Medicines & Healthcare products Regulatory Agency

MHRA Regulating Medicines and Medical Devices

Public Assessment Report

UK PAR

Ceftriaxone 1g and 2g Powder for Solution for Injection or Infusion

(Ceftriaxone sodium)

UK Licence No: PL 28395/0109-0110

Pharmadreams Ltd

LAY SUMMARY

Ceftriaxone 1g and 2g Powder for Solution for Injection or Infusion

(Ceftriaxone sodium)

This is a summary of the Public Assessment Report (PAR) for Ceftriaxone 1g Powder for Solution for Injection or Infusion (PL 28395/0109) and Ceftriaxone 2g Powder for Solution for Injection or Infusion (PL 28395/0110). It explains how the applications for Ceftriaxone 1g and 2g Powder for Solution for Injection or Infusion (PL 28395/0109-0110) were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use Ceftriaxone 1g and 2g Powder for Solution for Injection or Infusion.

For practical information about using Ceftriaxone 1g and 2g Powder for Solution for Injection or Infusion, patients should read the package leaflet or contact their doctor or pharmacist.

Ceftriaxone 1g and 2g Powder for Solution for Injection or Infusion may be referred to as 'Ceftriaxone Injection' in this Lay summary.

What is Ceftriaxone Injection and what is it used for?

These medicines are the same as Ceftriaxone 1g Powder for Solution for Injection or Infusion (PL 39655/0001; Stravencon Limited, UK) and Ceftriaxone 2g Powder for Solution for Injection or Infusion (PL 39655/0002; Stravencon Limited, UK), which are already authorised in the UK. The licence holder (Stravencon Limited, UK) for Ceftriaxone Powder for Solution for Injection or Infusion (PL 39655/0001-0002) has agreed that its own scientific data can be used as a basis for the grant of identical licences for Ceftriaxone Powder for Solution for Injection or Infusion (PL 28395/0109-0110) (informed consent).

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

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

How does Ceftriaxone Injection work?
Ceftriaxone Injection contains the active substance, ceftriaxone (as ceftriaxone sodium), which is an antibiotic. It belongs to a group of medicines called cephalosporins. It works by killing bacteria that cause infections.

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 into a 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 you 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.

Ceftriaxone Injection can only be obtained with a prescription.

Please read section 3 of the package leaflet for detailed information on dosing recommendations and the duration of treatment.

What benefits of Ceftriaxone Injection have been shown in studies?
The applications for Ceftriaxone Injection (PL 28395/0109-0110) are considered to be identical to the previously authorised licences for Ceftriaxone Injection (PL39655/0001-0002, Stravencon Limited, UK), with the same benefits and risks. So, no new studies have been provided for Ceftriaxone Injection (PL 28395/0109-0110). However, reference is made to the studies for Ceftriaxone Injection (PL 39655/0001-0002; Stravencon Limited, UK).

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

For the full list of all side effects reported with Ceftriaxone Injection, see section 4 of the package leaflet.

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

Why is Ceftriaxone Injection approved?
The MHRA considered that the benefits of Ceftriaxone Injection are greater than its risks and recommended the grant of Marketing Authorisations.

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 Summaries of Product Characteristics and the package leaflet for Ceftriaxone Injection (PL 28395/0109-0110), 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
Marketing Authorisations were granted in the UK to Pharmadreams Ltd on 04 May 2017.

The full PAR for Ceftriaxone Injection follows this summary.

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

This summary was last updated in July 2017.

Ceftriaxone 1g and 2g Powder for Solution for Injection or Infusion

(Ceftriaxone sodium)

PL 28395/0109-0110

SCIENTIFIC DISCUSSION

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I. INTRODUCTION

The Medicines and Healthcare products Regulatory Agency (MHRA) granted Pharmadreams Ltd Marketing Authorisations for the medicinal products Ceftriaxone 1g Powder for Solution for Injection or Infusion (PL 28395/0109) and Ceftriaxone 2g Powder for Solution for Injection or Infusion (PL 28395/0110) on 04 May 2017. Ceftriaxone 1g Powder for Solution for Injection or Infusion and Ceftriaxone 2 g Powder for Solution for Injection or Infusion may be referred to as 'Ceftriaxone Powder for Solution for Injection' in this Scientific discussion. The products are Prescription Only Medicines (POM) 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 may be used for:

- treatment of acute exacerbations of chronic obstructive pulmonary disease in adults.
- treatment of disseminated Lyme borreliosis (early (stage II) and late (stage III)) in adults and children including neonates from 15 days of age.
- 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 applications were submitted as simple abridged (informed consent) applications according to Article 10c of Directive 2001/83/EC, as amended. The applications for Ceftriaxone 1g Powder for Solution for Injection or Infusion (PL 28395/0109) and Ceftriaxone 2 g Powder for Solution for Injection or Infusion (PL 28395/0110) cross-refer to Ceftriaxone 1 g powder for solution for injection or infusion (PL 39655/0001) and Ceftriaxone 2 g powder for solution for injection or infusion (PL 39655/0002), which were authorised in the UK on 27 July 2011 to Stravencon Limited following a Change of Auhorisation (CoA) procedure of Ceftriaxone Sodium 1g Injection (PL 06831/0069; Genus Pharmaceuticals Limited, UK) and Ceftriaxone Sodium 2g Injection (PL 06831/0070; Genus Pharmaceuticals Limited, UK). Ceftriaxone Sodium 1g and 2g Injection (PL 06831/0069- 0070; Genus Pharmaceuticals Limited, UK) were authorised in the UK on 20 March 2001.

The active ingredient, ceftriaxone (as ceftriaxone sodium), is a well-established antibiotic. The mechanism of the bacterial action is due to inhibition of bacterial cell wall synthesis which leads to cell death.

No new data were submitted nor were they required for these applications, as the products are identical to those of the previously granted cross-reference products.

II. QUALITY ASPECTS

II.1 INTRODUCTION

These are informed consent applications for Ceftriaxone Powder for Solution for Injection (PL 28395/0109-0110), submitted under Article 10c of Directive 2001/83/EC, as amended.

The applications for Ceftriaxone Injection (PL 28395/0109-0110) cross-refer to Ceftriaxone Injection (PL 39655/0001-0002), which were authorised in the UK on 27 July 2011. The applications are considered valid.

II.2 Drug substance

The proposed drug substance specification is consistent with the details registered for the cross reference products.

II.3 Medicinal Product

Name

The proposed names of the products are Ceftriaxone 1g Powder for Solution for Injection or Infusion (PL 28385/0109) and Ceftriaxone 2g Powder for Solution for Injection or Infusion (PL 28385/0110). The products have been named in line with current requirements.

Strength, pharmaceutical form, route of administration, container and pack sizes

The products are powders for solution for injection or infusion. Each vial contains ceftriaxone sodium equivalent to 1g or 2g of ceftriaxone, as the active substance.

The products are administered parenterally by intravenous infusion (over at least 30 minutes), slow (intravenous injection over 5 minutes) or by deep intramuscular injection.

The products are packaged in 30 ml and 50 ml (2g strength only) colourless glass Type I or III vial closed with rubber stoppers and aluminium caps, in pack of 1, 5, 10, 25 or 50 vials.

Not all packs may be marketed.

The proposed shelf life of the unopened product is 24 months. 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.

The special storage conditions for the products:

1. Unopened product: ‘Do not store above 25ºC. Keep container in the outer carton’
2. Reconstituted solution: ‘Store at 2°C - 8°C.’

The packaging, proposed shelf-life and storage conditions are consistent with the details registered for the respective cross-reference products.

Legal status

The products are available as Prescription Only Medicines (POM).

Marketing Authorisation Holder/Contact Persons/Company

Pharmadreams Ltd, Old Police Station, Church Street, Swadlincote, DE11 8LN, United Kingdom.

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 products and evidence of Good Manufacturing Practice (GMP) compliance has been provided.

Qualitative and quantitative composition

The proposed compositions are consistent with the details registered for the respective cross-reference products.

Manufacturing process

The proposed manufacturing process is consistent with the details registered for the cross-reference products and the maximum batch sizes are stated.

Finished product/shelf-life specification

The proposed finished product specifications are consistent with the details registered for the cross-reference products.

TSE Compliance

The products contain no excipients.

Bioequivalence

No bioequivalence data are required to support these simple abridged applications because the proposed products are manufactured to the same formula and utilises the same processes as the reference products Ceftriaxone Injection (PL 39655/0001 and 0002).

Product Name and Appearance

See Section II.3 ‘Medicinal Product, Name’ for details of the proposed product names. The appearance of each product is identical to the respective cross-reference product.

Summaries of Product Characteristics (SmPCs)

The proposed SmPCs are consistent with the details registered for the respective cross-reference products.

Patient Information Leaflet (PIL) and Labelling

PILs

The PIL has been prepared in line with the details registered for the cross-reference products.

Carton and label

The proposed artwork is consistent with the artwork registered for the respective cross-reference products and complies with statutory requirements.

II.4 Discussion on chemical, pharmaceutical and biological aspects

The data submitted with the applications are acceptable. The grant of Marketing Authorisations is recommended.

III. NON-CLINICAL ASPECTS

Introduction

As these are informed consent applications 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 applications are identical versions of already authorised products, it is not expected that environmental exposure of ceftriaxone will increase following approval of the Marketing Authorisations for the proposed products.

Discussion on the non-clinical aspects

The grant of Marketing Authorisations is recommended.

IV. CLINICAL ASPECTS

Introduction

As these are informed consent applications submitted under Article 10c of Directive 2001/83/EC, as amended, no new clinical data have been supplied and none are required.

Pharmacovigilance and Risk Management Plan (RMP)

The Marketing Authorisation Holder has provided details of a suitable pharmacovigilance system that fulfils the requirements and provides adequate evidence that they have the services of a qualified person responsible for pharmacovigilance, and have the necessary means for the notification of any adverse reaction suspected of occurring either in the Community or in a third country.

An acceptable Risk Management Plan (RMP) has been submitted. A summary of safety concerns is listed in the following table.

Summary of safety concerns	
Important identified risks	**Resistance.** In suspected or proven infections with Pseudomonas aeruginosa, high resistance rates (> 60 %) for ceftriaxone in at least some European countries should be taken into consideration.
	***Clostridium difficile* associated diarrhoea (CDAD)** has been reported with use of nearly all antibacterial agents, including ceftriaxone, and may range in severity from mild diarrhoea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of C. *difficile.* C. *difficile* produces toxins A and B which contribute to the development of CDAD.
	Risk of precipitation of ceftriaxone-calcium if ceftriaxone is mixed or administered simultaneously with any calcium-containing IV solutions in patients of any age. Cases of fatal reactions with calcium-ceftriaxone precipitates in lungs and kidneys in premature and full-term newborns aged less than 1 month have been described.
	Pancreatitis/biliary sludging. Cases of pancreatitis, possibly of biliary obstruction aetiology, have been rarely reported in patients treated with ceftriaxone. Most patients presented with risk factors for biliary stasis and biliary sludge, e.g. preceding major therapy, severe illness and total parenteral nutrition.
	Hypersensitivity reactions. Ceftriaxone is contraindicated in patients who have had a previous hypersensitivity reaction to any cephalosporin.
	Risk of bilirubin encephalopathy in newborns & pre-term newborns. Hyperbilirubinaemic newborns and pre-term newborns should not be treated with ceftriaxone.

Summary of safety concerns	
	Super-infections Super-infections with non-susceptible organisms may occur as with other antibacterial agents.
	Severe skin reactions Severe skin reactions (EM, SJS & TEN)
	Severe haematological reactions Severe haematological reactions (agranulocytosis, haemolytic anaemia, thrombocytopenia)
	Contraindications to lidocaine Contraindications to lidocaine must be excluded before intramuscular injection of ceftriaxone when lidocaine solution is used as a solvent. See information in the Summary of Product Characteristics of lidocaine, especially contraindications. Ceftriaxone solutions containing lidocaine should never be administered intravenously.
Important potential risks	**Interaction 1.** Do not use diluents containing calcium, such as Ringer's solution or Hartmann's solution, to reconstitute ceftriaxone vials or to further dilute a reconstituted vial for IV administration because a precipitate can form.
	Interaction 2. Concomitant use with oral anticoagulants may increase the anti-vitamin K effect and the risk of bleeding.
Important missing information	**Effects on fertility.** Reproductive studies have shown no evidence of adverse effects on male or female fertility.

Routine pharmacovigilance and routine risk minimisation activities are proposed for all safety concerns.

Discussion on the clinical aspects
The grant of Marketing Authorisations is recommended.

V. USER CONSULTATION

A user consultation with target patient groups on the Patient Information Leaflet (PIL) has been performed on the basis of a bridging report making reference to the PIL for Ceftriaxone Injection (PL 39655/0001-0002). The bridging report has been found to be acceptable.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION

QUALITY

The data for these applications are consistent with those previously assessed for the cross-reference products and as such have been judged to be satisfactory.

NON-CLINICAL

No new non-clinical data were submitted and none are required for applications of this type.

EFFICACY

No new efficacy data were supplied or required for these applications. Ceftriaxone has a well-established efficacy profile. These products are identical to the previously granted licences for Ceftriaxone Injection (PL 39655/0001-0002).

SAFETY

No new safety data were supplied or required for these applications. Ceftriaxone has a well-established safety profile. These products are identical to the previously authorised Ceftriaxone Injection (PL 39655/0001-0002).

PRODUCT LITERATURE

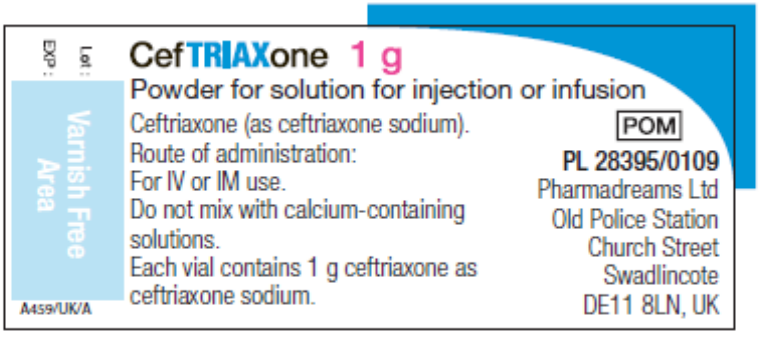
The SmPCs and PIL are satisfactory, and consistent with those for the respective cross-reference products. The labelling text complies with statutory requirements and is satisfactory.

BENEFIT/RISK ASSESSMENT

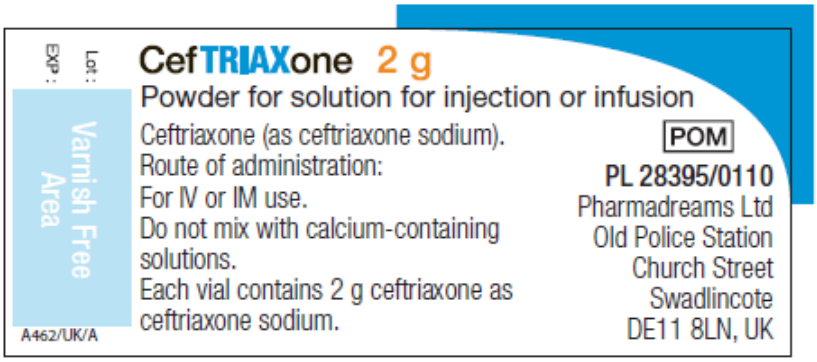
The quality of the products is acceptable, and no new non-clinical or clinical safety concerns have been identified. The applicant's products are identical to the cross-reference products. Extensive clinical experience with ceftriaxone is considered to have demonstrated the therapeutic value of the compound. The benefit/risk assessment is, therefore, considered to be positive.

In accordance with Directive 2010/84/EU, the current version of the SmPCs and PIL is available on the MHRA website. The current labelling is presented below:

Ceftriaxone 1 g Powder for Solution for Injection or Infusion:



Ceftriaxone 2 g Powder for Solution for Injection or Infusion:



Ceftriaxone 1g and 2g Powder for Solution for Injection or Infusion

(Ceftriaxone sodium)

PL 28395/0109-0110

STEPS TAKEN AFTER AUTHORISATION - SUMMARY

Date submitted	Application type	Scope	Outcome