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Veterinary Medicine and Product Data Management

Refusal EPAR for Naxcel

Type II variation (EMEA/V/C/000079/II/0013)

Scope of variation: Addition of a new indication for the treatment of bovine respiratory disease for the cattle presentation.

Table of contents

1. Background information on the variation

In October 2011, the marketing authorisation holder, Pfizer Limited (the applicant), submitted to the European Medicines Agency an application for a type II variation for a new indication for the cattle presentation for Naxcel: "Treatment of bovine respiratory disease (BRD), associated with *Pasteurella multocida, Mannheimia haemolytica* and *Histophilus somni*, in cases where treatment with another antimicrobial has failed."

During the meeting on 6-8 November 2012, the CVMP concluded that the benefit-risk balance for this new application was negative and recommended the refusal of the variation.

Scope of the proposed variation:

Addition of a new indication: Treatment of bovine respiratory disease (BRD), associated with *Pasteurella multocida, Mannheimia haemolytica and Histophilus somni*, in cases where treatment with another antimicrobial has failed.

2. Scientific discussion

2.1. Safety

2.1.1. Environmental risk assessment

A Phase I environmental risk assessment was provided.

The $PEC_{soil\ initial}$ for intensively reared animals on pasture was calculated in line with the guideline on environmental impact assessment for veterinary medicinal products, in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1). As recommended in the guideline, the following default values were used in the calculations:

- A value of 170 kg N/(ha x year) for maximum manure application rates, assuming that nitrogen is the limiting factor.
- The assumption that 50% of the animals in a herd will be treated (default value for antibiotics used in respiratory injections in cattle).
- A depth of 5 cm for penetration into soil from spreading of manure onto grassland or pasture.

The $PEC_{soil\ initial}$ values calculated for intensively reared calves, dairy cows, 0–1 year old cattle and >2 year old cattle were below the Phase I trigger value of 100 µg/kg. Therefore, no further assessment for intensively reared dairy cattle was required and the environmental risk assessment can stop at Phase I.

2.2. Residues

No new data were provided. As the posology (dose and duration of treatment) for the proposed new indication was the same as the one already approved in cattle, no changes or further data in regard to the residue part or the withdrawal periods of the product were considered necessary.

2.3. Efficacy

2.3.1. 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 mg/kg 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.

In addition to these data already assessed previously, the applicant submitted new data for this application.

2.3.1.1. Pharmacodynamics

Recent Minimum Inhibitory Concentration (MIC) values for the target pathogens for the proposed new indication (*Pasteurella multocida, Mannheimia haemolytica* and *Histophilus somni)* were provided, which showed good susceptibility against ceftiofur. The MIC values for all target pathogens ranged from ≤ 0.002 µg/ml to 0.12 µg/ml; the highest MIC_{90} was found to be 0.12 µg/ml for *Pasteurella multocida*. Sufficient detail (weight of animals, country of origin) was provided in regards to epidemiological background and geographical distribution of the isolates allowing conclusion that the strains are representative for the European situation (see also below). Ceftiofur has been shown to be bactericidal for the proposed new target pathogens.

2.3.1.2. Development of resistance

A comprehensive assessment was provided of the potential for development of resistance resulting from the use of the product in the proposed treatment of BRD in cattle.

Target pathogens

BRD pathogens are included in European antimicrobial resistance surveillance programmes. Ceftiofur has been authorised in the EU as a treatment for cattle infections for more than 18 years, and MICs for ceftiofur against the BRD pathogens have remained low over the years. The interpretive criteria (clinical breakpoints) approved by The Clinical and Laboratory Standards Institute (CLSI) for ceftiofur MICs against bovine respiratory *Mannheimia haemolytica*, *Pasteurella multocida* and *Histophilus somni* are ≤ 2 µg/ml for “susceptible”, 4 µg/ml for “intermediate”, and ≥ 8 µg/ml for “resistant”.

The data provided show that BRD pathogens can be considered “susceptible” to ceftiofur, with MIC_{50} and MIC_{90} values of ≤ 0.12 µg/ml. Higher MIC values than that should not be viewed as representative of the current field situation. A MIC of 0.12 µg/ml was calculated for isolates originating in countries where bovine production is present in large numbers and considered to be of the intensive kind. Therefore, this number was taken for worst-case calculations under European conditions. However, this does not mean that CVMP had any indication that there is an increasing trend of ceftiofur MIC values for BRD pathogens.

Food-borne pathogens, pathogenic *E. coli* and commensal (indicator) organisms.

Prevalence rates of cephalosporin-resistant indicator *Escherichia (E.) coli* and food-borne pathogens (*Salmonella* isolated from cattle in the EU) remain low. However, more recently there is a tendency of increasing resistance rates noted among *E. coli* isolated from infections in cattle in some countries. Extended-spectrum beta-lactamases (ESBL) has been identified as an emerging problem in food

derived from other animal species. Epidemiological MIC cut-off values for ceftiofur used by EFSA for surveillance of *Salmonella* and *E. coli* from animals and foods remain above 2.0 µg/ml and above 1.0 µg/ml, respectively.

Salmonella and *E. coli* strains that are cephalosporin-resistant are also cross-resistant to other beta-lactam substances due to the production of an ESBL or AmpC cephalosporinase. They are typically co-resistant to at least one other drug class. Animals can serve as reservoirs of resistance determinants, including multiresistant organisms that acquire ESBLs or AmpC cephalosporinases.

The potential for exposure of enteric organisms in the animal environment to the microbiologically active substance has been assessed before. The main route of excretion of ceftiofur is via urine and excretion via faeces is low. However, it should be considered that for this product formulation the exposure occurs over an extended period of time.

The applicant concluded that no major changes in the resistance development were noted in the general occurrence of antimicrobial resistance in indicator *E. coli* from animals and food in 2009 when compared to 2005 to 2008. However, the CVMP considered that this conclusion needed to be strengthened by more recent data:

- From recent surveillance data, it can be observed that the occurrence of ceftiofur-resistant *E. coli* has increased in an animal species other than cattle: broilers and other chickens.
- Significant findings since 2006 were noted in the resistance situation including in cattle in percentages of pathogenic *E. coli* strains. These data show an increasing trend in resistance across all groups of bovines, calves and adult cattle:
  Highest resistance rates were reported for *E. coli* in cattle (using French CA-SFM[1] breakpoints) with a considerable increase (4 to 7%) during 2006-2011.
- The overall percentages of non-wild-type/resistant strains found for *Salmonella* spp. and *E. coli* recently isolated from cattle were very low: 0.1–1% to low: >1–10% depending on the reporting programme.

It has to be noted that different breakpoints were used as interpretative criteria in these programs comprising epidemiological cut off values and clinical breakpoints (EUCAST[2], CLSI[3], national breakpoints). Thus, data are not directly comparable and interpretation as regards to resistance is difficult. Epidemiological cut off values distinguish between wild-type and non-wild-type strains (such with elevated MICs potentially harbouring resistance determinants) while clinical breakpoints distinguish between susceptible and resistant strains which is correlated to an expected therapeutic outcome (in case of human pathogens).

Potential impact of the proposed new indication on resistance development

The applicant indicated that the approval of the new indication would not be expected to substantially increase the total number of cattle treated with ceftiofur in the EU and that comprehensive prudent use warnings have been included in the SPC and product literature, in line with current SPC guidance and the CVMP "Reflection Paper on the use of 3rd and 4th generation cephalosporins in food-producing animals in the EU: Development of resistance and impact on human and animal health" (EMEA/CVMP/SAGAM/81730/2006-Rev.1).

The CVMP partially disagreed with the applicant's view in that there is no clear indication that the new indication would not further increase the use of ceftiofur in farms. The new proposed respiratory indication is not of the same nature as those currently authorised for Naxcel in cattle (interdigital

[1] CA-SFM – Committee for Antimicrobial Testing of the French Society of Microbiology
[2] EUCAST - European Committee on Antimicrobial Susceptibility Testing
[3] CLSI - Clinical and Laboratory Standards Institute

necrobacillosis and metritis), which are considered individual animal diseases. Since infectious respiratory disease will affect a larger number of animals in a group, the new indication is, therefore, expected to lead to a greater exposure of the cattle population.

In addition, some concern was expressed about the possibility to identify the target population ("animals that have responded poorly to other antimicrobials") under practical conditions, how to ensure that only these animals will be treated, and that the ease of administration of the product might result in off-label use.

Concern was also expressed that during treatment the intestinal ceftiofur-resistant *E. coli* population, which would be in contact with residue ceftiofur levels, would be increased at least temporarily due to resistance selection. Therefore, treated cattle could serve as reservoirs of resistance determinants, including multi-resistant organisms that acquire ESBLs or AmpC cephalosporinases. Coupled to an expected greater exposure to Naxcel, these risks are apparent enough to be taken into account.

Conclusions

The CVMP considered that the intended target pathogens for the proposed new indication showed good susceptibility against ceftiofur. However, recent data on *Salmonella* and *Escherichia coli* pathogenic isolates indicate an increasing trend in resistance development in different species. Although the proposed new indication was restricted to "animals that have responded poorly to other antimicrobials", this target population is not well defined under practical aspects, and the disease of the new indication is likely to affect a large population of animals. The CVMP expressed therefore concern that there is a considerable risk that Naxcel with the proposed respiratory claim might be used in a wider animal population, resulting in a greater exposure of the cattle population.

2.3.1.3. Pharmacokinetics

The recommended dose for this new indication (single subcutaneous injection of 6.6 mg/kg body weight, administered at the base of the ear) is the same as the currently recommended dose for treatment of cattle (foot rot and metritis claims). One pharmacokinetic study was provided which was assessed already in a previous application.

The mean total plasma concentration is above 0.2 µg/ml during 9 days following the single subcutaneous injection the proposed dose (6.6 mg/kg body weight). Only the total fraction was studied, instead of the free fraction, which would be necessary for efficacy assessment. However, levels of the free fraction were considered to exceed the highest MIC_{90} of 0.12 µg/ml for about 3 to 7 days depending on the level of protein binding applied (90 – 70%). In connection with the dose determination studies, the data were considered sufficient to justify the proposed dose.

2.3.1.4. Tolerance in the target species of animal

Naxcel was approved for use in cattle for the treatment of interdigital necrobacillosis (foot rot) in October 2009 and for acute postpartum metritis in June 2011. As the proposed posology was the same as the already authorised one, safety issues do not require an updating specific to the new claim.

The systemic and injection site tolerance data are appropriately reflected in the warnings in the summary of product characteristics, and include visible swellings at injection site, mild to moderate pain and rare cases (1 case out of 10,000 animals) of sudden death attributed to hypersensitivity and anaphylaxis.

2.3.2. Clinical studies

The applicant provided four pivotal clinical studies (dose determination, dose confirmation, and two field studies). Additionally, bibliographical references were provided to support various statements of the expert's report. These references that mainly describe the BRD are not reported here since they are not of any particular interest with regard to the assessment of this particular product.

2.3.2.1. Laboratory trial (dose determination)

A well designed, GCP compliant US dose determination study was provided, using doses of 0, 1.1, 3.3, 4.4, 5.5, 6.6 and 8.8 mg ceftiofur/kg body weight (subcutaneously) in 81 male calves that developed clinical sign after challenge with *Mannheimia haemolytica* (intratracheally).

The experimental model was considered satisfactory as the disease was present in all groups and with a high mortality rate in the negative control group. The efficacy parameters were considered adequate to evaluate the response to the different doses. Based on the more discriminating parameter (lung lesion score), the optimal dose appears to be at least 6.6 mg/kg body weight. Though not statistically different, there is a trend towards a more pronounced effect at the anatomical level with a dose which is 33% higher (8.8 mg/kg body weight). In absence of a robust PK/PD analysis, this study, nevertheless, allows the selection of 6.6 mg/kg for further examination.

2.3.2.2. Field trials

Dose confirmation

A well designed, GCP compliant US dose confirmation study was provided, using a dose of 0 or 6.6 mg ceftiofur/kg body weight (subcutaneously) in a total of 344 bullocks (6–8 months of age) that developed clinical signs of BRD, following naturally infection.

The study was carried out under US management practices, breeds and epidemiological conditions that differ from the European ones. It is noted that the posology (location of administration) is slightly different to how it is practiced in the EU. The final formulation was not used in this study.

The primary efficacy parameter was considered adequate, i.e. "animals that did not receive ancillary treatment from D4 to D14". Based on this criterion, the efficacy of the 6.6 mg/kg body weight dose was demonstrated to be significantly different (p=0.047) from the negative control treatment (70.4% compared to 54.7%). The self-cure rate in this study is relatively high (at day 28, over 60%). However, the applicant's assessment was based on a pre-planned one-sided Chi-square test, which is now considered inappropriate, and not on the currently recommended 2-sided test. Re-calculating by the CVMP of a significance level based on the 2-sided test shows that no significant difference could be demonstrated between treated and untreated (placebo) animals (p=0.094).

The CVMP concluded that based on this finding the non-inferiority margin of 15 percent points used in the field efficacy studies is considered not to be appropriate. "15 percent points worse than the reference product" could mean that the test product is just as good as the placebo. Therefore, the results of this study were considered insufficient to draw conclusions on the efficacy of ceftiofur for the proposed new indication.

Pivotal field studies

The applicant provided two GCP compliant multicentre pivotal field studies, conducted on commercial farms in France, Germany, Italy and Spain, comparing the efficacy of Naxcel with positive controls which are authorised for the treatment of naturally occurring BRD (caused by *Pasteurella multocida, Mannheimia haemolytica* and *Histophilus somni*) in many EU countries, i.e. florfenicol or cefquinome.

The inclusion criteria (rectal temperature ≥ 40 °C and respiratory score ≥ 1 and depression score ≥1 and ≤ 2) demonstrated early stages of BRD. All the enrolled animals were observed and rectal temperature taken on daily basis from day 0 to day 14. Clinical criteria (respiration and signs of depression) were assessed at enrolment (using a scoring index). Nasopharyngeal swabs were collected from all animals before treatment for pathogen isolation and identification. Blood samples were collected to be used only if required for diagnostic purpose and from 20% of animals on day 21. The primary decision variable was the cure rate at day 14. Any animal that completed study day 14 and did not meet criteria for clinical failure was considered a successful clinical cure.

Comparison with florfenicol

The florfenicol study was conducted in 2009-2010. Animals (50–500 kg body weight; up to 6 month) showing clinical signs of BRD were either treated with Naxcel (n=321) or an adequate comparator, containing florfenicol (n=321).

Both treatment groups achieved a clinical cure rate superior to 70%: the clinical cure analysis frequency distribution for all sites for each treatment group resulted in 73.3% of cattle treated with ceftiofur and 80.0% of cattle treated with florfenicol. The CVMP considered these study results not as non-inferior to the reference product because of the inadequacy of the non-inferiority margin of 15%.

As florfenicol has activity against *M. bovis* (but ceftiofur doesn't), the applicant performed a second analysis on all data excluding one study site where a severe outbreak of BVD together with a *Mycoplasma bovis* infection was suspected (by the applicant) to have occurred. The clinical cure rate in this second analysis resulted in 80% of ceftiofur-treated cattle and 84% of florfenicol-treated cattle achieving a clinical cure, indicating non-inferiority of Naxcel to florfenicol. However, the CVMP considered that exclusion of the one site was not acceptable since such exclusion option was not part of the study protocol, and only done retrospectively and not adequately justified. In addition, based on the data presented it was considered that the results from the particular site may represent a variation which is normal under field conditions. The exception of results from this site would, therefore, not be acceptable.

The CVMP therefore concluded that the results of this study did not support the efficacy of Naxcel for the proposed new indication (BRD) because the 15% non-inferiority margin used was inappropriate, based on the findings of the placebo controlled dose confirmation study.

Comparison with cefquinome

The cefquinome study was conducted in 2010-2011. Animals (50–400 kg; up to 6 month) showing clinical signs of BRD were either treated with Naxcel (n=480) or an adequate comparator, containing cefquinome (n=481).

Both treatment groups achieved a clinical cure rate superior to 70%: the cure rate for animals administered ceftiofur demonstrated non-inferiority to cefquinome at the 15% non-inferiority margin with a 90% CI of [-1.2%; 16.5%], thus non-inferiority was demonstrated even at a much stronger margin than the questionable 15 percent points-margin. The usual statistical approach would have resulted in [1.5%; 11.6%]. Thus, in fact, even superiority can be demonstrated (Fisher's exact test: p=0.012).

The study comparing Naxcel to cefquinome was conducted to a similar protocol as the other study comparing Naxcel to florfenicol.

However, in terms of inclusion criteria, the protocols though intended to be same, resulted in differences between the study populations. In the cefquinome study, animals were less sick than those in the florfenicol study: About 60% of the animals in the florfenicol study had a respiratory score

higher than 1 (compared to only about 35% in the cefquinome study), and about 37% had a depression score higher than 1 (compared to only about 26% in the cefquinome study). From these data, it appears that efficacy results might be better when the treatment is administered at early stages of BRD. However, a distinction of BRD cases in terms of stage of disease was not subject of the trials. The analysis of the study results under this aspect is, therefore, of informative value only. Nevertheless, for ceftiofur being a 3rd generation cephalosporin, the extrapolation of these results to the "treatment of cases where treatment with another antimicrobial has failed" (i.e. the proposed new indication) would be accompanied by serious doubts regarding the efficacy of the product when administered at later stages of BRD.

Both studies were in principle well conducted although the CVMP also noted that nasopharyngeal swabs (collected from all animals before treatment for pathogen isolation and identification) are not considered to be suitable alone to establish the bacteriological origin of the disease. Instead, trans-tracheal aspiration (TTA) or broncho-alveolar lavage (BAL) on at least some animals on each site should have been performed, and would have been more appropriate for lower respiratory tract infection pathogen identification. This is, however, not considered to be a major shortcoming.

Conclusions

Between 1996 and 2011, three GCP-compliant clinical studies were performed (placebo-controlled dose confirmation, florfenicol- or cefquinome-controlled field studies); however, only the cefquinome study showed non-inferiority of ceftiofur to a comparator, i.e. allowing positive conclusions on efficacy of Naxcel in the proposed new indication. The other two studies were inconclusive (placebo) or did not show non-inferiority to the positive control (florfenicol).

However, for the cefquinome study, the CVMP noted that the inclusion criteria allowed inclusion of less diseased animals than in the florfenicol study, indicating that treatment was started in animals at early stages of BRD. It appears, therefore, that efficacy results might perhaps be biased as the treatment in the cefquinome study was administered at early stages of BRD. However, extrapolation of the results of these clinical studies to the proposed restricted indication ("treatment of cases where treatment with another antimicrobial has failed") leads to serious doubts regarding the efficacy of the product when administered at later stages of BRD. For the field studies, it would have been preferable to include cattle from farms where other antibacterial agents had failed to address the problems (although it is accepted that this might not be feasible). However, a distinction of BRD cases in terms of severity was not subject of the trials. The analysis of the study results under this aspect is, therefore, of informative value only.

In summary, in the absence of clear data CVMP concluded that the clinical efficacy of Naxcel in the proposed new indication has not been satisfactorily demonstrated.

3. Benefit-risk assessment

Naxcel 200 mg/ml suspension for injection is a long-acting formulation containing ceftiofur. The proposed variation was to add a new indication to the existing product formulation for cattle, i.e. "treatment of bovine respiratory disease (BRD) in cases where treatment with another antimicrobial has failed", at a single subcutaneous injection of 6.6 mg/kg body weight.

3.1. Benefit assessment

Data provided by the applicant showed that relevant bovine target pathogens were found susceptible to ceftiofur and susceptibility has remained good over many years. A dose determination study under laboratory conditions gave support to the choice of dose of 6.6 mg/kg body weight.

The clinical efficacy was investigated in a placebo-controlled dose confirmation study under US field conditions, and in two well-conducted GCP compliant European field studies, one using florfenicol and the other using cefquinome as positive control.

Efficacy of Naxcel in the treatment of BRD at the recommended dosage regimen has not been clearly demonstrated. The dose confirmation study showed that the effect of Naxcel is a 15.7% increase in clinical cure rate when compared to placebo (70.4% versus 54.7%). However, this difference was statistically not significant.

The EU field trial comparing Naxcel to florfenicol did also not allow establishing non-inferiority; whereas the field study using cefquinome demonstrated non-inferiority of Naxcel to the authorised comparator within a 5% margin and, hence, superiority (with a clinical cure rates of of 83% for Naxcel and 76.7% for the comparator). While the field study using cefquinome demonstrated non-inferiority of Naxcel to the authorised comparator with clinical cure rates of 83% for Naxcel and 76.7% for the reference product, the other field study using florfenicol failed to show non-inferiority. However, it also appeared that animals included in the cefquinome study were less diseased than cattle included in the florfenicol study resulting in higher cure rates, and concerns that Naxcel might be more effective in early stages of the disease.

Additional benefit(s)

The use of a single administration for the new proposed indication would present an advantage compared to currently available treatments that necessitate more than one injection, resulting in a better compliance.

3.2. Risk assessment

As the proposed dosage regimen was the same as already authorised for other indications in cattle, tolerance in the target species is expected to be the same, the same withdrawal periods can be applied, and no change to the impact on the environment is envisaged. In addition, results from the new field studies confirmed the tolerance of the product.

A risk assessment has been provided by the applicant on antimicrobial resistance, namely in regards to the impact on *Salmonella* and indicator *E. coli*. As in other later generation cephalosporins the emergence of ESBL/AmpC in Gram-negative bacteria, particularly in *E. coli* is a non-negligible risk and is of concern also for Naxcel. Still the resistance levels are low in cattle and to keep that situation it is important that the overall use of ceftiofur to cattle is not increased. This is of special importance in intensive meat production where many animals soon to be slaughtered are kept together and where there could be potential spread of bacterial strains between animals. It is noted that BRD is an indication common in those premises.

3.3. Evaluation of the benefit-risk balance

The clinical efficacy study of Naxcel 200 mg/ml in BRD produced inconsistent results. The efficacy assessment was primarily based on two multi-centric field efficacy studies, which were conducted in accordance with current guidelines. In the florfenicol study Naxcel failed to demonstrate efficacy while efficacy was demonstrated in the cefquinome study. Since results are contradictory, the efficacy of Naxcel has not been adequately demonstrated for the proposed indication. Nevertheless, the matter weighs particularly in the balance since ceftiofur is a critically important antimicrobial which should be reserved for second line intention treatments (severe infections and/or resistance to first line antimicrobials).

By restricting the indication to cases that have responded poorly to other antimicrobials, the applicant intended to mitigate the risk for increased antimicrobial resistance (i.e. selection and spread to humans of ESBL via food following increased use in larger groups of animals such as intensively reared calves). However, as the efficacy of Naxcel has not been unambiguously demonstrated, it remains unclear whether satisfactory efficacy will be reached in the restricted target population. The target population has not been clearly defined by any other means, except that it should have failed treatment with other antimicrobials. If this implies treatment of cases where disease has progressed further despite of such treatment, the relevance of the clinical data presented is questionable. As resistance levels to the target pathogens are low, first-line treatment with other antimicrobials (e.g. penicillins, macrolides or florfenicol) is likely to be effective.

Naxcel is currently indicated in cattle for the treatment of individual animal diseases (interdigital necrobacillosis, metritis). BRD is a herd-level disease, which leads to group treatment and hence a larger cattle population can be expected to be treated with this long acting formulation. The ease of administration (single injection) when compared to current treatments (repeated administrations) in conjunction with the zero day milk withdrawal period may contribute to a potential increase of use of this third generation cephalosporin and consequently to an increased risk in development of resistance.

Conclusion

Taking into account that

- Efficacy of Naxcel for the new proposed indication has not been satisfactorily confirmed by clinical trials as only one out of three clinical studies showed significant efficacy. However, concerns were raised in regard to the inclusion criteria of the animals included in this study, and the clinical relevance of the data for the proposed new indication.
- Insufficient data have been presented on the use of Naxcel in the proposed (restricted) target population of animals to be treated ("cases where treatment with another antimicrobial has failed");
- The use of Naxcel in cattle and, subsequently, exposure of ceftiofur is anticipated to increase due to the nature of the disease to be treated, resulting in increased risk of development of resistance in bacteria;
- There is a trend of increase in resistance in bovine *E. coli* from mastitis and *E. coli* enteritis against ceftiofur, recently confirmed in some countries.

CVMP considered the benefit-risk balance for Naxcel for the proposed new indication is negative.

4. Overall conclusions of the evaluation and recommendations

The CVMP considers that this variation, accompanied by the submitted documentation, does not demonstrate that the conditions laid down in Commission Regulation No. 1234/2008 are met, and recommends the refusal of the variation to the terms of the marketing authorisation.

4.1. Changes to the community marketing authorisation

No changes are required to the annexes of the Community marketing authorisation.

5. Grounds for refusal of the variation

Whereas,

- Ground 1 for refusal

Efficacy of Naxcel for the new proposed indication has not been satisfactorily confirmed by clinical trials as only one out of three clinical efficacy studies showed significant efficacy. However, concerns were raised in regard to the inclusion criteria of the animals included in this study, and the clinical relevance of the data for the proposed new indication.

- Ground 2 for refusal

Insufficient data have been presented on the use of Naxcel in the proposed (restricted) target population of animals to be treated ("cases where treatment with another antimicrobial has failed").

- Ground 3 for refusal

The use of Naxcel in cattle and, subsequently, exposure of ceftiofur is anticipated to increase due to the nature of the disease to be treated, resulting in increased risk of development of resistance in bacteria.

- Ground 4 for refusal

There is a trend of increase in resistance in bovine *E. coli* from mastitis and *E. coli* enteritis against ceftiofur, recently confirmed in some countries.

The CVMP, on the basis of the safety and efficacy data submitted, considered that the benefit-risk balance for the proposed new indication for Naxcel was not demonstrated to be favourable, and therefore could not recommend the variation of the marketing authorisation.