CBG MEB

PUBLIC ASSESSMENT REPORT of the Medicines Evaluation Board in the Netherlands

Ceftriaxon Sandoz 0.25 g, 0.5 g and 1 g, powder and solvent for solution for injection Ceftriaxon Sandoz 1 g, powder and solvent for solution for injection or infusion Sandoz B.V., the Netherlands

ceftriaxone (as disodium 3.5 hydrate)/ lidocaine hydrochloride or water for injection

This assessment report is published by the MEB pursuant Article 21 (3) and (4) of Directive 2001/83/EC. The report comments on the registration dossier that was submitted to the MEB and its fellow –organisations in all concerned EU member states.
It reflects the scientific conclusion reached by the MEB and all concerned member states at the end of the evaluation process and provides a summary of the grounds for approval of a marketing authorisation.
This report is intended for all those involved with the safe and proper use of the medicinal product, i.e. healthcare professionals, patients and their family and carers. Some knowledge of medicines and diseases is expected of the latter category as the language in this report may be difficult for laymen to understand.

This assessment report shall be updated by a following addendum whenever new information becomes available.

General information on the Public Assessment Reports can be found on the website of the MEB.

To the best of the MEB's knowledge, this report does not contain any information that should not have been made available to the public. The MAH has checked this report for the absence of any confidential information.

EU-procedure number: NL/H/0423/004-007/DC
Registration number in the Netherlands: RVG 104063, 104062, 104064, 104073

2 November 2010

Pharmacotherapeutic group:	other beta-lactam antibacterials, third-generation cephalosporins
ATC code:	J01DD04
Route of administration:	intravenous, intramuscular
Therapeutic indication:	severe infections when known or likely to be due to micro-organisms that are susceptible to ceftriaxone and require parenteral treatment (see next page).
Prescription status:	prescription only
Date of authorisation in NL:	22 October 2010
Concerned Member States:	Decentralised procedure with IT
Application type/legal basis:	Directive 2001/83/EC, Article 10(1)

For product information for healthcare professionals and users, including information on pack sizes and presentations, see Summary of Product Characteristics (SPC), package leaflet and labelling.

I INTRODUCTION

Based on the review of the quality, safety and efficacy data, the member states have granted a marketing authorisation for Ceftriaxon Sandoz 0.25 g, 0.5 g and 1 g, powder and solvent for solution for injection and Ceftriaxon Sandoz 1 g, powder and solvent for solution for injection or infusion from Sandoz B.V. The date of authorisation was on 22 October 2010 in the Netherlands.

The product is indicated for use against severe infections when known or likely to be due to micro-organisms that are susceptible to ceftriaxone and require parenteral treatment:

- Bacterial meningitis (see section 4.2 of the approved SPC for the recommendation for the management of purpura fulminans)
- Pneumonia
- Abdominal infections: namely peritonitis and biliary infections. Ceftriaxone should be used in combination with another antibiotic, that can provide anaerobic coverage.
- Complicated skin and soft tissue infections
- Bone and joint infections
- Patients with late manifestations of Lyme disease (stage II and III)
- Gonorrhoea
- Otitis media in children and neonates (after failure with other treatment or impossibility to treat orally (see also section 4.4 of the approved SPC for further clarifications on these restrictions)).

A comprehensive description of the indications and posology is given in the SPC.

Ceftriaxone has bactericidal activity that results from the inhibition of bacterial cell wall synthesis. The extent of the bactericidal activity depends on the period of time when the serum level exceeds the minimal inhibitory concentration (MIC) of the pathogen.
Ceftriaxone may be active against organisms producing some types of beta-lactamase, for example TEM-1. However, it is inactivated by beta-lactamases that can efficiently hydrolyse cephalosporins, such as many of the extended-spectrum beta-lactamases and chromosomal cephalosporinases, such as AmpC type enzymes.
Ceftriaxone cannot be expected to be active against the majority of bacteria with penicillin-binding proteins that have reduced affinity for beta-lactam drugs. Resistance may also be mediated by bacterial impermeability or by bacterial drug efflux pumps. More than one of these four means of resistance may be present in the same organism.

This decentralised procedure concerns a generic application claiming essential similarity with the innovator products Rocephin, powder for solution for injection 0.25 g, 0.5 g and 1 g (NL License RVG 09911, 09915 and 09913, respectively) which have been registered in the Netherlands by Roche B.V. since 4 June 1984. In addition, reference is made to Rocephin authorisations in the individual member states (reference product).

The marketing authorisation is granted based on article 10(1) of Directive 2001/83/EC.

This type of application refers to information that is contained in the pharmacological-toxicological and clinical part of the dossier of the authorisation of the reference product. A reference product is a medicinal product authorised and marketed on the basis of a full dossier, i.e. including chemical, biological, pharmaceutical, pharmacological-toxicological and clinical data. This information is not fully available in the public domain. Authorisations for generic products are therefore linked to the 'original' authorised medicinal product, which is legally allowed once the data protection time of the dossier of the reference product has expired. As Ceftriaxon Sandoz is a product for parenteral use, it is exempted for biostudy (NfG CPMP/EWP/QWP 1401/98). The current products can be used instead of their reference products.

No new pre-clinical and clinical studies were conducted, which is acceptable for this abridged application.

No scientific advice has been given to the MAH with respect to these products and no paediatric development programme has been submitted, as this is not required for a generic application.

II SCIENTIFIC OVERVIEW AND DISCUSSION

II.1 Quality aspects

Compliance with Good Manufacturing Practice
The MEB has been assured that acceptable standards of GMP (see Directive 2003/94/EC) are in place for these product types at all sites responsible for the manufacturing of the active substance as well as for the manufacturing and assembly of this product prior to granting its national authorisation.

Active substance
The active substance is ceftriaxone sodium, an established active substance described in the European, British and USA Pharmacopoeia (Ph.Eur., BP and USP*). The drug substance is a white to yellowish crystalline powder, which is freely soluble in water, sparingly soluble in methanol and very slightly soluble in ethanol.

The CEP procedure is used for both suppliers of the active substance. Under the official Certification Procedures of the EDQM of the Council of Europe, manufacturers or suppliers of substances for pharmaceutical use can apply for a certificate of suitability concerning the control of the chemical purity and microbiological quality of their substance according to the corresponding specific monograph, or the evaluation of reduction of Transmissible Spongiform Encephalopathy (TSE) risk, according to the new general monograph, or both. This procedure is meant to ensure that the quality of substances is guaranteed and that these substances comply with the European Pharmacopoeia.

Manufacturing process
CEPs have been submitted; therefore no details on the manufacturing process have been included.

Quality control of drug substance
The active substance specification is considered adequate to control the quality and meets the requirements of the monograph in the Ph.Eur. and the additional CEP requirements. The specification is acceptable in view of the CEPs. Batch analytical data have been provided on 3 batches from each supplier.

Stability of drug substance
For both suppliers, stability assessment was part of granting the CEP and has been granted by the EDQM. The active substance from one of the suppliers is stable for 48 months when stored under the stated conditions. Stability for 24 months was demonstrated for the other supplier.

** Ph.Eur., USP, BP are official handbooks (pharmacopoeias) in which methods of analysis with specifications for substances are laid down by the authorities of the EU, USA, or UK respectively.*

Solvent
The solvent used for solution for injection is lidocaine hydrochloride, an established drug substance, which is described in the Ph.Eur., BP and USP. The drug substance is very soluble in water, freely soluble in alcohol and practically insoluble in ether.
The CEP procedure is used for the solvent.

Manufacturing process
A CEP has been submitted; therefore no details on the manufacturing process have been included.

Quality control of the solvent

The MAH refers to the specifications of the Ph.Eur. monograph for lidocaine hydrochloride and an additional CEP requirement regarding residual solvents. The specification is acceptable in view of the CEP.

Stability of solvent
The active substance is stable for 60 months when stored under the stated conditions. Data to support the proposed shelf-life has been provided.

Medicinal Product – Ceftriaxon Sandoz 0.25/0.5/1 g powder and solvent for solution for injection
Composition
The finished product Ceftriaxon Sandoz 0.25 g consists of one vial of 0.25 g ceftriaxone and one 5 ml ampoule of a 1% (20 mg/2 ml) lidocaine hydrochloride solution as a solvent.

The finished product Ceftriaxon Sandoz 0.5 g consists of one vial of 0.5 g ceftriaxone and one 5 ml ampoule of a 1% (20 mg/2 ml) lidocaine hydrochloride solution as a solvent.

The finished product Ceftriaxon Sandoz 1 g consists of one vial of 1 g ceftriaxone and one 5 ml ampoule of a 1% (35 mg/3.5 ml) lidocaine hydrochloride solution as a solvent.

The 15 ml powder vials are made of clear glass closed with halogenated butyl rubber stopper covered with aluminium caps and plastic flip-offs.
The solvent is packed in 5 ml clear glass ampoules.

The excipients are: no excipients are used in the powder ampoule, in the solvent for solution lidocaine hydrochloride, water for injections, sodium hydrogen carbonate.

Pharmaceutical development
The development of the ceftriaxone has been described, the choice of the diluent lidocaine hydrochloride is explained and justified. The drug preparation ceftriaxone has been developed to be equivalent to the corresponding brand leader products on the market. The quantity of ceftriaxone sodium per vial corresponds to the label claim of ceftriaxone. Similar to already existing products a solution of lidocaine hydrochloride in water for injections with adequate pH was formulated.
The product contains water for injections as solvent and sodium hydrogen carbonate for adjustment of the pH. Nitrogen is used during filling and is thus present as head space gas in the formulation.
The proposed products and the reference products concern both the active substance filled in injection vials without any excipients. In view of this and the reconstitution advice in the SPC, the products are essentially similar.

Manufacturing process
Due to the physical properties of the ceftriaxone sterilization in the primary packaging material is not applicable so pre-sterilized individual components and aseptic compounding and filling is used.
Lidocaine hydrochloride solution for injection is a sterile parenteral liquid formulation. The sterile solution is filled into sterile and depyrogenised ampoules. The ampoules are terminally sterilized. The manufacturing process has been adequately validated according to relevant European guidelines.
The manufacturing of ceftriaxone powder is a non-standard process; sufficient validation data have been provided.

Control of excipients
Nitrogen, water for injection and sodium hydrogen carbonate are tested with the analytical methods as described in their respective Ph.Eur. monographs. These specifications are acceptable.

Quality control of drug product
The product specification for ceftriaxone powder includes tests for appearance, identification, uniformity of dosage units, water content, fibres and suspended matter, clarity and colour of the solution, pH, dissolution time, related substances, assay, sterility, bacterial endotoxins, particulate contamination, suspended matter and specific optical rotation. The product specification for lidocaine hydrochloride

ampoules includes tests for appearance, identity, relative density, pH, refractive index, extractable volume, visible and sub-visible particles, sterility, bacterial endotoxins, related substances and assay. Release and end of shelf-life specification for ceftriaxone powder are identical except for water content, related substance, impurities and assay. For lidocaine hydrochloride the release specification and the end of shelf-life specification are identical. The analytical methods have been adequately described and validated. For ceftriaxone powder batch analytical data from the proposed production site were provided on three batches of each strength, demonstrating compliance with the specifications.
For lidocaine hydrochloride, analytical results on three production-scale batches of each product volume were presented.

Container closure system
The primary packaging materials for ceftriaxone are 15 ml glass vials closed with rubber stoppers crimp caps and for lidocaine 5 ml glass amoules. Since these container closure systems are standard for parenteral formulations, no further development studies were performed. The suitability of the chosen primary packaging materials was shown during the stability studies (see below).

Microbiological attributes
The drug preparation of ceftriaxone consists only of the sterile active substance. The drug preparation of lidocain is terminally sterilized. Since the formulation has been conceived as a single dose preparation, no preservatives are added.

Stability of drug product
Stability data on the ceftriaxon powder has been provided for several development/pilot-scale batches stored at 25°C/60%RH (36 months), 30°C/65%RH (36 months) and 40°C/75%RH (6 months). The product was stored in 10 ml or 15 ml glass vials closed with rubber stoppers and a flip-off crimp seal. The conditions used in the stability studies are according to the ICH stability guideline.
In all batches the results remained within the limits. Therefore the submitted data is sufficient to support the claimed shelf-life of 36 months for the ceftriaxone powder. The drug product should be protected from light; no other requirements are necessary based on the stability data.
Stability studies with lidocaine hydrochloride were performed at 25°C and 40°C, in accordance with the ICH guidelines. The claimed shelf-life of 24 months is supported by the stability data and can be granted. The shelf-life of the drug product that includes the ceftriaxone powder as well as the lidocaine hydrochloride should be the shortest shelf-life of the separate products, in this case 24 months. The drug substance is sensitive to light. The product does not require any special temperature storage conditions, but must be stored in the original package to protect from light.

In-use stability
Stability data on the reconstituted solution has been provided on several batches stored at 2-8°C (48 hours) and at a maximum of 25°C (24 hours). The stability of the reconstituted product has been tested at the beginning and at the end of shelf-life. Based on the stability data on the reconstituted product, an in-use shelf-life could be granted of 24 hours at 2-8°C.

Medicinal Product – Ceftriaxon Sandoz 1 g powder and solvent for solution for injection/infusion
Composition
The finished product Ceftriaxon Sandoz 1 g consists of one vial of 1 g ceftriaxone and one ampoule containing 10 ml water for injection as a solvent.

The 15 ml powder vials are made of clear glass closed with halogenated butyl rubber stopper covered with aluminium caps and plastic flip-offs.
The solvent is packed in 10 ml clear LDPE ampoules.

No excipients are used.

Pharmaceutical development
The development of the ceftriaxone has been described, the choice of the diluent water for injection is explained and justified. The drug preparation ceftriaxone has been developed to be equivalent to the

corresponding brand leader products on the market. The quantity of ceftriaxone sodium per vial corresponds to the label claim of ceftriaxone. The proposed products and the reference products concern both the active substance filled in injection vials without any excipients. In view of this and the reconstitution advice in the SPC, the products are essentially similar.

Manufacturing process

Due to the physical properties of the ceftriaxone end sterilization in the primary packaging material is not applicable so pre-sterilized individual components and aseptic compounding and filling is used. The plastic ampoules containing the water for injection are produced using the bottlepack blow-fill-seal technology producing and filling the plastic ampoules in one machine under aseptic conditions. The manufacturing process has been adequately validated according to relevant European guidelines. The manufacturing of ceftriaxone powder is a non-standard process; sufficient validation data have been provided.

Quality control of drug product

The product specification for ceftriaxone powder includes tests for appearance, identification, uniformity of dosage units, water content, fibres and suspended matter, clarity and colour of the solution, pH, dissolution time, related substances, assay, sterility, bacterial endotoxins, particulate contamination, suspended matter and specific optical rotation. The product specification for water for injection includes tests for appearance, odour and taste, identification, indices (including extractable volume), purity (including among others sterility and bacterial endotoxins) and assay. Release and end-of-shelf-life specifications for ceftriaxone powder are identical except for water content, related substances, unknown impurities and assay. For water for injection the extractable volume of the release specification differed from the end of shelf-life specification. The analytical methods have been adequately described and validated. Batch analytical data from the proposed production site were provided.

Container closure system

The primary packaging for ceftriaxone is 15 ml glass vials. The primary packaging for water for injection is 10 ml plastic ampoules. Since this container closure system is standard for parenteral formulations, no further development studies were performed. The suitability of the chosen primary packaging materials was shown during the stability studies (see below).

Microbiological attributes

The drug preparation consists only of the sterile active substance. Since the formulation has been conceived as a single dose preparation, no preservatives are added.

Stability of drug product

Stability data on the ceftriaxon powder has been provided for several development/pilot-scale batches stored at 25°C/60%RH (36 months), 30°C/65%RH (36 months) and 40°C/75%RH (6 months). The batches were stored in 10 ml or 15 ml glass vials closed with rubber stoppers and a flip-off crimp seal. The conditions used in the stability studies are according to the ICH stability guideline. In all batches, some slight increases in the impurities (identified as well as total) were noted, but the results remained within the limits. Therefore the submitted data is sufficient to support the claimed shelf-life of 36 months for the 1 g ceftriaxone powder. The drug substance should be protected from light; no other requirements are necessary based on the stability data.
Stability studies with respect to water for injection were performed at 25°C/60%RH, 30°C/65%RH and 40°C/75%RH. In accordance with the ICH guidelines, a calculation was performed to predict storage at long term conditions of 25°C/40%RH. The claimed shelf-life of 52 months is justified and can be granted. The shelf-life of the drug product that includes the ceftriaxone powder as well as the water for injection should be the shortest shelf-life of the separate products, in this case 36 months. The product does not require any special temperature storage conditions, but must be stored in the original package to protect from light.

In-use stability

Stability data on the reconstituted solution with 0.9% sodium chloride or 5% glucose has been provided on several batches stored at 2-8°C (48 hours) and at a maximum of 25°C (24 hours). The stability of the reconstituted product has been tested at the beginning and at the end of shelf-life. Based on the stability data on the reconstituted product, an in-use shelf-life could be granted of 24 hours at 2-8°C.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies
There are no substances of ruminant animal origin present in the products nor have any been used in the manufacturing of these products, so a theoretical risk of transmitting TSE can be excluded.

II.2 Non-clinical aspects

This product is a generic formulation of Rocephin, which is available on the European market. No new preclinical data have been submitted, and therefore the application has not undergone preclinical assessment. This is acceptable for this type of application.

Environmental risk assessment
The product is intended as a substitute for other identical products on the market. The approval of this product will not result in an increase in the total quantity of ceftriaxone released into the environment. It does not contain any component, which results in an additional hazard to the environment during storage, distribution, use and disposal.

II.3 Clinical aspects

Ceftriaxone is a well-known active substance with established efficacy and tolerability.

Ceftriaxon Sandoz 0.25 g, 0.5 g and 1 g, powder and solvent for solution for injection and Ceftriaxon Sandoz 1 g, powder and solvent for solution for injection or infusion are parenteral formulations and therefore fulfil the exemption mentioned in the Note for Guidance on bioequivalence “5.1.6 parenteral solutions”, which states that a bioequivalence study is not required if the product is administered as an aqueous intravenous solution containing the same active substance in the same concentration as the currently authorized reference medicinal product (NfG CPMP/EWP/QWP 1401/98). The quantitative composition of Cefriaxon Sandoz is entirely the same as the originator. Therefore, it may be considered as therapeutic equivalent, with the same efficacy/safety profile as known for the active substance of the reference medicinal product. The current products can be used instead of their reference products.

Discussion on indications
Although in principle no new data on clinical efficacy is required because this is an application for a generic product, some of the claimed indications were questioned and new indications were proposed during the procedure. The MAH was therefore asked for additional data to support the following proposed indications:

- Bone and joint infections
- Skin and soft tissue infections
- Peri-operative prophylaxis of severe postoperative infections.

The submitted publications provided supportive evidence for the beneficial use of ceftriaxone in the indications disputed. The presently claimed indications are in line with the updated SPC of the innovator product Rocephin in NL and the recently approved Ceftriaxon Sandoz (NL/H/423/001-003) in 13 other CMSs.

Bone and joint infections - Skin and soft tissue infections: Ceftriaxone is licensed for the treatment of *severe* skin and soft tissue infections (sSSTI) and bone and joint infections for many years (since 1984) in the Netherlands. Bone and SSTI have been also accepted as indications for the innovator Rocephin in other countries, including the UK. Moreover, these indications have been approved by the recent referral procedure (EMA/H//A-29/687) for Ceftriaxone Tyrol 1 g and 2 g, powder for solution for injection or

infusion. Furthermore, the pathogens most frequently isolated in SSTI are *Staphylococcus aureus* and ß-hemolytic streptococci, which are considered susceptible to ceftriaxone. Therefore, 'bone and joint infections' and '*severe* skin and soft tissue infections' are acceptable in line with the Dutch innovator SPC.

Peri-operative prophylaxis of severe postoperative infections: With regard to the prophylactic indication, it was noted that a general surgical prophylaxis has been accepted as an indication for the reference SPC of Rocephin in the Netherlands. The same applies in several other countries. Moreover, this indication has been approved by the recent referral procedure (EMA/H//A-29/687) for Ceftriaxone Tyrol 1 g and 2 g, powder for solution for injection or infusion. However, consensus could not be reached on inclusion of this indication. Therefore, it was deleted from the SPC.

In addition, the following newly proposed indications were considered:

- severe urinary infections (IV use)
- endocarditis (IV use)
- otitis media (after failure with other treatment) for IM use.

Urinary tract infections: Ceftriaxone is used in adults and paediatric patients with urinary tract infections (UTI). The studies described by the Applicant are supportive of the efficacy of ceftriaxone in patients with complicated UTI including acute and chronic pyelonephritis. This is also approved for the innovator product Rocephin in NL. The standard dosage would be 1g ceftriaxone daily for adults and 50 mg/kg/day for children. The indication is also in line with that approved in several EU countries.

Endocarditis: For Streptococcal endocarditis there is reasonable evidence in support of the use of ceftriaxone in adults with this condition. The experience in endocarditis due to HLAR *E. faecalis* and non-HLAR *E. faecalis* endocarditis is very limited. Furthermore, the situation is less clear for any paediatric patients (usually quite rare) and the dosage that might be needed.
The dosage recommendations of the Task Force on Infective Endocarditis of the European Society of Cardiology for streptococcal endocarditis can be considered for adoption in the SPC.

Acute otitis media (AOM): Overall, there is reasonable beneficial evidence in support of the use of ceftriaxone in children with adequately diagnosed OM of refractory or recurrent nature. Also the option to use a single shot of ceftriaxone in children with adequately diagnosed AOM in special cases (such as compromised ability to tolerate or absorb oral drugs, refusing or unable to take oral therapy) may also be considered acceptable.

It was concluded that, although within the context of this procedure additional indications would not be preferred, based on the review of the data and the MAH's response to the questions raised by member states, due consideration should be given to the addition of the three indications discussed above. These indications were discussed in the drafting group for antibacterials (19 January 2010).
The final wording of the indications as stated in the SPC was subject to the outcome of discussion between member states and an *ad hoc* drafting group for antibacterials within the context of a break out session of the CMD(h) for this procedure. Furthermore, it was agreed upon that the innovator ceftriaxone product Rocephin will be listed as candidate for harmonisation within an Art 30 procedure.

Clinical safety
Ceftriaxone is well tolerated and has good CNS and gastrointestinal tolerability when used for the treatment of severe bacterial infections in a wide range of adult and paediatric patient populations. The safety of ceftriaxone is well known and sufficiently documented in the innovator dossier for Rocephin, *i.e.* the safety of the innovator product can be extrapolated to the present products.

Risk management plan
Ceftriaxone was first approved in 1984, and there is now more than 10 years post-authorisation experience with the active substance. The safety profile of ceftriaxone can be considered to be well established and no product specific pharmacovigilance issues were identified pre- or post authorisation which are not adequately covered by the current SPC. Additional risk minimisation activities have not been identified for the reference medicinal product. The MAH has a pharmacovigilance system at their

disposal, which is based on the current European legislation. Routine pharmacovigilance activities are sufficient to identify actual or potential risks and a detailed European Risk Management Plan is not necessary for this product.

Product information

SPC
The MAH committed to adapt the SPC to the final text resulting from the article 30 referral that will be initiated for the innovator product.

Readability test
The package leaflet has not been evaluated via a user consultation study, but a bridging report was provided. The submitted PIL for Ceftriaxon Sandoz 0.25 g, 0.5 g, 1g powder for solution for injection was drafted in line with the “parent PIL” for procedure NL/H/423/001-003.
The “parent” PIL has been successfully user tested in September 2006 and has been assessed, literally amended in minor parts and approved during renewal. The current wording for the “daughter” PIL is completely in line with the current PIL for NL/H/423/001-003 and is therefore based on an already user tested leaflet. Readability has been sufficiently demonstrated.

III OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT

Ceftriaxon Sandoz 0.25 g, 0.5 g and 1 g, powder and solvent for solution for injection and Ceftriaxon Sandoz 1 g, powder and solvent for solution for injection or infusion have a proven chemical-pharmaceutical quality and are generic forms of Rocephin, powder for solution for injection 0.25 g, 0.5 g and 1 g. Rocephin is a well-known medicinal product with an established favourable efficacy and safety profile.

Since both the reference and current product are intended for parenteral use, no bioequivalence study is deemed necessary.

The MAH has provided written confirmation that systems and services are in place to ensure compliance with their pharmacovigilance obligations.

The SPC is consistent with that of the reference product. After a thorough discussion the indications and posology were agreed upon.

The Board followed the advice of the assessors.

A discussion on the indications was held in the drafting group for antibacterials. Agreement between member states was reached during the written procedure and this meeting. The member states, on the basis of the data submitted, considered that essential similarity has been demonstrated for Ceftriaxon Sandoz 0.25 g, 0.5 g and 1 g, powder and solvent for solution for injection and Ceftriaxon Sandoz 1 g, powder and solvent for solution for injection or infusion with the reference product, and have therefore granted a marketing authorisation. Furthermore, it was agreed upon that the innovator ceftriaxone product Rocephin will be listed as candidate for harmonisation in an Art 30 procedure.

The decentralised procedure was finished on 4 February 2010. Ceftriaxon Sandoz 0.25 g, 0.5 g and 1 g, powder and solvent for solution for injection and Ceftriaxon Sandoz 1 g, powder and solvent for solution for injection or infusion were authorised in the Netherlands on 22 October 2010.

A European harmonised birth date has been allocated (27 May 1982) and subsequently the first data lock point for ceftriaxone is February 2012. The first PSUR will cover the period from February 2010 to February 2012, after which the PSUR submission cycle is 3 years.

The date for the first renewal will be: 22 November 2012.

The following post-approval commitments have been made during the procedure:

<u>Quality - active substance</u>
- The MAH committed to perform annual stability monitoring on production-scale batches of ceftriaxone powder.

<u>Quality - lidocaine hydrochloride</u>
- The MAH committed to place one production batch of lidocaine drug substance each year on stability under long-term storage conditions.
- The MAH committed to place one commercial batch of lidocaine ampoules per year on stability according to protocol.

<u>Product information - SPC</u>
- The MAH committed to adapt the SPC to the final text resulting from the article 30 referral that will be initiated for the innovator product.

List of abbreviations

ASMF	Active Substance Master File
ATC	Anatomical Therapeutic Chemical classification
AUC	Area Under the Curve
BP	British Pharmacopoeia
CEP	Certificate of Suitability to the monographs of the European Pharmacopoeia
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
C_{max}	Maximum plasma concentration
CMD(h)	Coordination group for Mutual recognition and Decentralised procedure for human medicinal products
CV	Coefficient of Variation
EDMF	European Drug Master File
EDQM	European Directorate for the Quality of Medicines
EU	European Union
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GMP	Good Manufacturing Practice
ICH	International Conference of Harmonisation
IM	Intramuscular
IV	Intravenous
MAH	Marketing Authorisation Holder
MEB	Medicines Evaluation Board in the Netherlands
OTC	Over The Counter (to be supplied without prescription)
OM	Otitis Media
PAR	Public Assessment Report
Ph.Eur.	European Pharmacopoeia
PIL	Package Leaflet
PSUR	Periodic Safety Update Report
SD	Standard Deviation
SPC	Summary of Product Characteristics
$t_{½}$	Half-life
t_{max}	Time for maximum concentration
TSE	Transmissible Spongiform Encephalopathy
USP	Pharmacopoeia in the United States
UTI	Urinary Tract Infection

STEPS TAKEN AFTER THE FINALISATION OF THE INITIAL PROCEDURE - SUMMARY

Scope	Procedure number	Type of modification	Date of start of the procedure	Date of end of the procedure	Approval/ non approval	Assessment report attached
Change in test procedure for the finished product; minor changes to an approved test procedure.	NL/H/0423/ 004-007/IA/ 019	IA	17-7-2010	16-8-2010	Approval	N