SCIENTIFIC DISCUSSION

1. SUMMARY OF THE DOSSIER

Convenia is a powder and solvent for solution for injection containing a third generation cephalosporin, cefovecin sodium, for use in dogs and cats.

The product is presented in a single pack size composed of one vial containing the freeze-dried active substance (cefovecin sodium), and a second vial containing the diluent. Reconstitution yields 10.6 ml of solution for injection.

The route of administration is subcutaneous.

The active substance of Convenia is cefovecin (as the sodium salt) (ATCvet code: QJ01DD91), a third generation cephalosporin with a broad-spectrum of activity against Gram-positive and Gram-negative bacteria. Cefovecin differs from other cephalosporins in that it is highly protein bound and has a long duration of activity. As with all cephalosporins, the bactericidal action of cefovecin results from the inhibition of bacterial cell wall synthesis.

The benefits of Convenia are its long duration of activity. The product is well tolerated and no side effects have been reported to date.

The approved indications are:

Dogs:

For the treatment of skin and soft tissue infections including pyoderma, wounds and abscesses associated with *Staphylococcus intermedius,* β-haemolytic *Streptococci, Escherichia coli* and/or *Pasteurella multocida*.

For the treatment of urinary tract infections associated with *Escherichia coli* and/or *Proteus* spp.

Cats:

For the treatment of skin and soft tissue abscesses and wounds associated with *Pasteurella multocida*, *Fusobacterium* spp., *Bacteroides* spp., *Prevotella oralis*, β-haemolytic *Streptococci* and/or *Staphylococcus intermedius*.

For the treatment of urinary tract infections associated with *Escherichia coli*.

2. QUALITY ASSESSMENT

Composition

One vial of cefovecin sodium freeze dried powder contains:

Components	Function	Typical Unit [mg/vial] [2]	Composition [mg/ml] [3]	Reference to analytical quality
Cefovecin sodium [1]	Active substance	894.94	84.0	In house specification
Other ingredients				
Methyl parahydroxybenzoate	Preservative	19.17	1.8	Ph.Eur.
Propyl parahydroxybenzoate	Preservative	2.13	0.2	Ph.Eur.
Sodium citrate dihydrate	Buffer	x	x	Ph.Eur.
Citric acid monohydrate	Buffer	x	x	Ph.Eur.
Sodium hydroxide	pH adjustment	x	x	Ph.Eur.
Hydrochloric acid	pH adjustment	x	x	Ph.Eur.

1 based on a potency of 95.2 % cefovecin in cefovecin sodium. The amount added will vary based on the actual potency. Cefovecin sodium 84.0 mg/ml is equivalent to 80.0 mg/ml cefovecin.
2 composition of the lyophilised powder prior to reconstitution
3 composition following label instructions of reconstitution with 10 ml of diluent containing 1.3 % benzyl alcohol
x Confidential

Nitrogen meeting the requirements of the current Ph.Eur. monograph is used as a processing aid during the manufacture. Water for Injections, Ph.Eur., is used as a solvent in the fill solution and is removed during the lyophilisation process.

One vial of diluent contains:

Components	Function	Typical Unit [mg/vial]	Composition [mg/ml]	Reference to analytical quality
Benzyl alcohol	Preservative	140.40	13.0	Ph.Eur.
Water for injections	Solvent	q.s.	q.s.	Ph.Eur.

Container

Cefovecin sodium freeze dried powder is packaged in 20 ml colourless glass (Type 1) vials with 20 mm butyl elastomer stoppers and an aluminium flip-off seal with polypropylene button.

The diluent is provided in 15 ml colourless glass (Type 1) vials with 13 mm chlorobutyl elastomer stoppers and an aluminium flip-off seal with polypropylene button.

Development Pharmaceutics

Due to its poor stability, cefovecin could not be formulated as a ready-to-use solution for injection. A lyophilised powder and solvent was therefore developed. Its manufacture uses an aseptic manufacturing process employing a microbial retentive filter. To ensure the volume specified on the label can be withdrawn from each vial an overfill is used.

Optimisation of the pH and water content after lyophilisation was performed to minimise the formation of degradation products. Cefovecin sodium is freely soluble in different buffer systems and shows maximum stability in the range of pH 6 - 8. Citrate was chosen as the preferred buffer for this lyophilised formulation on the basis of the resultant physical and chemical stability of the lyophilised cefovecin powder. The pH of the reconstituted product was demonstrated to be effectively buffered by the chosen formulation.

A number of common preservatives were evaluated in order to identify an appropriate preservative system for this multi-dose product. Methyl- and propyl parahydroxybenzoate were suitable with regard to compatibility with the manufacturing process (lyophilisation), physical and chemical compatibility with cefovecin sodium and antimicrobial effectiveness at pH 7, but did not fulfil criteria A of the Ph.Eur. requirements for efficacy of antimicrobial preservation (Ph.Eur. 5.1.3) for *Staphylococcus aureus* at 6 and 24 hour time points. However, when used in combination with benzyl alcohol, the Ph.Eur. criteria A were met. Due to incompatibility with lyophilisation, the benzyl alcohol must be added to the diluent. The concentration of benzyl alcohol in the diluent vial was optimised at 13 mg/ml, resulting in 12.3 mg/ml in the reconstituted solution.

The suitability of the packaging materials, both for the lyophilised powder and the diluent, has been investigated. No evidence of interaction (sorption to container/leaching) with the glass vials or stoppers was observed.

Photostability studies indicated sensitivity to light, which is typical for cephalosporin compounds. Photodegradants were present at an acceptable level for the reconstituted product stored in clear vials within a compartmentalised Individual Folding Carton (IFC with inserts). These were then selected as the commercial packaging.

Method of manufacture

Manufacturing process development has taken place. The process is typical for products of this type, and for the powder vial comprises compounding, sterilising filtration (0.22 µm), aseptic filling and lyophilisation. After freeze-drying, the vacuum is broken with sterile filtered nitrogen prior to the vials being sealed. Sterilisation by filtration has been justified, as irradiation of cefovecin lyophilised powder with doses necessary to ensure a sterility assurance level (SAL) of 10^{-6} resulted in unacceptable levels of unknown degradation products and discolouration. The lyophilisation cycle has been studied extensively. The critical operations in the manufacturing process have been identified and the in-process controls justified. In addition to several pilot scale batches, three full production scale batches have been manufactured at the production site. All batch data indicate that the powder vial manufacturing process is reliable and reproducible.

The manufacturing process for the diluent vial comprises of standard methods of compounding, filtration, filling and terminal sterilisation. The diluent demonstrated compatibility with materials used during manufacture. Sealed vials are steam sterilised at 121°C for 20 minutes. The critical operations in the manufacturing process were identified and in-process controls justified. Three full commercial scale batches of diluent have been manufactured at the manufacturing facility, and these batches demonstrated the diluent manufacturing process is reliable and reproducible.

CONTROL OF STARTING MATERIALS

Active substance

The active substance, cefovecin sodium, is (6*R*,7*R*)-5-thia-1-azabicyclo[4.2.0]oct-2-ene-2-carboxylic acid, 7-[[(2*Z*)-(2-amino-4-thiazolyl) (methoxyimino) acetyl]amino]-8-oxo-3-[(2*S*)-tetrahydro-2-furanyl]-, monosodium salt (Chemical Abstracts Services Number of cefovecin sodium: 141195-77-9). The structure of cefovecin has been confirmed by elemental analysis, MS, IR, ^{1}H NMR and ^{13}C NMR. Cefovecin is a weak base and is highly water soluble. Cefovecin sodium is hygroscopic and should be stored in moisture protective containers. Cefovecin sodium produces an X-ray powder diffraction pattern that is consistent with an amorphous material. Investigations into its solid-state properties revealed no evidence of polymorphism.

Cefovecin sodium is produced by organic synthesis. Satisfactory control specifications are provided for the active substance and all starting materials, key intermediates, reagents and solvents. The limits for the relevant specified impurities have been justified in terms of safety. However some of the specification limits may be tightened or justified after further full-scale batches of drug product have been produced.

All analytical methods have been submitted as well as validation data, in accordance with the relevant EU and VICH guidance.

Batch analysis results of more than 10 lots of cefovecin sodium produced at two sites confirm satisfactory uniformity and compliance with the specification and demonstrate that active substance of the desired quality can be consistently produced.

The stability of cefovecin has been examined under a variety of stress testing conditions. Degradation products have been identified. Degradation occurs in aqueous solution, particularly with the application of heat. In the solid state cefovecin is hygroscopic and degrades upon exposure to high temperatures and moisture. In the solid state photodegradation takes place under light stress conditions (UV or fluorescent). The active substance should therefore be stored in light and moisture protective packaging such as that provided by the commercial packaging system.

Real-time and accelerated stability studies have been performed on cefovecin sodium. Stability data from three batches stored at 25°C/60%RH for up to 6 months (accelerated conditions) and

5°C/60%RH for up to 36 months demonstrate that all batches comply with the proposed specification. The retest period of 3 years when stored at 2°C to 8°C has been justified.

Excipients

Each of the excipients used in the manufacture of the lyophilised powder and the diluent, including the sterile nitrogen used to provide an inert atmosphere in the powder vial headspaces, comply with their respective Ph.Eur. monographs.

Packaging

The primary packaging for Convenia consists for the powder vial of 20 ml colourless Type 1 glass vials with 20 mm butyl elastomer stoppers, and for the diluent vial of 15 ml colourless Type 1 glass vials with 13 mm chlorobutyl elastomer stoppers. Both the powder and diluent vials have aluminium flip-off seals with polypropylene buttons. Satisfactory control specifications are provided. A maximum puncture study of the stoppers demonstrated their suitability for use on a multi-dose vial.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

The starting materials of animal origin used in the production of the final product have all been declared in compliance with the current regulatory texts related to the TSE Note for Guidance (EMEA/410/01-Rev.2) and Commission Directive 2001/82/EC as amended.

Control tests on the finished product

All specifications, both for the powder vial and the diluent vial, are justified and are regarded as sufficient to ensure adequate and constant quality. The methods of analysis have been validated in accordance with the relevant EU and VICH Notes for Guidance. Limits have been derived from the range of test results of pivotal/VICH and supportive stability lots, and in the case of degradation products are justified based on the levels of impurities present in the batches used to perform the safety studies. These specifications will be reviewed once additional manufacturing experience and stability data are obtained.

Data are presented from the manufacture of three commercial scale batches of the powder vial, plus three pivotal/VICH stability lots, produced from three different lots of active substance, plus a supportive batch. All results are in accordance with the specification and show uniformity from batch to batch.

Batch analysis data of three commercial batch scale batches of the diluent vials show that the specification is consistently met.

Stability

Powder vials

The end-of shelf-life specification for the powder vials is identical to the release specification except for the limits for cefovecin and for degradation products. This is justified.

Stability studies were performed on four batches of varying sizes of cefovecin sodium lyophilised powder, manufactured by the proposed manufacturer. Vials were stored in inverted position to allow assessment of potential interaction with the packaging material. Additionally, photostability, thermal cycling, and maximum puncture studies were conducted, as well as in-use stability studies of the reconstituted lyophile. Data from storage periods of up to 24 months at 5°C/60%RH and 6 months at 25°C/60%RH show that although all results are within specification that:
- the content of cefovecin sodium decreases slightly with increasing temperature;
- the content of degradation products increases slightly with increasing temperature;

- no significant loss in either methyl parahydroxybenzoate content or propyl parahydroxybenzoate content was observed;
- no significant changes in other parameters were observed.

Based on the data, 6 months of accelerated (25°C/60%RH) and 24 months of longer long-term (5°C/60%RH), the 24 month expiry period for cefovecin sodium for injection stored under refrigeration (+2°C to +8°C) is justified.

Photostability studies were performed according to VICH conditions with UV light (200 watt hours / m^2) followed by fluorescent light (1.2 million lux hours). No significant changes in sample appearance or composition were found for the lyophilised powder in the proposed commercial packaging, including the critical, secondary light-protective package. The same photostability study was performed on the lyophilised powder reconstituted according to label instructions. Significant changes in cefovecin content and degradation products were observed both with samples and foil-wrapped controls due to the thermal environment to which the vials had been exposed. An additional photostability study of the reconstituted powder in the proposed commercial packaging was performed with reduced VICH light exposure based on the four weeks in-use period of the reconstituted samples. No significant changes in sample appearance or composition were found in the exposed samples when compared to the foil-wrapped controls, and test results were within specification. The slight changes in composition that were observed in both exposed and control samples were therefore concluded to be due to thermal exposure. In conclusion, the photostability data generated demonstrate acceptable stability both of cefovecin sodium lyophilised powder and the reconstituted product when stored in the proposed commercial packaging.

A puncture study on vials of cefovecin sodium for injection demonstrated that package integrity and product quality are maintained after the maximum number of punctures (23) have been made.

Diluent vials

Stability studies were performed on three commercial scale lots of diluent manufactured by the proposed manufacturer. Vials were stored in upright and inverted positions. Additionally, photostability and thermal cycling studies were conducted. Data from storage up to 18 months at 5°C/60%RH and 25°C/60%RH, and also from up to 6 months at 30°C/60%RH and 40°C/75%RH, were provided and showed no significant changes in any parameters.

Photostability studies were performed according to VICH conditions with UV light (200 watt hours / m^2) followed by fluorescent light (1.2 million lux hours). No significant changes in sample appearance or composition were found. The photostability data generated demonstrate acceptable stability of diluent when stored in the proposed primary packaging.

No significant changes in sample appearance or composition were observed after subjecting the powder vials to thermal cycling (between –20°C and room temperature). Although some vial breakages occurred, the composition of the diluent in the intact vials was unchanged.

In-use stability studies were conducted on two lots of reconstituted cefovecin sodium for injection. Sample removal was accomplished by performing multiple punctures of the vials (twenty-two 0.2 ml aliquots), removing approximately half of the vial contents. The vials were stored refrigerated (2°C to 8°C) in the inverted orientation for 4 weeks. All test results were within specifications. A minor loss of potency and a small increase in degradation products was observed for samples stored at 25°C/60%RH up to 6 months followed by 4 weeks in-use stability at 5°C. No significant changes were observed for content of methyl parahydroxybenzoate, propyl parahydroxybenzoate and benzyl alcohol. These data justify the claimed in-use shelf life of 4 weeks.

Antimicrobial effectiveness testing was performed on two of the stability batches at the initial and 24 months stability time points for the 5°C/60%RH storage condition, following 4 weeks of in-use refrigerated storage. In all cases, the reconstituted finished product met the Ph.Eur. Criteria A

requirements, demonstrating antimicrobial preservative effectiveness at the end of the product's shelf life, and its in-use shelf life.

The following shelf lives for Convenia have therefore been justified:

- Cefovecin sodium lyophilised powder: 24 months when stored under refrigeration (+2°C to +8°C)
- Diluent: 36 months, but the shelf-life of the packed final product (2 vials) will be restricted to 2 years, based on the shelf-life of the powder vial
- Reconstituted solution: 4 weeks when stored under refrigeration (+2°C to +8°C)

The applicant has committed to monitor the stability of the first three production-scale batches of the active substance, powder vials and diluent vials.

OVERALL CONCLUSION ON QUALITY

Convenia contains cefovecin sodium, a third generation cephalosporin, and is indicated for use in dogs and cats for the treatment of skin and soft tissue infections and for the treatment of urinary tract infections. It is administered subcutaneously. The product is presented in a single pack size composed of one vial containing the freeze-dried active substance (cefovecin sodium), and a second vial containing the diluent.

In general the quality aspects of the product have been well documented. The active substance and finished product are manufactured and controlled in the appropriate manner, in compliance with current EU and VICH guidelines. Satisfactory information has been provided to demonstrate that the manufacture and control processes routinely and consistently generate a product of uniform quality.

3. SAFETY ASSESSMENT

Pharmacodynamics

This is summarised under Section 4, Efficacy.

Pharmacokinetics

In dogs, when cefovecin was administered as a single subcutaneous dose of 8 mg/kg bodyweight, absorption was rapid and extensive; peak plasma concentration at 6 hours was 120 µg/ml and bioavailability approximately 99%. Peak concentrations in tissue cage fluid of 31.9 µg/ml were measured 2 days after administration. No data on metabolism of cefovecin are available. Fourteen days after administration, the mean cefovecin concentration in plasma was 5.6 µg/ml. Plasma protein binding is high (96.0% to 98.7%) and the volume of distribution is low (0.1 l/kg). The elimination half-life is long – approximately 5.5 days. Cefovecin is primarily eliminated unchanged via the kidneys. At fourteen days after administration, urine concentrations were 2.9 µg/ml. In dogs, urinary cefovecin concentrations accounted for 60 % of the total administered dose 35 days post-dose.

In cats, the pharmacokinetics of cefovecin after subcutaneous administration is characterised by rapid and complete absorption. Following a single subcutaneous dose of 8 mg/kg bw, maximum cefovecin concentrations of 141 µg/ml in plasma were achieved approximately 2 hours post-dose. Bioavailability is approximately 99 %. No data on metabolism of cefovecin are available. Fourteen days after administration, the mean cefovecin concentration in plasma was 18 µg/ml. Cefovecin concentrations in plasma remained above 5 µg/ml for up to 32 days post-dose. Plasma protein binding is high (more than 99%) and the volume of distribution is low (0.09 l/kg). The elimination half-life is long – approximately 6.9 days. At ten and fourteen days after administration, urine concentrations were 1.3 µg/ml and 0.7 µg/ml, respectively. Cefovecin was shown to be predominantly eliminated unchanged via the kidneys over several weeks. In cats, about 50% of the administered radiolabelled dose was excreted in urine by 21 days post-dose. Urinary cefovecin concentrations of ≥ 1 µg/ml were present for up to 14 days following a single subcutaneous administration.

Repeated subcutaneous administration of cefovecin at the recommended dose, or at multiples of the dose resulted in an accumulation of plasma cefovecin between the 1st and the 4th injections in cats.

PK/PD analysis in dogs and cats supported the proposed treatment dose (8 mg/kg) and dosing interval (14 days for skin and soft tissue infections). Total cefovecin concentrations in plasma, tissue transudate and urine exceeded the MIC_{90} against relevant pathogens for approximately 14 days in dogs and approximately 10 to 14 days in cats. The time above the MIC is therefore sufficient for a cephalosporin antibiotic like cefovecin with time-dependent antimicrobial activity. The fraction of unbound cefovecin, which has been determined in plasma and tissue fluid, is noticeably lower than the total amount of the substance. Nevertheless, a level of approximately 1 µg/ml is maintained in tissue transudate for at least 12 days in dogs and 10-14 days in cats after administration of the recommended treatment dose. Moreover, the antibacterial efficacy of this dose has been demonstrated in serum, tissue transudate and exudate in an *ex vivo* study.

Toxicology

Three studies were provided in rats and dogs investigating the toxicity of a single dose of cefovecin after oral and subcutaneous administration. One study was provided investigating the toxicity in rats after administration of cefovecin via the dermal route. A Magnusson-Kligman sensitisation test proved the acute intradermal toxicity of cefovecin to guinea pigs. All the provided studies were conducted in accordance with GLP. The data prove the low acute toxicity of cefovecin in rats and dogs after single administrations via the oral, subcutaneous and dermal routes. This observation is consistent with the low acute toxicity for other cephalosporins. The results of the skin sensitisation test in guinea pigs revealed an acute toxicity after intradermal injection of approximately 50 mg/kg bw in that species. Cefovecin is an antibiotic, which can be toxic to rodents, as demonstrated in guinea pigs, due to the destruction of the natural flora of their intestinal tracts. Therefore the use of this product in small

herbivores (including guinea pigs and rabbits) is contraindicated, and section 4.3 of the SPC includes a contraindication to this effect.

No repeated dose toxicity studies in laboratory animals were provided. However, repeated dose studies have been submitted for the target species (dogs and cats) and have been addressed in section 3, User Safety, and section 4, Efficacy, Target Species Safety, of this report. The approach taken is acceptable and in accordance with Directive 2001/82/EC.

No special studies have been conducted concerning the reproductive toxicity of cefovecin. Since no alerting teratological effects have been found in compounds of this class to date, this was considered acceptable. Certain cephalosporins have, however, been shown to exert adverse effects on male fertility in rats. No data are available for cefovecin in this context. Considering the long-term activity of the substance and the duration of a spermiogenetic cycle (8-9 weeks in cats and dogs), a statement was, therefore, included in section 4.7 (Use during pregnancy, lactation and lay) of the SPC " The safety of Convenia in dogs and cats has not been established during pregnancy and lactation. Treated animals should not be used for breeding for 12 weeks after the last administration.".

Specific studies on possible effects on teratogenicity have not been performed in laboratory animals, or in the target species. However, data from published literature are available. Studies in pregnant mice, rats, rabbits, and ferrets suggested that treatment with cephalosporins studied in usual therapeutic doses was unlikely to greatly increase the risk of congenital abnormalities. Other data obtained from EMEA/CVMP Summary Reports for similar substances also suggest that cephalosporins present no embryotoxic or foetotoxic risk to animals.

Mutagenicity - Genotoxicity data *in vitro* demonstrated a weak positive effect in the mouse lymphoma forward mutation assay under non-activation conditions and a treatment time of 24 hours. The results of an *in vivo* micronucleus test in rats demonstrated that cefovecin does not induce a reproducible increase in chromosome damage.

No specific carcinogenicity studies have been carried out. Due to the negative results of the *in vivo* genotoxicity assay and the lack of a carcinogenic potential of other cephalosporins, it can be assumed that cefovecin has no carcinogenic risk.

Cefovecin is excreted mainly unchanged in the urine and no data on the metabolism of cefovecin are available. Both the specified and unspecified impurities in the test products used in the target animal safety studies were within the specification limits for the product. In the absence of any observed treatment-related adverse effects, impurities are not considered to be of toxicological relevance, to either the target species or the user.

Excipients in the reconstituted formulation are preservatives (methyl- and propyl parahydroxybenzoate and benzyl alcohol) and buffering agents (sodium citrate and citric acid). They are all either excipients which are well known and characterised in other veterinary (and human) medicinal products, are in the normal human diet/food additives, are GRAS/Inactive Ingredients Guide listed, or are present in sufficiently small quantities that they present no significant inherent toxicity, to either the target species or the user at the inclusion levels of the proposed formulation.

User safety

Although no data on the potential neurotoxicity of cefovecin were provided, published literature was referenced, as high doses of a number of cephalosporins, as well as other ß-lactam antibiotics, have been associated with reports of central neurotoxicity in man. The signs reported during early clinical use of these other cephalosporins included convulsions, encephalopathy and organic brain syndrome. However, it is prudent to note that no such effects have been observed in animals after cefovecin administration. The CVMP noted that although high dose cephalosporins have shown neurotoxic effects in humans, no adverse effects have been observed after repeated treatments with up to 7.5 times the recommended dose of cefovecin in dogs and cats.

Potential routes of user exposure are the dermal, ocular and subcutaneous routes. Irritation studies with the active substance indicate the product is unlikely to be irritating to the skin or eye. The recommended dosage is dependent upon the size of the animal, but is administered at 8 mg cefovecin/kg bodyweight or 1 ml of reconstituted product per 10 kg bodyweight. Therefore, following accidental self-subcutaneous injection, it is considered in a worst case scenario that the maximum quantity to which a user might be exposed, would be 4 ml (320 mg cefovecin) or 5.3 mg/kg bodyweight assuming a human bodyweight of 60 kg. Cefovecin sodium is not expected to pose a reproductive hazard to the user and a weight of evidence approach, using provided data and supportive data on other cephalosporins, indicates that cefovecin is devoid of mutagenic potential.

Like many ß-lactam structures, cefovecin has demonstrable hypersensitivity potential for users. Therefore, cefovecin should not be administered by persons with a known hypersensitivity to penicillins. Veterinarians with a known penicillin hypersensitivity should be aware that exposure to cefovecin may lead to hypersensitivity reactions and, therefore, the following statements are included in the SPC and package leaflet:

- Penicillins and cephalosporins may cause hypersensitivity (allergy) following injection, inhalation, ingestion or skin contact. Hypersensitivity to penicillins may lead to cross sensitivity to cephalosporins and vice versa. Allergic reactions to these substances may occasionally be serious.
- Do not handle this product if you know you are sensitised or if you have been advised not to work with such preparations.
- Handle this product with great care to avoid exposure, taking all recommended precautions.
- If you develop symptoms following exposure, such as a skin rash, you should seek medical advice and show the doctor this warning. Swelling of the face, lips or eyes or difficulty in breathing are more serious symptoms and require urgent medical attention.
- If you know you are allergic to penicillins or cephalosporins, avoid contact with contaminated litter. In the event of contact, wash skin with soap and water.

Resistance development in gut flora

The particular impact of cefovecin on the human and animal gut flora in respect of the development of antimicrobial resistance has not been investigated as Convenia is not indicated for the treatment of food-producing animals.

Environmental safety

The applicant provided a Phase I Environmental Assessment according to VICH GL6 (CVMP/VICH/592/98-Final) based on the characteristics and use pattern of the product. The determination of the environmental fate and effects of cefovecin in the environment is not necessary because the product is intended for use in non food-producing animals and therefore exempted from a Phase II assessment. The Phase I assessment was based on physico-chemical measurements and estimates of the predicted environmental concentrations of cefovecin. Cefovecin, like other antibiotics belonging to the ß-lactam class, is likely to be rapidly degraded in the environment by chemical and enzymatic hydrolysis. Due to the infrequent use of cefovecin in individual dogs and cats, it was concluded that the potential exposure of the environment to excreted cefovecin residues will be minimal, and the effects on the environment will be insignificant.

OVERALL CONCLUSIONS ON SAFETY

Cefovecin is a third generation cephalosporin with a broad-spectrum of bactericidal activity against Gram-positive and Gram-negative bacteria.

Cefovecin is of low acute toxicity in rats (oral and subcutaneous) and dogs (subcutaneous). A sensitisation test, however, revealed acute toxic effects in guinea pigs after intradermal injection, due to effects on their gut flora, and so the use in small herbivores (including guinea pigs and rabbits) is contraindicated (see section 4.3 of the SPC).

No studies on reproductive toxicity have been submitted, thus the safety of use in dogs and cats during pregnancy and lactation has not been established. Since cephalosporins have been shown to impact on male fertility in rats, it is advised that treated animals should not be used for breeding for 12 weeks after the last administration.

Cephalosporins at high doses showed neurotoxic, and in some cases nephrotoxic effects, in humans. However, no such data have been observed in dogs, and the CVMP concluded that such effects would be unlikely in dogs or cats, as no such signs were seen in target animal safety studies.

Cefovecin is not irritating to skin and only minimally irritating to the eye. However, cefovecin has skin sensitisation potential. The CVMP noted the risk of hypersensitivity reactions to the susceptible user and appropriate user warning has been included in the SPC.

The potential exposure of the environment to excreted cefovecin residues will be minimal, and CVMP concluded that the use of this product does not pose a risk to the environment.

4. EFFICACY ASSESSMENT

PRECLINICAL STUDIES

Pharmacodynamics

Cefovecin is a third generation cephalosporin with a broad-spectrum of activity against Gram-positive and Gram-negative bacteria. As with all cephalosporins, the action of cefovecin results from the inhibition of bacterial cell wall synthesis. Cefovecin has bactericidal activity. It differs from other cephalosporins in that it is highly protein bound and has a long duration of activity.

The antibacterial properties of cefovecin have been characterised in recent European and USA MIC determination studies with more than 1500 isolates, obtained from infections in dogs and cats. On the basis of MIC and MBC values and the resistance pattern to ß-lactamases, cefovecin was classified as a 3rd generation cephalosporin with bactericidal activity against numerous gram-positive and gram-negative bacteria. MIC_{90} values of cefovecin against the majority of the claimed bacterial species, including *Staphylococcus intermedius*, ß-haemolytic *Streptococci*, *Pasteurella multocida*, *Escherichia coli*, *Proteus spp*., *Fusobacterium spp*. and *Prevotella oralis,* were ≤ 2 µg/ml (*Bacteroides spp*. 4 µg/ml).

In vitro activity for these and other skin and urinary tract pathogens are listed below.

In vitro activity against pathogens, collected during a European (Denmark; France; Germany; Italy; UK) MIC survey (1999 – 2000) and during European (France; Germany; Spain; UK) clinical efficacy and safety field studies (2001 – 2003) are listed below:

Bacterial Pathogen	Origin	No. of Isolates	Cefovecin MIC (µg/ml)			
			Min	Max	MIC_{50}[1]	MIC_{90}[2]
Staphylococcus intermedius	Dog Cat	226 44	≤0.06 ≤0.06	8 8	0.12 0.12	0.25 0.25
β-haemolytic *Streptococcus* spp.	Dog Cat	52 34	≤0.06 ≤0.06	16 1	≤0.06 ≤0.06	0.12 0.12
Coagulase negative *Staphylococcus* spp.[4]	Cat	16	0.12	32	0.25	8
Staphylococcus aureus[3,4]	Dog[4] Cat[4]	16 20	0.5 0.5	1 >32	1 1	1 16
Coagulase positive *Staphylococcus spp.*[3,4]	Dog[4] Cat[4]	24	0.12	>32	0.25	0.5
Escherichia coli	Dog Cat	167 93	0.12 0.25	>32 8	0.5 0.5	1 1
Pasteurella multocida	Dog Cat	47 146	≤0.06 ≤0.06	0.12 2	≤0.06 ≤0.06	0.12 0.12
Proteus spp.	Dog Cat[4]	52 19	0.12 0.12	8 0.25	0.25 0.12	0.5 0.25
Enterobacter spp.[4]	Dog[4] Cat[4]	29 10	0.12 0.25	>32 8	1 2	>32 4
Klebsiella spp.[4]	Dog[4] Cat[4]	11	0.25	1	0.5	1
Prevotella spp.	Dog[4] Cat	25 50	≤0.06 ≤0.06	8 4	0.25 0.25	2 0.5
Fusobacterium spp.	Cat	23	≤0.06	2	0.12	1
Bacteroides spp.	Cat	24	≤0.06	8	0.25	4

[1] Lowest concentration, which completely inhibits visible growth of at least 50% of isolates
[2] Lowest concentration, which completely inhibits visible growth of at least 90% of isolates
[3] Some of these pathogens (e.g. *S. aureus*) exhibited natural *in vitro* resistance to Cefovecin
[4] The clinical significance of these *in vitro* data has not been demonstrated.

Resistance to cephalosporins results from enzymatic inactivation by ß-lactamases, from reduced permeability by porin mutations or change in efflux, or by selection of low-affinity penicillin-binding proteins. Resistance may be chromosomal or plasmid-encoded and may be transferred if associated with transposons or plasmids. Cross-resistance with other cephalosporins and other ß-lactam antibacterials can be observed.

When applying a proposed microbiological breakpoint of S ≤ 2 µg/ml, no resistance to cefovecin was detected in *Pasteurella multocida* and *Fusobacterium* spp. field isolates. When applying a proposed microbiological breakpoint of I ≤ 4 µg/ml, cefovecin resistance in *S. intermedius* and beta-haemolytic *Streptococci* isolates was less than 0.02%. The percentage of cefovecin resistant isolates in *E. coli*, *Prevotella oralis*, *Bacteroides* spp. and *Proteus* spp. were 2.3%, 2.7%, 3.1% and 1.4%, respectively. The percentage of cefovecin resistant isolates in coagulase negative *Staphylococci* spp. (e.g. *S. xylosus*, *S. schleiferi*, *S. epidermidis*) is 9.5%. *Pseudomonas* spp., *Enterococcus* spp, and *Bordetella bronchiseptica* isolates are inherently resistant to cefovecin.

Following advice given by the CVMP Scientific Advisory Group on Antimicrobials (SAGAM), the CVMP agreed the following statements should be included in section 4.5 of the SPC (special precautions for use) "*It is prudent to reserve third generation cephalosporins for the treatment of clinical conditions, which have responded poorly, or are expected to respond poorly, to other classes of antimicrobials or first generation cephalosporins.*" and "*Use of the product should be based on susceptibility testing and take into account official and local antimicrobial policies*".

Target animal safety

The tolerance of cefovecin was investigated in three controlled laboratory studies in dogs and three controlled laboratory studies in cats, using the final or nearly final (without benzyl alcohol) formulation. All studies have been conducted in compliance with GLP and the relevant EU guidelines and are well documented.

In both cats and dogs, the product proved to be well tolerated at a single subcutaneous dose of 180 mg/kg, corresponding to 22.5X the recommended dose. Following repeated subcutaneous administration at dose levels corresponding to 1.5X, 4.5X and 7.5X the recommended dose (5 doses, each given at 1 week intervals) or 1X, 3X and 5X the recommended dose (8 doses, each given at 14 day intervals), respectively, cefovecin was well tolerated in young (≥ 8 weeks) cats and dogs. Treatment related adverse effects were restricted to transient mild swelling and discomfort at the injection site in individual animals, consistent with the administration of high dose volumes. In the absence of any inflammatory signs these effects were not considered clinically relevant. No other treatment-related abnormalities occurred. In particular, no abnormalities based on clinical observations, haematology, clinical chemistry including urinalysis and histopathology were recorded.

The CVMP concluded that target species tolerance of the product is generally good. However, the use of the product is contraindicated in dogs or cats younger than 8 weeks, because no data on safety or efficacy in younger animals are available. In addition, as regards renal excretion of the active substance, animals with severe renal dysfunction should not be treated, in order to avoid potential adverse effects that may be associated with accumulation of the substance.

Conclusions on preclinical data

Cefovecin is a third generation cephalosporin with a broad-spectrum of bactericidal activity against Gram-positive and Gram-negative bacteria. The antimicrobial spectrum of activity of cefovecin has been well described based on susceptibility tests in more than 1500 bacterial isolates mainly collected in European countries and North America from infections in dogs and cats within the last 5 years. On the basis of the susceptibility tests against numerous bacteria and certain classes of ß-lactamases cefovecin has been characterised as a 3rd generation cephalosporin. The data indicate that cefovecin is active against the relevant pathogens associated with skin, soft tissue and urinary tract infections in dogs and cats and the corresponding MIC values are adequately reflected in the product literature.

Because of their high therapeutic value, third generation cephalosporins, including cefovecin, should be used only in clinical conditions which do not respond satisfactorily to other classes of antimicrobials or first generation cephalosporins. Use of the product should therefore be based on susceptibility testing and take into account both official and local antimicrobial policies.

The pharmacokinetic properties of cefovecin have been investigated in a set of GLP compliant studies in dogs and cats (summaries under Section 3, Safety). The most remarkable properties of cefovecin in both dogs and cats were its rapid and complete absorption following single subcutaneous administration at the recommended dose and its slow elimination from plasma. The maximum cefovecin concentrations in plasma were shown to be slightly higher on average in cats than in dogs. In addition, cefovecin at microbiologically active concentrations persisted remarkably longer in cat plasma than in dog plasma.

Cefovecin appears to be predominantly excreted in unchanged form in urine. In dogs, urinary concentrations exceeding the MIC90 of the relevant pathogens are present for approximately 14 days following single subcutaneous administration. In cats, urinary cefovecin concentrations exceeding the MIC90 of *E. coli* were present up to 10 to 14 days.

With respect to the claimed skin, soft tissue and urinary tract infections in dogs, the proposed treatment regimen of subcutaneous injection of 8 mg/kg bodyweight (1 ml per 10 kg bodyweight) is justified under PK-PD aspects. Moreover, the antibacterial efficacy of this dose has been demonstrated in serum, dermal transudate and exudate by an *ex vivo* study with the major skin pathogen *Staphylococcus intermedius* and in a dose titration study in a canine skin infection model.

A set of target animal safety studies for dogs and cats had been conducted. Under the conditions of these studies cefovecin proved to be well tolerated in young ($\geq$ 8 weeks) and adult cats and dogs at a single dose of 22.5 times the recommended dose, and after repeated treatment at doses up to 7.5 times the recommended doses. Since no data are available to show the safety and efficacy in animals younger than 8 weeks, the use in animals under this age is contraindicated. As regards the urinary excretion of the active compound, it is also recommended to exclude animals with severe renal dysfunction from treatment with cefovecin in order to avoid potential adverse effects that may be related to accumulation of the substance.

CLINICAL STUDIES

Laboratory studies

Dose finding studies for skin and soft tissue infections in dogs and cats were performed using three models: 1) PK/PD-analysis, 2) demonstration of antibacterial activity of cefovecin in serum, dermal transudate and exudate *ex vivo* and 3) dose titration in a skin infection model in dogs.

PK/PD-analysis has already been addressed in this report (under 3. Safety, Pharmacokinetics). Concerning the *ex vivo* pharmacodynamic activity, it was shown that cefovecin is rapidly detectable in plasma, dermal transudate and exudate following a single injection of cefovecin at the recommended dosage of 8 mg/kg b.w. The results show that bacterial growth of a *Staphylococcus intermedius* field strain was inhibited in serum from 30 minutes to 14 days and in transudate from 4 hours to 21 days. In exudate inhibition of bacterial growth started at 4 hours post cefovecin administration up to the end of exudate collection, i.e. 72 hours. In serum, transudate and exudates, the mean reduction of bacterial counts exceeded 2.4 $\log_{10}$ cfu/ml from 30 minutes to 72, 2.5 $\log_{10}$ cfu/ml from 8 hours to 14 days and 2.75 $\log_{10}$ cfu/ml at 24, 48 and 72 hours post injection, respectively.

Dose titration in a skin infection model in dogs using *Staphylococcus aureus* as a dose-limiting challenge strain included single dosages of 4 mg/kg b.w., 8 mg/kg b.w. and 12 mg/kg b.w. which were compared to a placebo treatment with saline. Following infection of animals 2 days before treatment administration, efficacy assessment was performed 7 days post treatment. The animals were challenged a second time on day 7 with an efficacy assessment on day 14. Based on the number of infected inoculation sites on day 7, the dosage of 8 mg/kg b.w. was found to be the optimum dose.

Dose finding in cats was based on PK/PD-analysis, extrapolation of tissue cage concentration data from the dog and the results from a tissue cage study in cats.

The CVMP considered these data sufficient to support the claimed dosing schedule. It was concluded that the proposed treatment dose (8 mg/kg) and interval (14 days) would be efficacious in skin and soft tissue infections in dogs and cats.

No dose finding studies concerning urinary tract infections were provided in dogs and cats. Justification of the dose was based on PK/PD-analysis. The CVMP considered this approach sufficient and concluded that the proposed treatment dose of a single injection of 8 mg/kg b.w. would be efficacious in urinary tract infections in cats and dogs.

Field trials

Dogs - Skin and soft tissue infections

Three field trials have been presented for the evaluation of the efficacy and safety of Convenia in the treatment of skin and soft tissue infections, including pyoderma, wounds and abscesses in dogs. Cefovecin was administered according to the claimed dosing schedule, i.e. 8 mg/kg bodyweight with repetition of the treatment at 14 day intervals up to a further three times, if necessary.

All of these studies included a positive control group, in which animals were treated with an amoxicillin and clavulanic acid containing product, in accordance with the authorised dosage regimen.

Two of these trials had comparable study designs. Due to the correspondence in relevant parameters, a combined analysis of the data from both trials was considered justified. As the originally scheduled time point for clinical success assessment was judged inappropriate, a new success assessment 28 days after the start of the final treatment cycle was performed. A sufficient number of animals were suitable for this re-analysis. Evaluation of efficacy was based on the reduction of defined clinical signs from moderate or severe to mild or absent. A success rate above 90% shows efficacy of cefovecin. Most of the enrolled and successfully treated cases had *Staphylococcus intermedius* as the predominant pathogen. Cases associated with *E. coli*, ß-haemolytic *Streptococci* and *Pasteurella multocida* clearly showed a lower prevalence.

The third field trial had stricter inclusion criteria and a more stringent definition of clinical success than the two earlier studies. Evaluation of efficacy was based on the reduction of defined clinical signs from mild, moderate or severe to absent. The performance of Convenia was similar to the amoxicillin and clavulanic acid containing reference product.

Despite the fact that the field trials regarding the skin and soft tissue infections had some weaknesses, the CVMP concluded that Convenia is efficacious in the treatment of canine skin and soft tissue infections.

Dogs - Urinary tract infections (UTIs)

One field trial was provided for the evaluation of the efficacy and safety of cefovecin in the treatment of UTIs in dogs. Cefovecin was administered once subcutaneously at a dose of 8 mg/kg bodyweight. The trial included a positive control group treated with cefalexin in accordance with the authorised dosage regimen. Dogs were enrolled in veterinary practices in three countries in Europe and animals were allocated to treatment groups in a ratio of 1:1. Evaluation of efficacy was based on bacteriological cure as the primary clinical end point. Clinical cure was introduced as a secondary efficacy parameter. Although the results of this trial do support the claimed indications with respect to urinary tract infections associated with *E. coli* and *Proteus spp.*, a few shortcomings were noted with the study presentation.

A second field trial, performed in the USA, with a design similar to that of the EU study, was also reported. The results are only considered as supportive to those obtained from the European field trial.

The CVMP concluded that cefovecin, at the recommended dosage regimen is safe and efficacious in the treatment of urinary tract infections in dogs.

Cats - Skin and soft tissue infections

A non-inferiority multi-centre European field trial in four countries to evaluate the efficacy of cefovecin for the treatment of feline skin and soft tissue infections at the proposed dosage of 8 mg/kg has been presented. Cats presenting mainly with abscesses or wounds were treated with cefovecin. The bacterial pathogens proposed as indications were isolated from the lesions. The clinical success rate was 100%. The trial demonstrates the efficacy of cefovecin in the treatment of skin and soft tissue abscesses and wounds in cats related to *Pasteurella multocida*, *Prevotella oralis*, ß-haemolytic *Streptococci*, *Staphylococcus intermedius*, *Bacteroides spp*. and *Fusobacterium spp.*

Cats - Urinary tract infections

A non-inferiority European multi-centre field trial in three countries to evaluate the efficacy of cefovecin for the treatment of UTIs at the proposed dosage of 8 mg/kg was presented. The bacteriological cure rate was about 76 to 80% and similar to that achieved with the reference substance, cefalexin. The clinical cure rate was somewhat lower than that in the reference group. The number of cats suffering UTIs caused by *E. coli* was small in both the test and control groups and the study design was not considered ideal. Although the population available for efficacy assessment was small, based on the statistical results cefovecin was nevertheless demonstrated to be non-inferior concerning the elimination of *E. coli* compared to cefalexin (both mono-infections and mixed infections). Bacterial elimination was considered to be an appropriate therapeutic end point when using an antibacterial drug to treat a UTI. In the cat this is particularly true because lower urinary tract clinical signs correlate very poorly with the presence of bacteria, however, persistent bacterial lower UTIs can lead to ascending infections of the kidney.

On the basis of the satisfactory results, the indication "For the treatment of urinary tract infections associated with *Escherichia coli.*" was accepted by the Committee.

OVERALL CONCLUSION ON EFFICACY

Concerning skin and soft tissue infections, the data demonstrated that the proposed treatment dose (8 mg/kg) and interval (14 days) was efficacious. Concerning urinary tract infections, dose finding was based on PK/PD-analysis.

For dogs, the results of three field trials demonstrated the efficacy of cefovecin in the treatment of skin and soft tissue infections including pyoderma, wounds and abscesses associated with *Staphylococcus intermedius*, ß-haemolytic *Streptococci*, *Escherichia coli* and/or *Pasteurella multocida.* The results of the European field trial demonstrated the efficacy of Convenia in the treatment of urinary tract infections associated with *Escherichia coli* and/or *Proteus* spp. Further supportive evidence for this claim was received from another trial carried out in the USA.

In cats, the efficacy in the treatment of skin and soft tissue abscesses and wounds associated with *Pasteurella multocida, Fusobacterium spp., Bacteroides spp., Prevotella oralis,* ß-haemolytic *Streptococci* and/or *Staphylococcus intermedius* was demonstrated by the results of one field trial. The efficacy of Convenia in the treatment of urinary tract infections associated with *E. coli* was supported by sufficient data from one field trial.

5. BENEFIT RISK ASSESSMENT

Convenia contains cefovecin sodium, a third generation cephalosporin, and is indicated for use in dogs and cats for the treatment of skin, tissue and urinary tract infections. It is administered subcutaneously. The product is presented in a single pack size composed of one vial containing the freeze-dried active substance (cefovecin sodium), and a second vial containing the diluent.

In general the quality aspects of the product have been well documented. The active substance and finished product are manufactured and controlled in the appropriate manner, in compliance with current EU and VICH guidelines. Satisfactory information has been provided to demonstrate that the manufacture and control processes routinely and consistently generate a product of uniform quality.

The starting materials of animal origin used in the production of the final product have all been declared in compliance with the current regulatory texts related to the TSE Note for Guidance (EMEA/410/01-Rev.2) and Commission Directive 2001/82/EC as amended.

Cefovecin is of low acute oral and parenteral toxicity and is considered non-mutagenic and non-carcinogenic. From the scientific literature certain cephalosporins have been shown to exert adverse effects on male fertility in rats. Considering the long term activity of the substance and period of spermiogenesis in dogs and cats, appropriate restrictions for use have, therefore, been included in the product literature.

Cefovecin proved to be non-irritant to intact skin and has a minimal irritating effect on eyes. Like other cephalosporins cefovecin has a potential to cause hypersensitivity or allergic reactions following injection, inhalation, ingestion or skin contact. Under field conditions, while handling the product, accidental skin or eye contact may occur. Adequate precautionary statements are, therefore, included in the product literature.

The environmental risk assessment concluded that cefovecin in the recommended posology would have minimal impact on the environment when used in the form of the final product.

In vitro data were provided demonstrating the susceptibility of bacteria involved in dogs and cats diseases against cefovecin, i.e., *Staphylococcus intermedius*, β-haemolytic *Streptococci, Escherichia coli, Pasteurella multocida* and *Proteus* spp in dogs and *Pasteurella multocida, Bacteroides* spp., *Prevotella oralis*, β-haemolytic *Streptococci*, *Fusobacterium spp., Staphylococcus intermedius* and *Escherichia coli* in cats respectively.

The potential for development of resistance was shown to be low. As cefovecin is a third generation cephalosporin, appropriate prudent use statements are included in the product literature.

Cefovecin is well tolerated in young and adult dogs and cats. The use in dogs and cats of less than 8 weeks old was contraindicated as such young animals were not included in the studies. No adverse reactions to the product have been reported to date and this is reflected in the product literature.

The concurrent use of other substances that have a high degree of protein binding (e.g., furosemide, ketoconazole or non-steroidal anti-inflammatory drugs) may compete with cefovecin binding and so may cause adverse effects. An appropriate statement to this effect has, therefore, been included in the product literature.

Considering the long duration of activity of the product and the duration of a spermatogenetic cycle (8-9 weeks in cats and dogs), an appropriate statement has been included in the product literature "The safety of Convenia in dogs and cats has not been established during pregnancy and lactation. Treated animals should not be used for breeding for 12 weeks after the last administration.".

Preclinical data were considered sufficient to confirm the proposed treatment dose of 8 mg/kg bodyweight. The repeated treatment in skin diseases with a dosing interval of 14 days was also adequately supported by the data provided.

For dogs, the results of three field trials demonstrated the efficacy of cefovecin in the treatment of skin and soft tissue infections including pyoderma, wounds and abscesses, associated with *Staphylococcus intermedius*, ß-haemolytic *Streptococci*, *Escherichia coli* and/or *Pasteurella multocida*. Data from one pivotal and one supportive field trial have demonstrated efficacy in the treatment of urinary tract infections associated with *Escherichia coli* and/or *Proteus* spp in dogs.

For cats, the CVMP concluded that the efficacy in the treatment of skin and soft tissue abscesses and wounds associated with *Pasteurella multocida, Fusobacterium spp., Bacteroides spp., Prevotella oralis,* ß-haemolytic *Streptococci* and/or *Staphylococcus intermedius* was demonstrated by the results of one clinical trial. The efficacy in the treatment of urinary tract infections associated with *E. coli* was supported by sufficient data from one field trial.

Based on the original and supplementary data presented, the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the quality, safety and efficacy of Convenia were considered to be in accordance with the requirements of Directive 2001/82/EC as amended.

