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EMA/CVMP/115706/2010
Veterinary Medicines and Product Data Management

Withdrawal assessment report

Naxcel 200 mg/ml suspension for injection for horses

International Non-proprietary Name: Ceftiofur

(EMEA/V/C/079/X/008)

Extension (new target species)
Withdrawal at Day 120

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1 - Summary of the Dossier

On 5 May 2009, Pfizer Limited submitted an application for an extension of the Community marketing authorisation for Naxcel for a new target species, horses (200 mg/ml suspension for injection for horses), in accordance with Article 2(a) of Commission Regulation (EC) No 1085/2003 and Annex II.

Naxcel 200 mg/ml suspension for injection for horses used the same formulation and presentation as for Naxcel 200 mg/ml suspension for injection for cattle and was presented in 100 ml glass vials. The proposed indication was for the treatment of respiratory tract infections in horses associated with *Streptococcus equi* subsp. *zooepidemicus* and other relevant susceptible bacterial pathogens. The proposed route of administration was intramuscular use.

Since this application concerned the extension to an already authorised veterinary medicinal product, cross-reference was made to relevant sections of dossier(s) already submitted and assessed by the CVMP, which was acceptable.

The CVMP on the basis of quality, safety and efficacy data submitted, considered that the application was not approvable at Day 120 since major objections had been identified, which precluded a recommendation for marketing authorisation. The concerns were mainly in relation to the efficacy at the suggested dose level but tolerance was also an issue to be taken into consideration in the benefit-risk assessment.

On 4 February 2010, Pfizer Limited withdrew the application at Day 120 of the procedure.

Part 2 - Quality

The composition, manufacture and other pharmaceutical details of the finished product Naxcel 200 mg/ml suspension for injection for horses is the same as the finished product for cattle (200 mg/ml) and cross-reference has been made to the cattle dossier (please see the Naxcel EPAR for further information). However, further information was considered necessary in relation to the product development regarding the two administrations proposed for the horse application (as compared to the single administration in cattle).

Part 2 - Safety

The composition of the finished product Naxcel 200 mg/ml suspension for injection for horses is the same as the finished product for cattle (200 mg/ml) and cross-reference has been made to the cattle dossier for the safety part of the application (please see the Naxcel EPAR for further information).

Most of safety studies were already submitted in the original MRL dossier and in the original Naxcel application and thus have already been assessed by the CVMP. The MRL summary report (as approved by the CVMP) is applicable equally to the sodium salt, the hydrochloride salt and the crystalline free acid form of ceftiofur (CCFA). Indeed, once ceftiofur is administered to the animal, regardless if it is the sodium salt, the hydrochloride salt or the free acid, it dissociates into the ceftiofur anion and the positive charged counterion.

User safety

The most likely route of exposure is the skin. Moreover, accidential injection by the user and spillage into eyes should also be considered as a potential route of exposure.

The risk encountered from a single accidental self-injection is considered acceptable while repeated injections may present some risk to sensitive individuals. Irritation of abraded skin and mild delayed-type dermal sensitisation may occur in the user when the product is (repeatedly) spilled onto the (abraded) skin. Results of the eye irritation tests submitted indicated that 100 mg of ceftiofur is minimally irritating to rabbit eyes.

The following precautions to be taken by the person administering Naxcel 200 mg/ml for horses should therefore be included in the SPC and product literature :

- "Penicillins and cephalosporins may cause hypersensitivity following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may lead to cross reactions to cephalosporins and vice versa. Allergic reactions to these substances may occasionally be serious.
- Do not handle this product if you know you are hypersensitive.
- Avoid contact with skin and eyes. In the event of contact, wash with clean water. If you develop symptoms following exposure such as skin rash or persistent eye irritation, you should seek medical advice. Swelling of the face, lips or eyes or difficulties with breathing are more serious symptoms and require urgent medical attention."

Environmental risk assessment

In line with VICH Topic GL6 (Ecotoxicity Phase I - Guideline on Environmental Impact Assessment (EIAS) for Veterinary Medicinal Product – Phase I), a PEC_{soil} should be estimated. Different values should be used in order to follow a worst-case scenario.

Estimates of the worst-case PEC_{soil} values for intensively reared horses or horses on pasture were less than 100 µg/kg, the phase I trigger limit. Therefore, no further assessment for Naxcel was considered to be necessary, and a phase II assessment was not needed for Naxcel 200 mg/ml suspension for injection for horses.

The environmental exposure of to ceftiofur from the use of Naxcel was considered to be negligible.

Overall conclusions on the safety documentation

For the toxicity tests, the conclusions as outlined in the MRL summary report apply.

The user safety assessment was correctly performed accordingly to the current guideline. No important risk was identified and the warnings proposed in the product literature were considered sufficient.

For the environmental risk, the applicant performed a phase I assessment which shows that the PEC soil value was below the trigger point of 100 µg/kg. A phase II assessment was not needed.

Residues documentation

Identification of the product concerned

The active substance of Naxcel 200 mg/ml suspension for injection for horses is ceftiofur crystalline free acid (CCFA). This product is indicated for horses. The recommended posology is two intramuscular injections of 6.6 mg of ceftiofur/kg bw administered 4 days apart. The injection volume is limited to a maximum of 20 ml per site of injection.

Residue studies

Depletion of residues

A depletion study was provided following administration in horses of the final formulation at the recommended dose. This depletion study was performed following two intramuscular administrations 4 days apart, at a dose slightly above the recommended dose: 6.89 and 6.83 mg/kg *versus* 6.6 mg/kg bw, on the neck. The product used in this study was the final formulation with a mean *in vitro* release rate of 73 to 78%. All edible tissues were sampled. The mean volumes of injection was 17 ml (12.93 to 21.48 ml).

In kidney and liver samples, the marker residue levels were below the specific MRL value from the first sampling time i.e. 2 days. In fat and muscle samples, the marker residue levels were below the specific MRL value from the second sampling time, i.e. 25 days. In core and surrounding injection site samples, the marker residue levels were below the muscle MRL value from 225 days. In some samples, the marker residue levels measured in core were below the levels measured in surroundings of the injection site.

MRLs

All constituents of the intended product are included in table 1 of the annex to Commission Regulation (EU) No 37/2010 or are considered as not falling within the scope of the Regulation.

Withdrawal periods

Meat & offal

From the residues levels observed in kidney, liver, fat and muscle, the statistical approach could not be used to determine the withdrawal period because there are only one or two sampling times with residue levels above LOQ values. From the residues levels observed in the injection sites, it was possible to determine the withdrawal period by the statistical approach.

The applicant proposed a withdrawal period of 219 days.

According to the CVMP guideline on injection sites residues (EMEA/CVMP/542/03), in case of multiple injection sites, sampling should include the site of the last injection. The results from both the analysis of core and surrounding injection site samples should be considered. If for an animal the residues concentrations for the surrounding samples are higher than the core samples, unless an acceptable justification is provided, the point should not be included in the statistical calculations.

Therefore, the CVMP concluded that a satisfactory "meat & offal" withdrawal period should be 256 days calculated from residues observed in the core of the last injection site. However, the practicability of such a long withdrawal period was questioned.

Milk

No data were provided for equine milk. Therefore, the product should not be used in horses from which milk is produced for human consumption. Appropriate warnings should be added to the SPC and product literature.

Analytical methods

The analytical method used in the depletion study to assay ceftiofur marker residue in equine edible tissues was satisfactory validated.

Overall conclusions on the residues documentation

A GLP tissue depletion study was performed in horses following two intramuscular administrations 4 days apart, of ceftiofur crystalline free acid at a dose slightly above the recommended dose: 6.89 and 6.83 mg/kg versus 6.6 mg /kg bw, in the neck. This study was performed according to the CVMP guideline "approach towards harmonization of withdrawal periods" (EMEA/CVMP/036/95).

The analytical method to assay ceftiofur marker residue in equine edible tissues was satisfactorily validated. The withdrawal period for "meat and offal" was based on depletion of residues from the injection sites.

Based on the data provided, the CVMP concluded on a withdrawal period of 256 days for meat & offal. In the absence of data for milk, the product is not to be used in horses from which milk is produced for human consumption. According to the body weight of horses used in the depletion study, the recommended maximum volume of injection would be 13 ml.

Part 4 – Efficacy

Pharmacodynamics

Ceftiofur is a 3rd generation cephalosporin. Ceftiofur disrupts bacterial synthesis of the peptidoglycan cell wall by targeting the penicillin-binding proteins (PBP).

The pharmacodynamic data provided by the applicant were considered satisfactory. MIC values of ceftiofur against the target pathogen associated with equine respiratory disease and recently isolated in Europe were provided. CLSI breakpoint for ceftiofur against *Streptococcus equi* subsp. *zooepidemicus* is ≤ 0.25 µg/ml for susceptible strains.

The MIC_{90} generally observed was 0.12 µg/ml in studies from the applicant. However it was reported to be of 0.25 µg/ml in the German monitoring programme for resistance of veterinary medicinal pathogens. A MIC_{90} equal to 0.25 µg/ml for *Streptococcus equi* subsp. *zooepidemicus* was also obtained in a recently completed AFSSA study.

The kinetics of bacterial killing of ceftiofur against target pathogens was characterised. A bactericidal effect is achieved for ceftiofur against *Streptococcus equi* subsp. *zooepidemicus* for concentrations equivalent to or twice the MIC_{90} proposed by the applicant of 0,12 µg/ml.

Pharmacokinetics

Only the kinetic studies performed in horses following the intramuscular administration of Naxcel 200 mg/ml suspension for injection for horses at 6.6 mg ceftiofur/kg bw are assessed. Two GLP compliant studies were performed:

- Determination of bioavailability of ceftiofur following a single intramuscular injection of Naxcel for horses at 6.6 mg ceftiofur/kg bw;
- Assessment of the linearity of the kinetics parameters (C_{max} and AUC) with the dose following two intramuscular injections of 6.6, 3.3 and 13.2 mg ceftiofur/kg bw 4 days apart.

From these GLP studies, the plasma kinetics of ceftiofur in horses were characterised as follows:

- A full and complete absorption (bioavailability close to 100%),
- C_{max} of approximately 0.8 µg/ml was observed 24 hours after the 1st injection, and C_{max} of 1.0 µg/ml was observed approximately 12 hours after the 2nd injection, 96 h apart,
- An elimination according to a flip-flop effect (terminal half-life close to 4 days),
- The kinetic parameters AUC and C_{max} increased with the dose,
- The plasma concentrations above 0.2 µg/ml of ceftiofur and its active metabolite are maintained during for at least 10 days following two intramuscular injections of the final formulation at 6.6 mg ceftiofur/kg bw administered four days apart.

Development of resistance

The potential for resistance development resulting from the use of Naxcel 200 mg/ml suspension for injection for horses for the treatment of respiratory disease in horses, was reviewed by the applicant based on several published papers, studies, CVMP reflection papers in target, commensal and food-borne pathogens.

However, the CVMP did not fully agree with the applicant who claimed similarity of kinetics of ceftiofur as ceftiofur sodium and ceftiofur crystalline free acid following intramuscular injection. Although metabolism and distribution are similar, absorption and elimination phases are not. Ceftiofur crystalline free acid exhibited sustained release properties. The T_{max}, terminal elimination half-life, and AUC are totally different. While it is noted that these differences were not considered to lead to a major risk in terms of resistance when used in pigs or cattle, the dose of Naxcel 200 mg/ml suspension for injection for horses in this indication and target species is doubled when compared to the dose in cattle. The pharmacokinetic studies and residue depletion study also demonstrate that the commensal organisms are exposed to ceftiofur during an extended period following the treatment.

The applicant was therefore asked to further demonstrate that the expected increase in the selection for resistance to ceftiofur in target pathogen, commensal flora and food-borne pathogens can still be considered as acceptable, with regards to animal safety and public health. Also, the CVMP recommendations outlined in the CVMP reflection paper on the "use of 3rd and 4th generation Cephalosporins in food-producing animals in the European Union." (EMEA/CVMP/SAGAM/81730/2006-Rev.1) should be added in the section 4.5 of the SPC.

Dose determination / justification

PK/PD analysis

According to the mode of action of ceftiofur, principally time dependant, the time where the plasma concentration of ceftiofur crystalline free acid are above the MIC_{90} of ceftiofur against target pathogens, should be equal to 50-80% of the interval of administration.

A nonlinear mixed effect pharmacokinetic model was developed for plasma ceftiofur equivalent concentrations in horses following two intramuscular injections of ceftiofur crystalline free acid at 6.6 mg/kg bw, 96 hours apart. From this model, more than 85 and 97.5% of horses were predicted to have plasma ceftiofur equivalent concentrations of at least 0.2 µg/ml for 96 hours after the first and the second injections, respectively.

This prediction from the nonlinear mixed effect pharmacokinetic model is confirmed by the values of the parameter "T" (Time when plasma concentrations of ceftiofur crystalline free acid are above 0.2 µg/ml), calculated in the various plasma kinetic studies. Plasma concentrations above 0.2 µg/ml of ceftiofur and its active metabolite are maintained during for at least 10 days following two intramuscular injections of 6.6 mg ceftiofur/kg bw, administered four days apart.

However, the MIC_{90} for ceftiofur against the target pathogen *Streptococcus equi* subsp. *zooepidemicus* of 0.12 µg/ml determined by the applicant was not accepted as standard in view of the much higher MIC_{90} of 0.25 µg/ml derived from the German GermVet programme. The threshold of [T>0.2 µg/ml] is thus considered inappropriate for PK/PD-analysis of ceftiofur in horses when taking the MIC_{90} of 0.25 µg/ml into account. This is further emphasised by the fact that no information on protein binding of ceftiofur in horse plasma was available in the dossier. In other species, the protein binding is substantial (70-90%). Assuming 70% protein binding, a total plasma concentration of 0.8 mg/l would be needed to achieve 0.25 mg/l of free drug.

This substantially affects the discussions on time above or below MIC, and the CVMP expressed concern that the concentrations achieved with the current dosing might be suboptimal. The applicant was therefore asked to further justify several assumptions and to take into account additional data in the PK/PD analysis supporting the dose determination. In light of the new results, the optimal dose and interval of administration was required to be further discussed.

Target animal tolerance

Two pivotal target animal safety studies were presented in support of the present application.

- In a **pharmacokinetic study**, reactions at the injection site were also investigated. The product proposed for marketing was administered intramuscularly at 0.5 x, 1 x and 2 x the proposed recommended treatment dose to adult horses. For animals in the target dose group (6.6 mg/kg bw), the dose volumes administered at a single site were close to the maximum recommended dose volume of 20ml (ranged from 15 to 20 ml, approximately).
- In an overdose study, the local and systemic safety of the test product when administered intramuscularly to adult horses on six occasions (3x maximum proposed duration) at 6.6, 13.2 or 19.8 mg ceftiofur equivalents /kg bw (1x, 2x or 3x proposed dose) was monitored.

Based on the findings of both studies, it is accepted that the test item was well tolerated systemically; however, administration of the product at a dose of 6.6 mg/kg bw can result in reactions at the injection site. Swelling at the injection site following administration of the recommended treatment dose was common. Injection site swelling reduced rapidly and typically resolved within 4-7 days after

treatment; however, small swelling may persist for prolonged periods. In addition to swelling, reactions may be characterised by firmness and sensitivity/pain.

In the overdose study, injection site lesions recorded in animals that were administered 2 and 3 times the recommended therapeutic dose (RTD) tended to be more severe than those recorded at the RTD, on occasion resulting in reduced neck movement and altered demeanour (due to neck pain). It is noted that for one animal in the 2x RTD group, injection site reaction was recorded as extreme swelling and extreme pain on palpation. Also, this animal was noted to be depressed. While it is accepted that this animal was administered a dose of 13.2 mg/kg, it is noted, based on the protocol, that the maximum volume for administration at a single site is 20 ml. Therefore, it can be assumed that severe injection site reactions may occur when the product is used as recommended.

In addition to the specific target animal safety studies, the applicant provided US pharmacovigilance data relating to other ceftiofur containing products (ceftiofur sodium and ceftiofur hydrochloride) authorised in that region. While the absolute number of reported adverse reactions in horses is low, it is not possible to calculate an incidence figure because no sales data have been provided. Gastrointestinal and anaphylactic reactions were the most common adverse reactions reported. The proposed SPC includes statements indicating that use of antimicrobials in horses under stress may result in diarrhoea which could be fatal. Based on the information provided by the applicant, the proposed statement appears to be appropriate. The SPC also includes a statement contraindicating use in horses with known sensitivity to ceftiofur or other beta-lactam antibiotics. While anaphylactic reaction was not recorded in any of the ceftiofur crystalline free acid-specific studies presented in support of the present application, there are rare reports of such reaction following administration of ceftiofur (as evidenced by the US Pharmacovigilance data presented). Further, all cephalosporins have the potential to cause unpredictable anaphylactic reactions. In view of the above, consideration should be given to including a clear statement advising of the potential for analphylactic reactions following product administration.

The applicant was also requested to further document the rate of anaphylactic reactions associated with ceftiofur based on the pharmacovigilance data of its first ceftiofur formulation marketed in the EU.

The number of adverse reactions reported from the field studies was low. Based on these data, there is no suggestion of systemic intolerance. The main treatment related adverse effects relate to injection site reaction, which was recorded for 4% of horses that were administered the test product. The difference in incidence of recorded injection site reactions between the field studies and the pivotal target animal safety studies may be related to the volume of product administered at any single site, the site of administration (neck muscle v pectoral muscle) and the thoroughness of injection site examination.

Limited target animal safety data have been provided in relation to foals. The pivotal target animal safety studies were conducted using adult horses. While foals were included in the field studies, very few were aged less than 6 months. Therefore, information was considered insufficient regarding the safety of the product in foals.

Potential effects of the long elimination phase of ceftiofur crystalline free acid in regard to the risk for antibiotic associated diarrhoea (AAD) have not been clarified. When signs of AAD occur, it is important to immediately discontinue the use of the antimicrobial. The long elimination phase of the this ceftiofur crystalline free acid formulation is problematic in that respect, as active concentrations of the drug may remain in the system for many days after the decision to discontinue the treatment.

Dose confirmation

No dose confirmation studies specific to this indication and target species have been provided.

Field trials

Two field efficacy studies (GCP compliant) were presented in support of the present application. The dose selected for the field studies is based on pharmacokinetic analysis and was not arrived at by conventional dose determination studies.

In the European field study, no analysis was conducted on efficacy for the treatment of equine acute respiratory disease associated with specific bacteria. The results were presented as an overall cure rate. However, based on the findings of the US study**,** there would appear to be a clear treatment effect relative to placebo for 'clinical cure rate' for horses diagnosed with moderate to severe *Streptococcus equi subsp. zooepidemicus*.

Given that there are no clinical data confirming efficacy of the proposed treatment regimen for respiratory disease associated with other pathogens, the CVMP did not accept a claim for "other susceptible bacterial pathogens" as proposed by the applicant. Deleting "other susceptible bacterial pathogens" leaves a proposed claim for the treatment of respiratory tract infections in horses associated with *Streptococcus equi* subsp. *zooepidemicus*.

However, the CVMP questioned the appropriateness of authorising a veterinary medicinal product containing ceftiofur with such a narrow indication that is reported as uniformly susceptible to penicillins. The Committee considered it likely that this product would be used as a first line therapy in horses with clinical signs of acute respiratory disease, resulting in the treatment of a large proportion of horses, that are affected by bacterial pathogens for which efficacy has not been proven or against which the product may be ineffective. This is evidenced by the moderate clinical cure rates achieved in both field studies and the relatively high relapse rate that occurred in the EU field study.

The **European Field Study** was conducted at multiple sites across four EU Member States (the majority of test animals were enrolled in France). Ceftiofur sodium was used as a positive control. The animals selected for the study were presented with clinical signs of respiratory tract infection. The main target pathogen (*Streptococcus equi subsp. zooepidemicus*) was confirmed in approximately half of the enrolled cases. Only two thirds of enrolled animals were included in the efficacy calculations. Notwithstanding the low numbers recruited, the statistical analysis conducted indicate that ceftiofur crystalline free acid when administered on two occasions 96 hours apart can be considered non-inferior to ceftiofur sodium administered by intramuscular injection once daily for 10 days for the primary efficacy parameter 'clinical cure'.

However, based on the parameters selected, the clinical cure rates were only 62.8% and 50% for the test and control products, respectively. Based on sample size calculations detailed in the protocol, a cure rate of 80% was anticipated. In addition, the relapse rates recorded for both groups were 38.1% and 44.5%, respectively. Supplementary analysis conducted by the CVMP indicated that non-inferiority of the test product to the reference product is thus not proven for this secondary parameter.

The applicant was requested to provide a new field study, to substantiate the proposed claim which would give consideration to other potential respiratory pathogens.

The **US Field study** was a placebo controlled study conducted at multiple sites in North America. Given that the study was conducted outside the EU, the study is considered supportive only.

However, based on the findings for the overall rate of withdrawal and the 'clinical cure rate' for horses diagnosed with moderate to severe *Streptococcus equi subsp. zooepidemicus*, there would appear to be a clear treatment effect: on study day 25, clinical cure for animals assigned to the treatment group was 63.4% compared to 32.8% for placebo treated horses. However, the clinical cure rate achieved for this specific pathogen in the treated group appears to be disappointing when viewed against an anticipated 80% cure rate (detailed in the protocol of the EU study). Also, a large number of horses

were withdrawn from the study. Of those horses that did not complete the study, 10 died or were euthanized. The applicant was asked to comment on the significance of the number of pneumonia–related deaths in the treated group versus the lower number in the placebo group.

Overall conclusion on efficacy

Based on the preclinical and clinical studies submitted in support of this application, the claimed efficacy of Naxcel 200 mg/ml suspension for injection for horses in the proposed indication in horses is at present not considered as sufficiently substantiated to outweigh the potential risks, i.e. antimicrobial resistance and risks for adverse effects (swellings, diarrhoea, anaphylaxis).

Part 5 – Benefit risk assessment

Benefit assessment

Direct therapeutic benefit

Naxcel 200 mg/ml suspension for injection for horses contains ceftiofur. Its use and activity as a third-generation cephalosporin is well known. The mode of action is typical of a late generation beta-lactam-type antibiotic with activity against a large number of Gram-negative and Gram-positive pathogens.

The product is intended for use in the treatment of respiratory tract infections in horses associated with *Streptococcus equi subsp. zooepidemicus* or other susceptible bacterial pathogens, which is a serious disease causing delay in growth, interruption of use and possibly death.

Given the efficacy was proven, the direct benefits to the animal would include recovery from a serious and possibly life-endangering disease. Systemic antibiotic treatment is normal practice for treatment of such conditions in horses.

Beyond the direct benefits to the animal, if treated early, this disease is not debilitating and horses will be able to go back to their normal use. It is therefore expected that the active life expectancy of effectively treated horses is increased.

However, at present efficacy and, therefore, the benefit of treatment with Naxcel 200 mg/ml suspension for injection for horses has not been proven.

Additional benefits

Provided that Naxcel 200 mg/ml suspension for injection for horses is proven effective for the treatment of respiratory tract infections in horses associated with *Streptococcus equi subsp. zooepidemicus* and other susceptible bacteria, only two administrations would be necessary.

Currently, ceftiofur is administered for 10 days at 2.2 mg/kg for treatment of respiratory tract infections in horses associated with *Streptococcus equi subsp. zooepidemicus*. Reduction in animal handling and increased compliance are expected to provide an additional advantage to the treatment by this veterinary medicinal product.

However, as there are major questions on maximum injection site volume, the issue of reduced animal handling may not fully outweight the lack of tolerance in this target species.

Risk assessment

Quality

This product is presented as an extension to the existing marketing authorisation of Naxcel for pigs and for cattle. Naxcel for cattle, which is the same formulation as this product, had been reformulated in order to keep injection volume in cattle, which are much heavier than pigs, relatively low. The authorised 100 mg/ml formulation for pigs is more concentrated resulting in a 200 mg/ml formulation.

Safety

The basic safety profile of ceftiofur is known from previous applications.

A new user safety assessment was provided by the marketing authorisation holder and detailed safety warnings have been proposed to the SPC and product literature with regard to accidental contact with the product. These instructions are in line with those recommended for all penicillins and cephalosporins and have already been accepted for Naxcel 100mg/ml for pigs as well as for Naxcel 200 mg/ml for cattle. In horses, the second injection does not seem to pose an additional risk to the user. Consequently no particular warning in regards to this new posology scheme would be necessary in the SPC and product literature.
The environmental risk assessment allows halting the assessment in Phase I due to a PEC inferior to 100 µg/kg. The excipients used in this formulation are no cause for concern in terms of animal, user and/or consumer safety.

Ceftiofur is annexed in table 1 of the annex to Commission Regulation (EU) No 37/2010. A residue depletion study was performed.

The withdrawal period of 219 days for meat and offal as proposed by the applicant cannot be supported, as the CVMP guideline on injection sites residues (EMEA/CVMP/542/03) was not followed. Therefore, the CVMP proposed a "meat & offal" withdrawal period of 256 days, calculated from residues observed in the core of the last injection site. As no residue depletion study was performed in the milk, a warning should be added as follows "Not for use in animals from which milk is produced for human consumption." It is noted that this very long withdrawal period in meat and offal prevents the use of this product in horses intended for food production as well as in mares producing milk for human consumption.

According to the actual volumes administered in the depletion study, the recommended maximum volume of injection should not be 20 ml but lower than or equal to 13 ml.

Based on the tolerance studies in the target species, it is accepted that the product was well tolerated systemically; however, administration of the product at a dose of 6.6 mg/kg can result in reaction at the injection site. Injection site swelling reduced rapidly and typically resolved within 4-7 days after treatment; however, small swelling may persist for prolonged periods. In addition to swelling, reactions may be characterised by firmness and sensitivity/pain. Severe injection site reactions may also occur when the product is used as recommended, which may be related to the volume of product administered at any single site. Regarding the injection site reactions observed, the actual information given in sections 4.6 (adverse reactions) and 4.9 (amounts to be administered) of the SPC on the quality of injection site reactions and the need to reduce the maximum injection volume, are not considered adequate.

Limited target animal safety data have been provided in relation to foals. As the safety of the actual treatment recommendations of the product has, therefore, not been proven in foals of all age classes, additional safety data for the foal should be provided or the SPC should be restricted to horses over a certain age.

In addition to the specific target animal safety studies, the applicant provided US pharmacovigilance data relating to other ceftiofur containing products (ceftiofur sodium and ceftiofur hydrochloride) authorised in that region. Gastrointestinal and anaphylactic reactions were the most common adverse reactions reported. The applicant was also requested to further document the rate of anaphylactic reactions associated with ceftiofur based on the pharmacovigilance data of its first ceftiofur formulation marketed in the EU. The proposed SPC includes statements indicating that use of antimicrobials in horses under stress may result in diarrhoea which could be fatal, and this appears to be appropriate.

The SPC also includes a statement contraindicating use in horses with known sensitivity to ceftiofur or other beta-lactam antibiotics. While anaphylactic reaction was not recorded in any of the product-specific studies presented in support of the present application, there are rare reports of such reactions following administration of ceftiofur in the USA. The potential of the product to provoke analphylactic reactions has, therefore, not been sufficiently indicated as a possible side effect in the product literature.

Efficacy

The dose determination and dose justification was based on the **PK/PD analysis** in respect to tolerance. No dose confirmation studies specific to this indication and target species have been provided. However, the CVMP expressed concern that the concentrations achieved with the current dosing might be suboptimal. The applicant was therefore asked to further justify several assumptions and to take into account additional data in the PK/PD analysis supporting the dose determination. In light of the anticipated new results, the optimal dose and interval of administration would need to be further discussed.

In the pivotal **EU study** where the main target pathogen (*Streptococcus equi* subsp. *zooepidemicus*) was confirmed in approximately half of the enrolled cases, the results were presented as an overall cure rate because of the low numbers recruited. The statistical analysis conducted indicate that ceftiofur crystalline free acid when administered on two occasions 96 hours apart can be considered non-inferior to ceftiofur sodium administered by intramuscular injection once daily for 10 days for the primary efficacy parameter 'clinical cure'.

However, based on the parameters selected, the clinical cure rates were only 62.8% and 50% for the test and control products, respectively. Based on sample size calculations detailed in the protocol, a cure rate of 80% was anticipated. In addition, the relapse rates recorded for both groups were 38.1% and 44.5%, respectively. Supplementary analysis conducted by the CVMP indicated that non-inferiority of the test product to the reference product is thus not proven for this secondary parameter.

The CVMP concluded that this study was not appropriate to demonstrate efficacy of Naxcel in the proposed claims.

Given there are no pre-clinical or clinical data supporting and confirming, respectively, efficacy of the proposed treatment regimen for respiratory disease associated with other pathogens, a claim for "other susceptible bacterial pathogens" as proposed in the SPC cannot be accepted. The proposed indication should be reduced to *Streptococcus equi* subsp. *zooepidemicus* only. However the applicant did not justify the appropriateness of such a narrow indication, especially in the light of susceptibility of this target pathogen to penicillins G, as there is a possibility that this product would be used as a first line therapy in horses that present with clinical signs of acute respiratory disease.

Specific potential risks

Third generation cephalosporins are listed by WHO as critically important antimicrobials for human use and recent monitoring data indicate increased frequency of resistance due to Extended-Spectrum Beta-Lactamases (ESBL).

The metabolism and the distribution of ceftiofur following ceftiofur sodium or ceftiofur crystalline free acid intramuscular injection are similar but not the absorption phase, which drives the depletion of drug from the animal due to flip-flop kinetics. Ceftiofur crystalline free acid exhibited sustained release properties. The T_{max}, terminal phase half-life (governed by the absorption rate, causing flip-flop kinetics), and AUC are very different.

Although the CVMP acknowledged that resistance to beta-lactam antimicrobials has yet never been reported in beta-haemolytic streptococci from any animal species, the assessment of safety for the target species should also include possible impact on resistance in other pathogens relevant for animal health. Septicaemia caused by, e.g. *E. coli* in foals, is a condition with a high fatality rate unless appropriate treatment is rapidly administrated. In situations where resistance to standard alternative drugs such as aminoglycosides and trimethoprim sulphonamides occurs, 3rd or 4th generation cephalosporins may be the only available alternative. Increased resistance to cephalosporins could therefore have a substantial impact on animal health.

The CVMP also expressed concerns that the use of this product in horses increases the probability of colonization with MRSA and might increase risk of infection with MRSA of the exposed horse. The most important risk, however, is that colonisation with MRSA increases the risk of spread of MRSA to other animals and/or to people in contact with the animals.

A number of prudent use warnings should be added to the SPC, in line with the CVMP reflection paper on late-generation cephalosporins (EMEA/CVMP/SAGAM/81730/2006-Rev.1).

Risk management or mitigation measures

Some risk management or mitigation measures could not be defined due to incomplete data and would require further discussion based on responses to questions.

Evaluation of the benefit risk balance

Naxcel 200 mg/ml suspension for injection for horses does not offer a positive benefit risk balance at day 120 of the procedure, since "major objections" in relation to efficacy and the dose regimen have been identified which preclude a recommendation for marketing authorisation.

The formulation and manufacture of Naxcel 200 mg/ml suspension for injection for horses is well described and specifications set will ensure that product of consistent quality will be produced.

Its safety however has not been sufficiently discussed (i.e. antimicrobial resistance, risks for adverse effects) and has not been adequately been reflected in the SPC.

The product presents a low risk for the user and the environment with the appropriate warnings as included in the SPC. A sufficiently long withdrawal period would need to be set.

The product has shown a somewhat limited efficacy for the treatment of respiratory tract infections in horses associated with *Streptococcus equi* subsp*. zooepidemicus* and other susceptible bacterial pathogens. Non-inferiority of the test product to the reference product was proven for the primary parameter "cure", but not for the secondary parameters ("relapse".)

The proposed dose and administration interval are not sufficiently justified.

Therefore, demonstrative results from an appropriately designed clinical study, that would need to be supported by a reviewed PK/PD analysis including all target pathogens, were requested.

Conclusion

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP considers that the application for the product Naxcel 200 mg/ml suspension for injection for horses is not approvable at the present time since "major objections" have currently been identified which preclude a recommendation for marketing authorisation.