHORISATION NUMBER(S)

PL 33155/0012

13. BATCH NUMBER

Lot:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

Dosage: as directed by your doctor

16. INFORMATION IN BRAILLE

Clindamycin 300 mg capsules
Module 5
Scientific discussion during initial procedure

I INTRODUCTION
Based on the review of the data on quality, safety and efficacy, Norway, Sweden and the UK considered that the application for Clindamycin 300 mg capsules, hard could be approved. This product is a prescription only medicine (POM) and is indicated for the treatment of serious infections caused by anaerobic bacteria, including intra-abdominal infections, skin and soft tissue infections. As needed, clindamycin should be administered in conjunction with another antibacterial agent that is active against gram negative aerobic bacteria. Examples of infections include:
- Tonsillitis
- Dental infection

This application for Clindamycin 300 mg capsules, hard is submitted as an abridged application according to Article 10(3) of Directive 2001/83/EC, claiming to be a hybrid medicinal product to Dalacin C phosphate capsule 150 mg, authorised in the UK to Pharmacia Limited on 20th February 1989 (PL 00032/5007R).

The legal basis for this application in the concerned member states (CMS), Norway and Sweden is Article 10(1) of Directive 2001/83/EC, claiming to be generic medicinal products of Dalacin 300 mg kapslar, hårda, authorised in Sweden to Pfizer AB 191 90 Sollentuna on 27th March 1987.

Clindamycin is a lincosamide antibacterial agent with a primarily bacteriostatic action against gram-positive aerobes and a wide range of anaerobic bacteria. In common with other members of this class, and similarly to macrolides such as erythromycin, it binds to the 50S subunit of the bacterial ribosome and inhibits the early stages of protein synthesis. Its action is mainly bacteriostatic, although in high concentrations it may be slowly bactericidal against sensitive strains.

No new non-clinical studies were conducted, which is acceptable given that the products contain a widely-used, well-known active substance. No clinical studies, with the exception of the bioequivalence study, have been performed and none are required for these applications as the pharmacology of clindamycin hydrochloride is well-established.

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 manufacturing sites outside the community, the RMS has accepted copies of current GMP Certificates or satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.
## II. ABOUT THE PRODUCT

<table>
<thead>
<tr>
<th>Name of the product in the Reference Member State</th>
<th>Clindamycin 300 mg Capsules, Hard</th>
</tr>
</thead>
<tbody>
<tr>
<td>Name(s) of the drug substance (INN)</td>
<td>Clindamycin hydrochloride</td>
</tr>
<tr>
<td>Pharmacotherapeutic classification (ATC code)</td>
<td>Antimicrobial, systemic (J01FF)</td>
</tr>
<tr>
<td>Pharmaceutical form and strength</td>
<td>300 mg hard capsules</td>
</tr>
<tr>
<td>Reference numbers for the Decentralised Procedure</td>
<td>UK/H/4176/001/DC</td>
</tr>
<tr>
<td>Reference Member State</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>Member States concerned</td>
<td>Norway (NO) and Sweden (SE)</td>
</tr>
<tr>
<td>Marketing Authorisation Number</td>
<td>PL 33155/0012</td>
</tr>
<tr>
<td>Name and address of the authorisation holder</td>
<td>Rivopharm UK Limited 6th floor, 28 Kingsway London WC2B 6JR United Kingdom</td>
</tr>
</tbody>
</table>
III SCIENTIFIC OVERVIEW AND DISCUSSION
III.1 QUALITY ASPECTS
S. Drug substance

INN/Ph.Eur name: Clindamycin hydrochloride

Chemical name: Methyl 7-chloro-6,7,8-trideoxy-6-[[[2S,4R)-1-methyl-4-propyl-2-pyrrolidinyl]carbonyl]amino]-1-thio-l-threo-α-d-galacto-octopyranoside

Structural formula:

![Structural formula image]

Molecular formula: $\text{C}_{18}\text{H}_{34}\text{Cl}_{2}\text{N}_{2}\text{O}_{5}\text{S}$

Molecular weight: 461.5

Appearance: A white, or almost white, crystalline powder

Solubility: Very soluble in water, slightly soluble in ethanol (96 %)

Clindamycin hydrochloride is the subject of a European Pharmacopoeia monograph.

The source of clindamycin hydrochloride used in the product complies with the European Pharmacopoeia monograph.

The manufacturer of the drug substance holds a valid EDQM (European Directorate for the Quality of Medicines and Healthcare) Certificate of Suitability. The quality of the substance is suitably controlled in line with the current edition of the European Pharmacopoeia Monograph.

The manufacturing process, control of materials, control of critical steps, validation and process development for clindamycin hydrochloride were assessed and approved by the EDQM in relation to the granting of the Certificate of Suitability and are therefore satisfactory.

An appropriate specification with suitable test methods and limits are provided for the drug substance. The methods of testing and limits for impurities and residual solvents are in compliance with current guidelines. Batch analysis data are provided and comply with the proposed specifications.

The container closure system and re-test period for clindamycin hydrochloride complies with the container closure and re-test period specified on the Certificate of Suitability.
P. Medicinal Product

Other Ingredients

Other ingredients in the tablet core consist of pharmaceutical excipients lactose monohydrate, maize starch, talc and magnesium stearate.

The ingredients in the capsule shell are gelatin and titanium dioxide (E171). The ingredients in the printing ink are shellac, iron oxide black (E172) and propylene glycol (E1520).

With the exception of iron oxide black, all excipients comply with their respective European Pharmacopoeia monographs. Iron oxide black is listed in Japanese Pharmaceutical Excipients.

With the exception of lactose and gelatin, none of the excipients used contain material of animal or human origin. The supplier of the gelatin used in this product has provided valid Certificates of Suitability for transmissible spongiform encephalopathies (TSE) risk. Confirmation has been provided that the magnesium stearate used is of vegetable origin. The applicant has provided a declaration that the milk used in the production of anhydrous lactose is sourced from healthy animals under the same conditions as those intended for human consumption.

No genetically modified organisms (GMO) have been used in the preparation of this product.

Pharmaceutical Development

The reference product used in the pharmaceutical development was Dalacin 300 mg kapseli, licensed to Pfizer Oy, Helsinki in Finland. The objective of the development programme was to produce a safe, efficacious product containing clindamycin hydrochloride that could be considered a generic product to Dalacin 300 mg kapslar, hård.

The applicant has provided suitable product development sections. Valid justifications for the use and amounts of each excipient have been provided.

Comparative in vitro dissolution profiles and impurity profiles have been provided for the finished product versus the reference product.

The reference product used in the bioequivalence study is Dalacin 300 mg kapseli, licensed to Pfizer Oy, Helsinki in Finland.

Manufacturing Process

A satisfactory batch formula has been provided for the manufacture of the product, along with an appropriate account of the manufacturing process. The manufacturing process has been validated and has shown satisfactory results. Process validation data on pilot-scale batches have been provided and are satisfactory. The applicant has committed to perform process validation on future commercial-scale batches.

Finished Product Specification

The finished product specification proposed for the product is acceptable. Test methods have been described and have been adequately validated, as appropriate. Batch data have been provided and comply with the release specification. Certificates of Analysis have been provided for any working standards used.
Container-Closure System
This product is packaged in blister packs composed of polyvinyl chloride (PVC) and aluminium. Pack sizes are 20, 32 and 100 capsules.

Satisfactory specifications and Certificates of Analysis have been provided for all packaging components. All primary product packaging complies with the relevant EU directives and EU legislation regarding contact with food.

Stability of the product
Stability studies were performed on batches of the finished product in the packaging proposed for marketing and in accordance with current guidelines. These data support a shelf-life of 15 months. Storage instructions are ‘Do not store above 30°C’ and ‘Store in the original package in order to protect from light’.

Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling
The SmPC, PIL and labelling are pharmaceutically acceptable. The UK approved SmPC, PIL and labelling (text only) are included in modules 2, 3 and 4 of this report.

A satisfactory bridging report has been provided, referencing the PIL user testing for an approved product, Clindamycin 150 mg capsules, hard (PL 33155/0009; UK/H/4176/001/DC).

MAA form
The MAA form is pharmaceutically satisfactory.

Pharmaceutical Expert Report
The pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical dossier.

Conclusion
From a quality point of view, it is recommended that a Marketing Autorisation is granted for this application.
III.2 NON-CLINICAL ASPECTS

The pharmacodynamic, pharmacokinetic and toxicological properties of clindamycin hydrochloride are well-known. As clindamycin hydrochloride is a widely used, well-known drug substance, the applicant has not provided any additional studies and none are required. An overview based on literature is therefore appropriate.

Non-Clinical Overview
The non-clinical overview has been written by an appropriately qualified person and is a suitable summary of the non-clinical aspects of the dossier.

Impurities
The impurities identified in the drug substance and drug product exceeds the limits specified by the international conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH) guidelines. However, the level of each impurity complies with the levels specified in the European Pharmacopoeia; therefore the levels are considered to be acceptable. The proposed limit for residual solvents within the drug substance is considered to be acceptable.

Environmental Risk Assessment
A satisfactory justification has been provided for the absence of an Environmental Risk Assessment.

Conclusion
From a non-clinical point of view, it is recommended that a Marketing Authorisation is granted for this application.
III.3 CLINICAL ASPECTS
Clinical Pharmacology

With the exception of the following bioequivalence study, no new pharmacokinetic or pharmacodynamic data were submitted with this application and none were required.

Pharmacokinetics

Bioequivalence study

A single-centre, randomised, single-dose, laboratory-blinded, 2-period, 2-sequence, crossover study to compare the pharmacokinetics of the test product Clindamycin 300 mg capsules versus the reference product Dalacin 300 mg kapseli (clindamycin hydrochloride) in healthy subjects under fasted conditions.

Blood samples were taken pre- and up to 14 hours post dose. The washout period between each treatment period was 7 days. Pharmacokinetic parameters were measured from the plasma and statistically analysed.

Results for clindamycin hydrochloride are presented below as log-tranformed values for geometric means:

<table>
<thead>
<tr>
<th>Clindamycin hydrochloride</th>
<th>Treatment</th>
<th>AUC_{0-t} (ng.h/mL)</th>
<th>C_{max} (ng/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Test (T)</td>
<td>11889.9</td>
<td>3512.2</td>
<td></td>
</tr>
<tr>
<td>Reference (R)</td>
<td>11351.2</td>
<td>3337.9</td>
<td></td>
</tr>
<tr>
<td>T/R Ratio (90 % CI)</td>
<td>104.75</td>
<td>(98.25 – 111.67)</td>
<td>(105.22, 113.07)</td>
</tr>
</tbody>
</table>

\( AUC_{0-t} \) area under the plasma concentration-time curve from time zero to t hours

\( C_{max} \) maximum plasma concentration

The results for the primary variables indicated that the 90 % confidence intervals test/reference ratio of geometric means for \( AUC_{0-t} \) and \( C_{max} \) for clindamycin hydrochloride lie within acceptable limits (80-125 %). Thus, bioequivalence has been shown between the test and reference products in this study.

Efficacy

No new efficacy data were submitted with this application and none were required.

Safety

With the exception of the data submitted during the bioequivalence study, no new safety data were submitted with this application and none were required. No new or unexpected safety concerns were raised during the bioequivalence study.

The Pharmacovigilance System and Risk Management Plan

The RMS considers that the pharmacovigilance system as described by the applicant fulfils the requirements and provides adequate evidence that the applicant has the services of a qualified person responsible for pharmacovigilance and has the necessary means for the
notification of any adverse reaction suspected of occurring either in the Community or in a third country.

A satisfactory justification has been provided for the absence of a Risk Management Plan.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**
The SmPC, PIL and labelling are clinically satisfactory and consistent with those for the reference product, where appropriate.

**Clinical Expert Report**
The clinical expert report has been written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

**MAA Form**
The MAA form is clinically satisfactory.

**Conclusions**
From a clinical point of view, it is recommended that a Marketing Authorisation is granted for this application.
IV  OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT
QUALITY
The important quality characteristics of Clindamycin 300 mg capsules, hard are well-defined and controlled. The specification 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.

NON-CLINICAL
No new non-clinical data were submitted and none are required for an application of this type.

CLINICAL
Bioequivalence has been demonstrated between the applicant’s Clindamycin 300 mg capsules, hard and the reference product Dalacin 300 mg kapseli.

No new or unexpected safety concerns arose from the bioequivalence study.

The SmPC, PIL and labelling are satisfactory and consistent with that for the reference product.

RISK-BENEFIT ASSESSMENT
The quality of the product is acceptable and no new non-clinical or clinical safety concerns have been identified. Extensive clinical experience with clindamycin hydrochloride is considered to have demonstrated the therapeutic value of the compound. The benefit-risk ratio is, therefore, considered to be positive.
Module 6

STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

<table>
<thead>
<tr>
<th>Date submitted</th>
<th>Application type</th>
<th>Scope</th>
<th>Outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>