

**Public Assessment Report**  
**Decentralised Procedure**

**Clindamycin 150mg Capsules Hard**

**Clindamycin hydrochloride**

**UK/H/4176/01/DC**

**UK licence no: PL 33155/0009**

**Applicant: Rivopharm (UK) Limited**

## **Clindamycin 150mg Capsules, hard**

### **LAY SUMMARY**

On 5<sup>th</sup> November 2010, the Concerned Member States (CMSs) and the Reference Member State (RMS) agreed to grant Marketing Authorisation to Rivopharm (UK) Limited for the medicinal product Clindamycin 150mg Capsules, hard. This Marketing Authorisation was granted via the Decentralised Procedure (DCP), with the UK as RMS. After the national phase, a licence was granted in the UK on 22<sup>nd</sup> November 2010. This medicine is only available on prescription from your doctor.

Clindamycin 150mg capsules, hard 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 150mg Capsules, hard outweigh the risks, hence a Marketing Authorisation has been granted.

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Module 6: Steps taken after initial procedure	Not applicable

## Module 1

<b>Product Name</b>	Clindamycin 150mg Capsules, hard
<b>Type of Application</b>	Generic, Article 10.1
<b>Active Substance</b>	Clindamycin hydrochloride
<b>Form</b>	Capsules, hard
<b>Strength</b>	150mg
<b>MA Holder</b>	Rivopharm UK Limited 6 <sup>th</sup> Floor 28 Kingsway London WC2B 6JR, UK
<b>RMS</b>	UK
<b>CMS</b>	Norway and Sweden
<b>Procedure Number</b>	UK/H/4176/01/DC
<b>Timetable</b>	Day 210 – 5 <sup>th</sup> November 2010

## Module 2

### SUMMARY OF PRODUCT CHARACTERISTICS

#### 1 NAME OF THE MEDICINAL PRODUCT

Clindamycin 150 mg capsules, hard.

#### 2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains:

clindamycin hydrochloride equivalent to 150 mg clindamycin.

Excipient: 214 mg lactose/ Clindamycin 150 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 150' 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 150-450mg 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 formulations 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 gastro-intestinal 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 Pregnancy and lactation

##### *Pregnancy*

Safety for use in pregnancy has not yet been established. *Animal studies do not indicate reproductive toxicity (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: Second generation cephalosporin

ATC classification: J01DC04

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<sub>B</sub>) type of resistance, which may be constitutive or inducible.

Breakpoints

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

Eucast

Staphylococci: sensitive  $\leq 0.5$  resistant  $> 0.5$

Streptococci ABCG and pneumoniae: sensitive  $\leq 0.5$  resistant  $> 0.5$

Gram positive anaerobes: sensitive  $\leq 4$  resistant  $> 4$

Gram negative anaerobes:  $\leq 4$  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.

<b>Species</b>
<p><b>Susceptible</b></p> <p><b>Gram-positive aerobes</b></p> <p><i>Staphylococcus aureus*</i>  <i>Staphylococcus epidermidis</i>  <i>Streptococcus pneumonia</i>  <i>Streptococcus pyogenes</i>  <i>Streptococcus viridans</i></p> <p><b>Anaerobes</b></p> <p><i>Bacteriodes fragilis</i> group  <i>Bacteroides melaninogenicus</i>  <i>Bifidobacterium</i> spp.  <i>Clostridium perfringens</i>  <i>Eubacterium</i> spp  <i>Fusobacterium</i> spp.  <i>Peptococcus</i> spp.  <i>Peptostreptococcus</i> spp.  <i>Propionibacterium</i> spp.  <i>Veillonella</i> spp.</p>
<p><b>Resistant</b></p> <p><i>Clostridia</i> spp.  <i>Enterococci</i>  <i>Enterobacteriaceae</i></p>

\*Up to 50% of methicillin-susceptible *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**

Preclinical data reveal no special hazard for humans based on studies of repeat dose toxicity, reproductive toxicity or genotoxicity. Carcinogenicity studies have not been conducted. In dogs, repeated high oral doses produced ulceration of the mucosa of the stomach and gall bladder.

**6 PHARMACEUTICAL PARTICULARS****6.1 List of excipients**

Lactose monohydrate  
Maize starch  
Talc  
Magnesium Stearate

Capsule shell

Gelatin  
Titanium dioxide (E 171)

Printin ink

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

**6.2 Incompatibilities**

Not applicable.

**6.3 Shelf life**

2 years

**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 24 or 100 capsules, respectively.  
Not all pack sizes may be marketed.

**6.6 Special precautions for disposal**

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

**7 MARKETING AUTHORISATION HOLDER**

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

**8 MARKETING AUTHORISATION NUMBER(S)**

PL 33155/0009

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION**

22/11/2010

**10 DATE OF REVISION OF THE TEXT**

22/11/2010

## Module 3

PACKAGE LEAFLET: INFORMATION FOR THE USER

### Clindamycin 150 mg capsules, hard clindamycin hydrochloride

**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 150 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 capsules

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.

Please see read the back of this leaflet.



**Adults and the elderly:**

The usual dose is 150 mg – 450 mg (1-3 capsules) every six hours, depending on the severity of your infection.

**Children (over 1 month):**

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 that 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).
- blistering 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 you:

- Nervous system: Impaired sense of taste
- Skin: Reddening of the skin, skin rash, red itchy bumps on your skin (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 weakening of 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 150 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 150' on the capsule body. They are available in blister packs of 24 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**  
Laboratoires BTT  
ZI de Krafft, 67150 Erstein, France

**Distributed by:**  
Creo Pharma Limited,  
Felsted Business Centre,  
Felsted, Essex CM6 3LY

This leaflet was last revised in {11/2010}.



# Module 4 Labelling

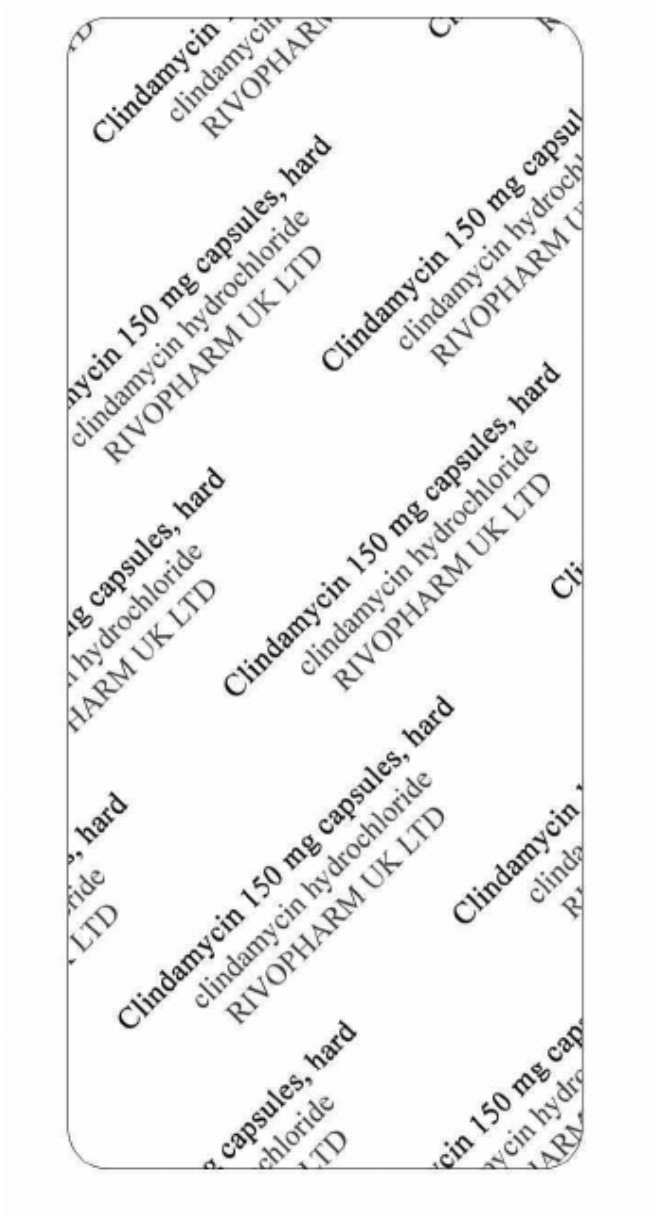
AT4662 PB AL3086 AS/017  
LATO STAMPA  
CLINDAMYCIN  
#150MG CAPSULES  
TEF871 AS/017

17

<p><b>REGISTRATO</b> N° 196/0884 219/01 AS/017</p> <p><b>INDICAZIONE</b> ASTITICICLO Clindamicina 150 mg RIVESTIMENTO 100 caps 14/02/17/04</p> <p><b>COMPOSIZIONE</b> Clindamicina 150 mg 2 196/0884 219/01 AS/017/12 Glimepina</p>	<p><b>INDICAZIONE</b> ASTITICICLO Clindamicina 150 mg RIVESTIMENTO 100 caps 14/02/17/04</p> <p><b>COMPOSIZIONE</b> Clindamicina 150 mg 2 196/0884 219/01 AS/017/12 Glimepina</p>	<p><b>INDICAZIONE</b> ASTITICICLO Clindamicina 150 mg RIVESTIMENTO 100 caps 14/02/17/04</p> <p><b>COMPOSIZIONE</b> Clindamicina 150 mg 2 196/0884 219/01 AS/017/12 Glimepina</p>
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**INFORMAZIONI**  
Il presente medicinale è un medicinale registrato in Gran Bretagna. La NICE è il dipartimento responsabile di assicurare che il medicinale sia sicuro, efficace, di buona qualità e di valore per i pazienti. Per informazioni sui prezzi e sui costi di fornitura del medicinale, visitate il sito [www.nice.org.uk](http://www.nice.org.uk).  
 Distribuire con precauzioni rigorose sul prescrivere.  
 Distribuire con precauzioni rigorose sul prescrivere.  
 Distribuire con precauzioni rigorose sul prescrivere.  
**DATA** ..... **FINNA & TIMBERO CLINSTER** .....





## Module 5

### Scientific discussion during initial procedure

#### I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the Reference Member State (RMS) and Concerned Member States (CMSs) consider that the application for Clindamycin 150mg Capsules, hard in the treatment of serious infections caused by anaerobic bacteria, including intra-abdominal infections, skin and soft tissue infections, could be approved.

As needed, clindamycin should be administered in conjunction with another antibacterial agent that is active against gram negative aerobic bacteria.

- Tonsillitis
- Dental infection

This is a decentralised application submitted under Article 10(1) of Directive 2001/83/EC as amended. The reference medicinal product is Dalacin C 150mg capsules (PL 00032/5007R) held by Pharmacia Limited, granted on 20<sup>th</sup> February 1989.

With UK as the RMS in this Decentralised Procedure (UK/H/4176/01/DC), Rivopharm (UK) Limited applied for the Marketing Authorisation for Clindamycin 150mg Capsules, hard in Norway and Sweden.

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.

No new preclinical or clinical studies were conducted, which is acceptable given that the application was based on being generic medicinal product of the originator product that have been licensed for over 10 years. The bioequivalence study was carried out in accordance with Good Clinical Practice (GCP).

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.

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 suitable justification has been provided for non-submission of a Risk Management Plan.

All member states agreed to grant respective licence for the above product at the end of procedure (Day 210 – 5<sup>th</sup> November 2010). After a subsequent national phase, the UK granted a licence for this product on 22<sup>nd</sup> November 2010 (PL 33155/0009).

**ABOUT THE PRODUCT**

Name of the product in the Reference Member State	Clindamycin 150mg capsules, hard
Name(s) of the active substance(s) (INN)	Clindamycin hydrochloride
Pharmacotherapeutic classification (ATC code)	J01FF Lincosamides
Pharmaceutical form and strength(s)	Capsules, hard
Reference number for the Mutual Recognition Procedure	UK/H/4176/01/DC
Reference Member State	United Kingdom
Concerned Member States	Norway and Sweden
Marketing Authorisation Number(s)	PL 33155/0009
Name and address of the authorisation holder	Rivopharm UK Limited 6 <sup>th</sup> Floor 28 Kingsway London WC2B 6JR, UK

### III SCIENTIFIC OVERVIEW AND DISCUSSION

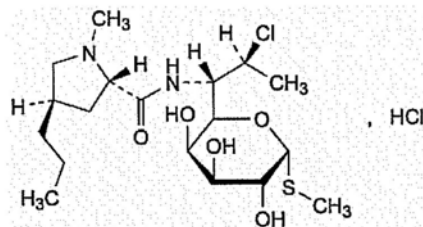
#### III.1 QUALITY ASPECTS

##### DRUG SUBSTANCE

##### INN: Clindamycin hydrochloride

Chemical Name: Methyl 7-chloro-6,7,8-trideoxy-6-[[[(2S,4R)-1-methyl-4-propyl-2-pyrrolidinyl]carbonyl]amino]-1-thio-1-threo- $\alpha$ -d-galacto-octopyranoside

Structure:



Molecular Formula:  $C_{18}H_{34}ClN_2O_5S$

Molecular Weight: 461.5

Appearance and solubility: A white, or almost white, crystalline powder, very soluble in water, slightly soluble in ethanol (96%).

All aspects of the manufacture and control of the active substance are covered by a European Directorate for the Quality of Medicines (EDQM) Certificate of Suitability.

#### DRUG PRODUCT

##### Other ingredients

Other ingredients consist of the pharmaceutical excipients lactose monohydrate, maize starch, talc, magnesium stearate, gelatin, titanium dioxide (E 171), Shellac, iron oxide black (E172) and propylene glycol (E1520)

All excipients comply with their respective European Pharmacopoeia monographs with the exception of iron oxide black which complies with the Japanese Pharmacopoeia monograph.

It has been confirmed that the excipients used are free of TSE/BSE and the corresponding certificates issued by each supplier were provided. This is acceptable.

##### Pharmaceutical Development

The aim of pharmaceutical development was to achieve a generic formulation similar to that of the reference product Dalacin C 150mg Capsules, marketed by Pharmacia Limited in the UK.

Comparative impurity and dissolution profiles have been presented for the test and reference products.

**Manufacture**

A description and flow-chart of the manufacturing method have been provided. In-process controls are satisfactory, based on process validation data and controls on the finished product. Process validation has been carried out on batches of the product. The results are satisfactory.

**Finished Product Specification**

The finished product specification is satisfactory. Test methods have been described and 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**

The capsules are packed in polyvinylchloride/aluminium blister packs. Pack sizes are 24 and 100 capsules.

Specifications and Certificates of Analysis for all packaging materials have been provided. These are satisfactory. All primary packaging complies with EU legislation regarding contact with food.

**Stability**

Finished product stability studies have been conducted in accordance with current guidelines and in the packaging proposed for marketing.

Based on the results, a shelf-life of 2 years with storage conditions 'Do not store above 30°C' and 'Store in the original package in order to protect from light' are set, and these are acceptable.

**Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labelling**

The SPC, PIL and labels are pharmaceutically acceptable.

A package leaflet has been submitted to the MHRA along with results of consultations with target patient groups ("user testing"), in accordance with Article 59 of Council Directive 2001/83/EC. The results indicate that the package leaflet is well-structured and organised, easy to understand and written in a comprehensive manner. The test shows that the patients/users are able to act upon the information that it contains.

**Marketing Authorisation Application (MAA) Forms**

The MAA form is pharmaceutically satisfactory.

**Expert Report**

A pharmaceutical expert report has been written by an appropriately qualified person and is a suitable summary of the pharmaceutical aspects of the dossier.

**Conclusion**

There are no objections to the approval of this product from a pharmaceutical point of view.

**III.2 PRE-CLINICAL ASPECTS****PHARMACODYNAMICS, PHARMACOKINETICS, TOXICOLOGY**

The pharmacological, pharmacokinetic and toxicological properties of clindamycin hydrochloride are well-known.

No new preclinical data have been supplied with this application and none are required for applications of this type. The pre-clinical expert report has been written by an appropriately qualified person and is a suitable summary of the pre-clinical aspects of the dossier.

A suitable justification has been provided for non-submission of the environmental risk assessment.

There are no objections to the approval of this product from a pre-clinical point of view.

**III.3 CLINICAL ASPECTS*****Pharmacokinetics***

In support of the application, the applicant has submitted a bioequivalence (BE) Study under fasting conditions.

**Study 1**

This was a single centre, randomised, single dose, laboratory-blinded, 2-period, 2-sequence crossover single-dose bioequivalence study comparing Clindamycin 150mg capsule (Rivopharm S.A Manno, Switzerland) and Dalacin C 150mg capsule (Pharmacia Limited, UK).

The study drug was administered after an overnight fast of 10 hours with 240 ml water. 19 blood samples were collected at pre-dose (0.0) and at 0.25, 0.33, 0.5, 0.67, 0.84, 1, 1.33, 1.67, 2, 2.5, 3, 4, 5, 6, 8, 10, 12, 14 hours post-dose after administration of each product with a washout period of 7 days between study drug administrations.

**Results**

Parameter	Intra-subject CV%	Geometric LSMeans*		Ratio (%)	90% Confidence Limits (%)	
		Test	Reference		Lower	Upper
C <sub>max</sub>	11.7	2003.9	2002.3	100.08	94.05	106.49
AUC <sub>T</sub>	9.3	6282.2	6123.2	102.60	97.65	107.79
AUC <sub>inf</sub>	10.6	6474.0	6322.4	102.40	96.77	108.35

The 90% confidence intervals for C<sub>max</sub> and AUC were within the pre-defined limits. Bioequivalence has been shown for the test formulation (Clindamycin 150mg capsules) and the reference formulation (Dalacin C 150mg capsules).

***Pharmacodynamics***

No new data have been submitted and none are required for applications of this type.

***Clinical Efficacy***

No new data have been submitted and none are required for applications of this type.

***Clinical Safety***

No new data have been submitted and none are required for applications of this type.

***Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and labelling***

The SPC, PIL and labelling are medically satisfactory and consistent with those for the reference product.

***Clinical Expert Report***

The clinical expert report is written by an appropriately qualified physician and is a suitable summary of the clinical aspects of the dossier.

***Marketing Authorisation Application (MAA) Forms***

The MAA form is medically satisfactory.

***Clinical Conclusion***

There are no objections to the approval of this product from a clinical point of view.

#### **IV . OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT QUALITY**

The important quality characteristics of Clindamycin 150mg Capsules, hard 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 applications of this type.

#### **EFFICACY**

Bioequivalence has been demonstrated between the applicant's Clindamycin 150mg Capsules and the reference product.

No new or unexpected safety concerns arise from this application.

The SPC, PIL and labelling are satisfactory and consistent with that of the reference product.

#### **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 clindamycin hydrochloride is considered to have demonstrated the therapeutic value of the compound. The risk benefit is, therefore, considered to be positive.

## Module 6

### STEPS TAKEN AFTER INITIAL PROCEDURE - SUMMARY

Date submitted	Application type	Scope	Outcome