Public Assessment Report

UKPAR

Ceftriaxone 1g Powder for Solution for Injection or Infusion

(Ceftriaxone sodium)

UK Licence No: PL 42671/0001

Cox Pharmaceutical Limited
LAY SUMMARY

Ceftriaxone 1g Powder for Solution for Injection or Infusion

(Ceftriaxone sodium, powder for solution for injection or infusion, 1 gram (g) per vial)

This is a summary of the Public Assessment Report (PAR) for Ceftriaxone 1g Powder for Solution for Injection or Infusion (PL 42671/0001). It explains how Ceftriaxone 1g Powder for Solution for Injection or Infusion was assessed and its authorisation recommended, as well as its conditions of use. It is not intended to provide practical advice on how to use Ceftriaxone 1g Powder for Solution for Injection or Infusion.

The product will be referred to as Ceftriaxone Injection throughout the remainder of this public assessment report (PAR).

For practical information about using Ceftriaxone Injection patients should read the package leaflet or contact their doctor or pharmacist.

What is Ceftriaxone Injection and what is it used for?
Ceftriaxone Injection is used in adults and children (including newborn babies) to treat infections of:
- the brain (meningitis).
- the lungs.
- the middle ear.
- the abdomen and abdominal wall (peritonitis).
- the urinary tract and kidneys.
- bones and joints.
- the skin or soft tissues.
- the blood.
- the heart.

It can be given:
- to treat specific sexually transmitted infections (gonorrhoea and syphilis).
- to treat patients with low white blood cell counts (neutropenia) who have fever due to bacterial infection.
- to treat infections of the chest in adults with chronic bronchitis.
- to treat Lyme disease (caused by tick bites) in adults and children including newborn babies from 15 days of age.
- to prevent infections during surgery.

This medicine is the same as Ceftriaxone 1g Powder for Solution for Injection or Infusion (PL 39655/0001) which is already authorised. The company (Stravencon Limited) that makes Ceftriaxone 1g Powder for Solution for Injection or Infusion (PL 39655/0001) has agreed that its scientific data can be used as a basis for the grant of an identical licence for Ceftriaxone Injection (informed consent).

How does Ceftriaxone Injection work?
Ceftriaxone Injection contains the active ingredient ceftriaxone sodium which is an antibiotic. It works by killing the bacteria that cause infections. It belongs to a group of medicines called cephalosporins.
How is Ceftriaxone Injection used?
The pharmaceutical form of this medicine is a powder for solution for injection or infusion and the route of administration is as a drip (intravenous infusion) or as an injection directly into a vein or muscle.

Ceftriaxone Injection is usually given by a doctor or a nurse. It is made up by the doctor, pharmacist or nurse and will not be mixed with or given to the patient at the same time as calcium-containing injections.

The usual dose
The patient’s doctor will decide the correct dose of Ceftriaxone Injection for them. The dose will depend on the severity and type of infection; whether the patient is on any other antibiotics; their weight and age; how well their kidneys and liver are working. The number of days or weeks that the patient is given Ceftriaxone Injection depends on what sort of infection they have.

Please refer to section 3 of the package leaflet for information on how to use this medicine.

Ceftriaxone Injection can be obtained only with a prescription.

For further information on how Ceftriaxone Injection is used, refer to the package leaflet and Summary of Product Characteristics available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

What benefits of Ceftriaxone Injection have been shown in studies?
Ceftriaxone Injection is considered identical to previously authorised Ceftriaxone 1g Powder for Solution for Injection or Infusion (PL 39655/0001), with the same benefits and risks. So no new studies have been provided for Ceftriaxone Injection but reference is made to the studies for Ceftriaxone 1g Powder for Solution for Injection or Infusion (PL 39655/0001).

What are the possible side effects from Ceftriaxone Injection?
Like all medicines, this medicine can cause side effects, although not everybody gets them.

Ceftriaxone Injection is considered to be identical to the previously authorised application for Ceftriaxone 1g Powder for Solution for Injection or Infusion (PL 39655/0001) with the same benefits and risks.

For a full list of all the side effects reported with Ceftriaxone Injection see section 4 of the package leaflet, available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

For the full list of restrictions, see the package leaflet.

Why is Ceftriaxone Injection approved?
The MHRA decided that the benefits of Ceftriaxone Injection are greater than its risks and recommended that it be approved for use.
What measures are being taken to ensure the safe and effective use of Ceftriaxone Injection?
A Risk Management Plan has been developed to ensure that Ceftriaxone Injection is used as safely as possible. Based on this plan, safety information has been included in the Summary of Product Characteristics and the package leaflet for Ceftriaxone Injection including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Ceftriaxone Injection
A Marketing Authorisation was granted in the UK on 03 March 2016.

The full PAR for Ceftriaxone Injection follows this summary.

For more information about treatment with Ceftriaxone Injection read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in April 2016.
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I INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Cox Pharmaceutical Limited a Marketing Authorisation for the medicinal product Ceftriaxone Injection (PL 42671/0001) on 03 March 2016. The product is a prescription-only medicine (POM) and is indicated for the treatment of the following infections in adults and children including term neonates (from birth):

- Bacterial Meningitis
- Community acquired pneumonia
- Hospital acquired pneumonia
- Acute otitis media
- Intra-abdominal infections
- Complicated urinary tract infections (including pyelonephritis)
- Infections of bones and joints
- Complicated skin and soft tissue infections
- Gonorrhoea
- Syphilis
- Bacterial endocarditis

Ceftriaxone Injection may be used:

- For treatment of acute exacerbations of chronic obstructive pulmonary disease in adults.
- For treatment of disseminated Lyme borreliosis (early (stage II) and late (stage III)) in adults and children including neonates from 15 days of age.
- For pre-operative prophylaxis of surgical site infections.
- In the management of neutropenic patients with fever that is suspected to be due to a bacterial infection.
- In the treatment of patients with bacteraemia that occurs in association with, or is suspected to be associated with, any of the infections listed above.

Ceftriaxone should be co-administered with other antibacterial agents whenever the possible range of causative bacteria would not fall within its spectrum (see section 4.4 of the SmPC).

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

The application was submitted as simple abridged (informed consent) application according to Article 10c of Directive 2001/83/EC, as amended.

The application cross-refers to the reference product Ceftriaxone 1g Powder for Solution for Injection or Infusion (PL 39655/0001), which was originally authorised to Genus Pharmaceuticals Limited on 20 March 2001 (PL 06831/0069) and subsequently underwent a change of ownership procedure to the current marketing authorisation holder Stravencon Limited (PL 39655/0001) on 27 July 2011.

Ceftriaxone sodium belongs to the pharmacotherapeutic group ‘Antibacterials for systemic use, third-generation cephalosporins’ (ATC code: J01DD04). Its mode of action is by inhibition of bacterial cell wall synthesis following attachment to penicillin binding proteins (PBPs). This results in the interruption of cell wall (peptidoglycan) biosynthesis, which leads to bacterial cell lysis and death.

No new data were submitted nor were necessary to be submitted for this application, as the data are identical to that of the previously authorised cross-referenced product.
II QUALITY ASPECTS

II.1 Introduction
This is an abridged application for Ceftriaxone Injection (PL 42671/0001) submitted under Article 10c of Directive 2001/83/EC, as amended.

The application cross-refers to Ceftriaxone 1g Powder for Solution for Injection or Infusion (PL 39655/0001), which was originally authorised to Genus Pharmaceuticals Limited on 20 March 2001 (PL 06831/0069) and subsequently underwent a change of ownership procedure to the current marketing authorisation holder Stravencon Limited (PL 39655/0001) on 27 July 2011.

II.2 Drug Substance
Drug substance specification
The proposed drug substance specification is consistent with the details registered for the cross-reference product.

II.3 Medicinal Product
Name
The proposed product name for this application is Ceftriaxone 1g Powder for Solution for Injection or Infusion. The product has been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack size
Each vial contains 1 g ceftriaxone as ceftriaxone sodium. The finished product is packaged into 30ml colourless glass Type I or III vials closed with a rubber stopper and aluminium cap, in packs of 1, 5, 10, 25 or 50 vials. Not all pack sizes may be marketed.

The proposed shelf life of the unopened product is 24 months with the storage conditions ‘Do not store above 25°C. Keep container in the outer carton.’

After reconstitution:
Chemical and physical in-use stability has been demonstrated for 4 days at 2-8°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and would not normally be longer than 24 hours at 2-8°C, unless reconstitution/dilution has taken place in controlled and validated aseptic conditions.

The proposed packaging, shelf-life and storage conditions are consistent with the details registered for the cross-reference product.
Legal status
On approval, the product will be available as a prescription-only medicine (POM).

Marketing Authorisation Holder/Contact Persons/Company
Cox Pharmaceutical Limited, 788-790 Finchley Road, London, NW11 7TJ.

The Qualified Person (QP) responsible for pharmacovigilance is stated and a satisfactory CV has been provided.

Manufacturers
The proposed manufacturing sites are consistent with those registered for the cross-reference product and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

Qualitative and quantitative composition
The proposed composition is consistent with the details registered for the cross-reference product.

Manufacturing process
The proposed manufacturing processes are consistent with the details registered for the cross-reference product and the maximum batch size is stated.

Finished product/shelf-life specification
The proposed finished product specification is in line with the details registered for the cross-reference product.

TSE Compliance
This product contains no other excipients; hence the product contains no materials of animal or human origin.

Bioequivalence
No bioequivalence data are required to support this simple abridged application because the proposed product is manufactured to the same formula utilising the same processes as the cross-reference product, Ceftriaxone 1g Powder for Solution for Injection or Infusion (PL 39655/0001).

Expert Report
The applicant cross-references to the data for Ceftriaxone 1g Powder for Solution for Injection or Infusion (PL 39655/0001) to which this application is claimed to be identical. This is acceptable.

Product Name and Appearance
See Section II.3 ‘Medicinal Product; Name’ for details of the proposed product name. The appearance of the product is identical to that of the cross-reference product.

II.4 Discussion on chemical, pharmaceutical and biological aspects
The data submitted with the application is acceptable. The grant of a Marketing Authorisation is recommended.
III   NON-CLINICAL ASPECTS
Introduction
As this is an abridged application submitted under Article 10c of Directive 2001/83/EC, as amended, no new non-clinical data have been supplied and none are required.

Ecotoxicity/environmental risk assessment (ERA)
Suitable justification has been provided for non-submission of an Environmental Risk Assessment. As the application is an identical version of an already authorised product, it is not expected that environmental exposure will increase following approval of the Marketing Authorisation for the proposed product.

Discussion on the non-clinical aspects
The grant of a Marketing Authorisation is recommended.

IV   CLINICAL ASPECTS
Introduction
As this is an abridged application submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

Risk Management Plan (RMP)
The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ceftriaxone Injection.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
Summary table of safety concerns:

<table>
<thead>
<tr>
<th>Important identified risks</th>
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</thead>
<tbody>
<tr>
<td>Resistance</td>
</tr>
<tr>
<td><em>Clostridium difficile</em> associated diarrhoea (CDAD)</td>
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<tr>
<td>Risk of precipitation of ceftriaxone-calcium if ceftriaxone is mixed or administered simultaneously with any calcium-containing IV solutions in patients of any age</td>
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<tr>
<td>Pancreatitis/biliary sludging</td>
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<tr>
<td>Hypersensitivity reactions</td>
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<tr>
<td>Risk of bilirubin encephalopathy in newborns &amp; pre-term newborns. Hyperbilirubinaemic newborns and pre-term newborns should not be treated with ceftriaxone. This is a contra-indication for ceftriaxone.</td>
</tr>
<tr>
<td>Super-infections with non-susceptible organisms may occur as with other antibacterial agents. This is included as a special warning/precaution.</td>
</tr>
<tr>
<td>Severe skin reactions (EM, SJS &amp; TEN)</td>
</tr>
<tr>
<td>Severe haematological reactions (agranulocytosis, haemolytic anaemia, thrombocytopenia)</td>
</tr>
<tr>
<td>Severe skin reactions (EM, SJS &amp; TEN)</td>
</tr>
<tr>
<td>Contraindications to lidocaine must be excluded before intramuscular injection of ceftriaxone when lidocaine solution is used as a solvent.</td>
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</tbody>
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<table>
<thead>
<tr>
<th>Important potential risks</th>
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<tr>
<td>Interaction. Concomitant use with oral anticoagulants may increase the anti-vitamin K effect and the risk of bleeding.</td>
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<th>Missing information</th>
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<td>Fertility. There are limited data on the effects of ceftriaxone on fertility in humans</td>
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</tbody>
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Routine pharmacovigilance and routine risk minimisation are proposed for all safety concerns.

**Discussion on the clinical aspects**
The grant of a Marketing Authorisation is recommended.

**V User consultation**
A user consultation with target patient groups on the package information leaflet (PIL) has been performed on the basis of a bridging report making reference to the PIL for Ceftriaxone 1g Powder for Solution for Injection or Infusion (PL 39655/0001). The bridging report submitted by the applicant has been found acceptable.
VI Overall conclusion, benefit/risk assessment and recommendation
The quality of the product is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applicant’s product is identical to the cross-reference product. Extensive clinical experience with ceftriaxone sodium is considered to have demonstrated the therapeutic value of the compound. The benefit/risk balance is, therefore, considered to be positive.

Summaries of Product Characteristics (SmPC), Patient Information Leaflets (PIL) and Labels
The Summary of Product Characteristics and Patient Information Leaflet (PIL) are consistent with the details registered for the cross-reference products.

In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPCs) and Patient Information Leaflets (PILs) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for Ceftriaxone Injection is presented below:
CefTRIAXone 1g

Powder for solution for injection or infusion
Contains 1g ceftriaxone as ceftriaxone sodium.
Directions: See leaflet.
For IV use: Dissolve in 10 ml Water for Injections.
For IM use: Dissolve in 3.5 ml 1% Lignocaine HCl Injection BP.
Do not mix with calcium containing solutions
Do not store above 25°C. Keep container in the outer carton.

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