EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines and Product Data Management

Committee for Medicinal Products for Veterinary Use

CVMP assessment report
Naxcel (EMEA/V/C/000079/II/012)

International Non-proprietary Name: Ceftiofur

Scope :
New indication: Acute post-partum (puerperal) metritis in cattle, in cases where treatment with another antimicrobial has failed

Assessment Report as adopted by the CVMP with all information of a commercially confidential nature deleted.

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Product information on the variation

Invented name	Naxcel
Active substances:	Ceftiofur
Pharmaceutical form:	Suspension for injection
Strength:	200 mg/ml
Packaging and Package size:	Cardboard box with 1 vial
Route of administration:	Subcutaneous use (base of ear)
Target species:	Cattle
Therapeutic indication:	Treatment of acute interdigital necrobacillosis also known as Panaritium or foot rot, in cattle (New:) Acute post-partum (puerperal) metritis in cattle, in cases where treatment with another antimicrobial has failed
ATCvet code	QJ01DD90 Third generation cephalosporin
Marketing Authorisation Holder (name and address):	Pfizer Limited Ramsgate Road Sandwich Kent CT13 9NJ United Kingdom

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1. Background information on the variation

1.1. Submission of the variation application

Pursuant to Article 16 of Commission Regulation (EC) No. 1234/2008, the Marketing Authorisation Holder, Pfizer Limited, submitted to the Agency on 5 August 2010 an application for a Type II variation for Naxcel. The variation was to add a new indication for cattle: treatment of acute post-partum (puerperal) metritis.

1.1.1 Documentation submitted

In accordance with the requirements laid down in Article 16 of Commission Regulation (EC) No. 1234/2008, the Marketing Authorisation Holder submitted the following documentation:

- Administrative data
- Attachment to the Expert Report (environmental safety, antimicrobial safety, pre-clinical and clinical expert report)
- A new clinical field study
- New preclinical studies
- References

1.1.2 Changes to the dossier held by the European Medicines Agency

This variation relates to the following part of the current dossier held by the Agency:

- Part 4 (efficacy)

1.2. Steps taken for the assessment of this variation

- The dossier was submitted on 4 August 2010, and the procedure started on 13 August 2010.
- The rapporteur and co-rapporteur circulated their assessment on 22 September 2010 and 1 October 2010, respectively.
- The CVMP adopted a list of questions during its meeting held in November 2010 and the clock stopped.
- The applicant circulated the responses to the CVMP list of questions on 10 January 2011, and the clock was restarted.
- The joint rapporteur and co-rapporteur assessment report on the responses to the consolidated list of questions was circulated to all CVMP Members on 8 February 2011.
- The CVMP adopted a list of outstanding issues during its meeting in March 2011.
- The applicant circulated the responses to the CVMP list of outstanding issues on 23 March 2011, and the rapporteurs circulated an amended assessment report on 28 March 2011.
- The CVMP adopted an opinion and CVMP assessment report on 5 May 2011.
- On 14 June 2011, the European Commission adopted a Commission Decision for this variation.

Scientific discussion

In cattle, Naxcel is currently authorised for the treatment of acute interdigital necrobacillosis (*Panaritium,* foot rot) at the dosage of a single subcutaneous injection of 6.6 mg ceftiofur per kg bw. The current application is to add a new indication for cattle (treatment of acute post-partum (puerperal) metritis) at the same dosage.

In order to demonstrate the safety and efficacy of the product in the proposed new indication, the Marketing Authorisation Holder provided a new environmental risk assessment, pre-clinical studies including an assessment in regard to the risk of development of resistance, as well as a new multi-centre field efficacy study. Reference was also made to some preclinical studies already assessed with previous application, and additionally, some bibliographical references were provided.

2. Safety

2.1 Environmental risk assessment (ERA)

A Phase I EIA was provided to assess the potential exposure from use of this product, and to show that the extent of environmental exposure to residues of ceftiofur or its relevant metabolites present in the excreta from treated animals will be insignificant.

For maximum manure application rates, it is assumed that nitrogen is the limiting factor and a value of 170 kg N/(ha x year) is used in the calculations. It is assumed that for metritis in cattle, 50% of the herd will be treated [19]. Additionally, it is assumed that the total dose is excreted as parent ceftiofur and no biodegradation of ceftiofur residues occurs in manures or soils. Manure would normally be ploughed into the soil (to a depth of ≥20 cm), but assessments for unploughed soil (soil depth of 5 cm, as for grassland or pastureland) have been included.

The worst-case PEC $soil_{\_initial}$ value for ceftiofur for intensively reared dairy cows was 10.6 µg/kg and for dairy cows on pasture is 9.2 µg/kg. Because these values are less than the Phase I trigger limit of 100 µg/kg, further assessment for intensively reared dairy cattle was not required.

The CVMP considered that the equations and parameters used by the applicant are in line with the revised guideline on environmental impact assessment for VMP in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282).

As estimates of the worst-case PEC$soil_{_initial}$ values were less than 100 µg/kg, the Phase I trigger limit, the CVMP agreed with the applicant's conclusions that further environmental risk assessment for was not required.

2.2 Microbiological properties of residues

See section 2.1.2 (resistance).

2.3 Withdrawal period

As the posology (dose and duration of treatment) for the proposed new indication is the same as the already approved one in cattle, the residue part of the dossier has already been assessed in previous applications. No changes or further data in regard to the residue part or the withdrawal period of the product were considered necessary.

3. Efficacy

3.1 Preclinical Studies

The mechanism of action of ceftiofur, mechanisms of resistance, cross-resistance and co-resistance, the antimicrobial spectrum of activity (except against new target pathogen), pharmacokinetic data and additional information (mutation frequency, antimicrobial drug activity in the intestinal tract, degradation of ceftiofur after excretion) were previously assessed in the extension application of Naxcel 200 Suspension for Injection for Cattle. Also, the dose regimen proposed for the treatment of the new indication is the same as the one of the previous indication.

The proposed new indication, puerperal metritis, is a mixed infection, most frequently caused by *Arcanobacterium (Actinomyces) pyogenes* in association with gram-negative bacteria such as *Fusobacterium necrophorum* or *Escherichia coli.*

3.1.1 Pharmacodynamics

The applicant provided the results from a Minimum Inhibitory Concentration (MIC) determination study determining the *in vitro* activity of ceftiofur against *A. pyogenes, F. necrophorum* and *E. coli* isolated in 2009 during a clinical study conducted in several EU Member States from dairy cattle with acute puerperal metritis. The CVMP concluded that the pharmacodynamics of ceftiofur in support of the new claim were fully documented. MIC values of ceftiofur against the new target pathogens are listed below.

	No of strains	Range (µg/ml)	MIC_{50} (µg/ml)	MIC_{90} (µg/ml)
A. pyogenes	50	0.25 – 1.00	0.50	1.00
E. coli	52	0.12 – > 128	0.50	0.50
F. necrophorum	48	≤ 0.002 – 2.00	≤ 0.002	0.12

3.1.2 Development of resistance

Target pathogens

A comprehensive assessment of the potential for development of resistance resulting from the use of Naxcel 200 Suspension for Injection for Cattle for the treatment of metritis in cattle was provided according to VICH guideline 27.

Antimicrobial resistance levels are difficult to determine for metritis target pathogens due to the nature of the infection and the lack of interpretive criteria (breakpoints) for ceftiofur against pathogens involved in the development of bovine metritis, i.e. *Escherichia coli, Arcanobacterium pyogenes* and *Fusobacterium necrophorum.* In addition*, a* recent publication (Santos, Gilbert *et al., 2011)* confirms that uterine microbiota are very diverse and that it is difficult to define specific pathogens. Although resistance surveillance data are not available for specific metritis pathogens, the applicant provided a listing of data from various studies undertaken in Europe and Japan (1995-2009) for the target pathogens isolated from bovine non-enteric tissues sources over the past ten years.

In general, MICs for ceftiofur are low and indicate little resistance for *E. coli, A. pyogenes* or *F. necrophorum*, with MIC_{90} for ceftiofur against these three organisms ranging from 0.125 to 1.0 µg/ml. Less than 5% of the *E. coli* and less than 7% of the *F. necrophorum* have ceftiofur MIC values of 8 µg/ml or above. The results of recent studies show that ceftiofur remains active against bacterial

pathogens associated with bovine metritis with no shift in MIC patterns for *A. pyogenes, E. coli*, or *F. necrophorum*.

Commensals

MIC epidemiological cut-off values for ceftiofur used by the European Food Safety Agency (EFSA) for surveillance of *Salmonella* and *Escherichia coli* from animals and foods are above 2 µg/ml and 1 µg/ml, respectively.

Prevalence rates of cephalosporin-resistant *Salmonella* and *Escherichia coli* isolated from cattle in the European Union remain low, according to the applicant, but the CVMP was concerned by the increased occurrence of bacterial strains producing extended-spectrum beta-lactamases (ESBL) and/or acquired AmpC β-lactamases. An important part of the selection pressure would appear to take place via the gastrointestinal tract before the active substance is inactivated. A risk of emergence of ESBL/AmpC in *E. coli* is identified with the use of products containing cephalosporins, especially those of 3rd and 4th generation.

Impact of resistance

The CVMP considered that overall the impact of the use of the product in the new indication on the potential risk for development of antimicrobial resistance, both for pathogens and commensal flora, was sufficiently documented. Some of the assessment was already performed, namely for commensals, during the initial cattle product extension procedure.

The applicant stated that "the use of formularies that preferentially select penicillins or narrow-spectrum cephalosporins may not minimize emergence and dissemination of ESBL-containing bacteria already present in the population, as these can also exert selection pressure." The CVMP considered this statement by the applicant as correct; however, Naxcel contains a third generation cephalosporin, which can select for resistance, but whose relative selection pressure has not been compared directly with the mentioned antimicrobials.

The CVMP, therefore, considered it appropriate to restrict the indications of use, i.e. Naxcel should only be used where first line treatments have failed in the treatment of acute puerperal metritis. The intention of this "restricted" claim is that Naxcel is used only when strictly required and not in a generalised manner, as this would be against the CVMP current considerations on third and fourth generation cephalosporins.

3.1.3 Pharmacokinetics

Three kinetic studies were provided; however, only one was fully documented and performed with the final formulation of the product.

A GLP compliant pharmacokinetic study conducted in 2008 investigating plasmakinetics of not only ceftiofur but also of related desfuroylceftiofur metabolites such as desfuroylceftiofur acetamide (DCA, marker residue) in cattle following intravenous or subcutaneous injection of Ceftiofur, had already been assessed in the initial application for use in cattle. The observed mean total plasma concentrations were maintained above 1 µg/ml at 56, 96 and 144 hours following ceftiofur crystalline free acid subcutaneous injection at 3.3, 6.6 and 13.2 mg/kg bw, respectively.

A second study (2005) compared the uterine (endometrium, lochial fluid, caruncle) and interdigital tissue concentrations of ceftiofur-equivalent residues at 1, 3 and 5 days following a single subcutaneous injection of ceftiofur crystalline free acid (CCFA) at doses of 6.6 or 11 mg/kg bw in the base of the ear versus daily (up to five total) subcutaneous injections of Ceftiofur hydrochloride at 1.1

or 2.2 mg/kg bw in the neck. Plasma DCA-concentrations were determined as well. The time during which DCA-plasma concentrations after administration of CCFA at 6.6 mg/kg bw remain at least 0.5 µg/ml or above 1 µg/ml is 4.5-5 days and 2- 4 days, respectively. However, the data from this study should be considered with care since the sampling intervals were rather long, and the number of animals with data for the whole 5 day period was low (only 4 animals per treatment group).

A third study (2000) only investigated ceftiofur hydrochloride, and also showed some deficiencies, and was therefore not considered in the assessment of this application.

3.1.4 Dose justification and analysis of harmacokinetics/pharmacodynamic (PK/PD)

The plasma kinetics of DCA following subcutaneous injection of 6.6 mg/kg bw of CCFA at the base of the ear showed that the formulation provided for sustained release of ceftiofur above the pharmacodynamic threshold of 1.0 µg/ml (i.e. the highest MIC_{90} of the new target pathogens). Mean plasma DCA-concentrations above this value are observed during 4 days following the injection. The PK/PD approach was considered not fully robust, as it used not only free fraction of ceftiofur but also desfuroylceftiofur related metabolites.

The CVMP nevertheless considered that the proposed dose of 6.6 mg/kg was sufficiently justified for the treatment of acute puerperal metritis as clinical data also showed a high cure rate (comparable to the positive control group). This reasoning was already used for the assessment of dose selection for the initial interdigital necrobacillosis claim.

Conclusions

The pharmacodynamics of ceftiofur have been fully documented. MIC values of ceftiofur against *Escherichia coli, Arcanobacterium pyogenes* and *Fusobacterium necrophorum* recently isolated from dairy cattle with acute puerperal metritis in Europe was provided.

The risk for spread of resistance to ceftiofur was sufficiently documented. A comprehensive assessment of the potential for development of resistance resulting from the use of Naxcel 200 Suspension for Injection for Cattle for the treatment of metritis in cattle was provided according to the VICH guideline 27. As there was a certain risk identified related to emergence and spread of ESBL, the CVMP considered it appropriate to restrict the indications of use, i.e. Naxcel should only be used where first line treatments have failed in the treatment of acute puerperal metritis.

3.2 Field studies

The applicant provided a well conducted new multicentre, randomised, blinded GCP compliant field study conducted in several European countries (France, Germany and Italy) in 2009. The study involved a large number of cows of various breeds (88% Holstein/Friesian breed) in the early post-partum phase with acute puerperal metritis (naturally acquired infection).

Inclusion criteria were cows in early post-partum ($\leq$ 14 days) with rectal temperatures of at least 39.5°C and a vaginal discharge score of 2 (i.e. fetid, thin, serous or watery, purulent or mucopurulent, with or without necrotic tissue). Exclusion criteria at enrolment were treatment with antimicrobials, anti-inflammatory, estrogenic or prostaglandin agent since calving, treatment with antimicrobials during the 14 days prior to parturition, fetotomy, caesarian section delivery or uterine prolapse at calving, and concomitant disease. It is noted that there was no information whether or not treatment of the cows with a 3rd generation cephalosporin was justified in terms of a second line treatment.

Cows were either treated subcutaneously with one single dose of 6.6 mg/kg bw of Naxcel (ceftiofur crystaline free acid) or with a single dose of 1 mg/kg bw of ceftiofur hydrochloride over 5 days (positive control). The comparator (ceftiofur hydrochloride) is authorised for this indication in 12 Member States and was considered suitable as positive control product. Cows were observed for clinical signs, and uterine swabs were collected from all cows enrolled in the study. Pre-treatment micro-flora analysis confirmed the presence of pathogens typical for acute puerperal metritis (mainly *Escherichia coli, Arcanobacterium pyogenes, Streptococcus uberis,* or *Fusobacterium necrophorum).*

Efficacy

The primary decision parameter was the clinical cure rate at D14. Efficacy of treatment was analysed for non-inferiority (15% margin) to the positive comparator using a general linear mixed model. Cure rate with Naxcel (87.44%) was not inferior to that achieved with the comparator (86.35%).

The CVMP considered that clinical diagnosis took into account clinical parameters which are typical for acute puerperal metritis and that analysis of study results was comprehensive. As the efficacy of Naxcel under European field conditions was not inferior to the efficacy of the reference product at D14 in the well conducted field study, the CVMP concluded that a single subcutaneous administration of Naxcel at the dose of 6.6 mg/kg bw is effective in the treatment of acute post-partum metritis in dairy cows.

Tolerance

As the dose for the new indication of Naxcel is the same as that already approved in the treatment of interdigital necrobacillosis, no additional tolerance data were provided. Three adverse events related to treatment in the new clinical study were reported in both treatment groups (Naxcel and comparator), with swelling at the injection site (base of the ear, side of the neck).

From the results of the new clinical study, as well as from pharmacovigilance reports observed until now for cattle, it is expected that the tolerance profile of the product will remain unchanged.

4. Benefit-risk assessment

4.1 Benefit assessment

Naxcel 200 mg/ml is a long-acting formulation containing ceftiofur. It has the advantage, in the indication for the treatment of metritis, that a single injection is sufficient to treat the disease. This represents an advantage in terms of compliance.

In terms of field data, the data from a multicentre trial show clearly that for cure rate at Day 14 non-inferiority (at 15% margin) has been established between test and control product, confirming efficacy of the product for the proposed new indication.

4.2 Risk assessment

As the dose is the same as already authorised for cattle, tolerance in the target species is expected to be the same, and the same withdrawal periods can be applied. An ERA has been presented and indicates that the assessment can stop at phase I of the decision tree.

The pharmacodynamics section has been adequately referenced, indicating by recent data, that the MIC_{90} for the relevant pathogens are low (up to 1 µg/ml).

A thorough risk assessment has been provided by the applicant on antimicrobial resistance. The emergence of ESBL/AmpC in *E. coli* should be considered as a particular risk for extended spectrum beta-lactam antibiotics like Naxcel.

The ease of administration when compared to current treatments (that necessitate more than one injection) in conjunction with the zero day milk withdrawal period, show an advantage for the user, and the CVMP expressed some concern that this might result in a potential for increase of use of this third generation cephalosporin. In line with current CVMP recommendations, third generation cephalosporin should not be used as a first-line treatment.

Naxcel has not been specifically investigated in cases that have responded poorly to first line treatments of acute puerperal metritis, and there remains a risk of lack of efficacy in such cases. However, conduct of such studies was not specifically requested.

4.3 Risk management or mitigation measures

In view of concerns in regard to the risk related to emergence and spread of ESBL, the indications were restricted, i.e. Naxcel should only be used where first line treatments have failed in the treatment of acute puerperal metritis. No other new risk mitigation measures / warnings were considered necessary for the current application.

4.4 Evaluation of the benefit risk balance

The CVMP considers the safety and efficacy of the product for the treatment of metritis in dairy cows at the proposed dose to be satisfactorily addressed.

However, in line with current CVMP antimicrobial strategy, the Committee considered it appropriate to restrict the indications of use to "treatment of acute puerperal metritis only where first line treatments have failed".

5. Conclusion

The CVMP considers that this variation, accompanied by the submitted documentation demonstrates that the conditions laid down in Commission Regulation (EC) No. 1234/2008 for the requested variation are met.

The variation requires changes in the SPC and product literature are required.