SCIENTIFIC DISCUSSION

Invented name:	Ibaflin
Active substance/INN:	Ibafloxacin
Target species:	**Dogs** - 30mg-150mg-300mg-900mg tablets, 3% and 7.5% oral gel **Cats** - 3% oral gel
Therapeutic indication:	**Dogs-tablets** Dermal tissue infections (pyoderma – superficial and deep, wounds, abscesses) caused by susceptible strains of *Staphylococci*, *E. coli* and *Proteus mirabilis* Acute, uncomplicated urinary tract infections (acute) caused by susceptible strains of *Staphylococci*, *Proteus spp., Enterobacter spp., E. coli* and *Klebsiella spp.* Respiratory tract infections (upper tract) caused by susceptible strains of *Staphylococci*, *E. coli*, and *Klebsiella spp.* **Dogs – oral gel** Dermal infections (pyoderma – superficial and deep, wounds, abscesses) caused by susceptible pathogens such as *Staphylococcus spp., E. coli and Proteus mirabilis.* **Cats-oral gel** Dermal infections (soft tissue infections – wounds, abscesses) caused by susceptible pathogens such as *staphylococci, E. coli, Proteus spp.* and *Pasteurella spp.* Respiratory tract infections (upper or lower tract) caused by susceptible pathogens such as *Staphylococcus spp., E. coli, Klebsiella spp.* and *Pasteurella spp.*
Withdrawal period:	Not applicable
Pharmaceutical form:	Tablet Oral gel
ATCvet code:	QJ 01 MA 96
Pharmaco-therapeutic group:	Antibacterial quinolone
Marketing Authorisation Holder:	Intervet International B.V. Wim de Körverstraat 35 5831 AN Boxmeer The Netherlands

1. SUMMARY OF THE DOSSIER

Ibafloxacin, a fluorinated 4-quinolone, is a broad spectrum antibiotic with bactericidal action against Gram-positive and Gram-negative bacteria. Ibaflin is presented in the form of a tablet/oral gel containing a racemic mixture of S- and R-ibafloxacin. The antimicrobial activity of the racemate originates mainly from the S-enantiomer. The tablets are intended for once daily oral administration in dogs. Four different strengths are now available: a tablet containing 30 mg ibafloxacin, 150 mg ibafloxacin, 300 mg ibafloxacin and one containing 900 mg ibafloxacin.

Ibaflin tablets are intended for use in dogs for treatment of respiratory tract infections, urinary tract infections and dermal infections caused by ibafloxacin susceptible pathogens. The clinical dose is 15 mg of ibafloxacin/kg given orally once daily for up to 10 days, depending on the infection being treated. For cases of deep pyoderma, treatment may be continued for 21 days. It is, however, recommended in the SPC that, if in cases of deep pyoderma sufficient improvement is not seen after a treatment course of 21 days, the treatment is reconsidered.

An extension to Ibaflin tablets of two tablet strengths 30mg and 900mg, to the product that was first authorised for dogs (150mg and 300mg tablets) on 13 June 2000 was applied for and the extension granted on 23 February 2004. The extension concerns the addition of a small tablet (30 mg) and a tablet for large dogs (900 mg) with the same active substance.

The target species for all the tablet strengths are dogs. The SPC was in accordance with the previously approved SPC, with the exception of section 4.1 (Pharmacodynamic properties) where the Applicant now mentions *Pasteurella spp.* instead of strains of *Pasteurella spp.*

Given the increase in the higher strength tablet from 300mg to 900mg, it was recommended that an additional user safety warning should be included in the SPC and package insert. A warning was added for medical advice to be sought in the event of accidental ingestion, particularly by a child.

Ibaflin oral gel is an extension to Ibaflin tablets and two strengths were authorised; for cats (3%) and dogs (3% and 7.5%) on 20 March 2003.

Ibaflin oral gel is presented in the form of an oral gel, using Carbopol 974PNF as gelling agent and containing ibafloxacin as active substance. Two strengths of Ibaflin oral gel are available: Ibaflin 3% gel in a 15-ml polyethylene injector and Ibaflin 7.5% gel in a 30-ml polyethylene injector, containing 30 mg/g and 75 mg/g of ibafloxacin, respectively.

The most common side effects seen with Ibaflin are diarrhoea, soft faeces, vomiting, dullness and anorexia. These reactions are generally of a transitory nature and are reversible when the treatment is stopped.

2. QUALITY ASSESSMENT

Composition

150mg and 300mg tablets

	Ibaflin 150 mg	Ibaflin 300 mg
Active substance:		
Ibafloxacin	150 mg	300 mg
Excipients:	450 mg	900 mg
Total weight	600 mg	1200 mg
Tablet diameter	12.8 mm	16.2 mm

The excipients in Ibaflin tablets are all standard tablet excipients which are, except for yeast, all subject to European Pharmacopoeia monographs.

30mg and 900mg tablets

The product contains ibafloxacin 30 mg or 900 mg in compliance with an internal monograph and all other excipients comply with the Ph.Eur. with the exception of yeast which complies with an internal monograph.

Drawings of both Ibaflin 30 mg and 900 mg off-white single break bar tablets have been submitted.

3% and 7.5% Oral Gel

	Ibaflin3% Gel	Ibaflin 7.5% Gel
Active substance:		
Ibafloxacin	30 mg	75 mg
Excipients:	1.25 mg	1.25 mg
Methyl parahydroxybenzoate		
Total weight	1000 mg	1000 mg

Container

150mg and 300mg tablets
Ibaflin 150 mg and 300 mg tablets are packaged in polyvinylchloride (PVC) blisters and PVC/polyvinylidenechloride laminate blisters sealed with aluminium foil: 10 tablets per blister strip for Ibaflin 150 mg and 5 tablets per blister strip for Ibaflin 300 mg. The blister strips are packed in multi-pack cardboard boxes of 2 or 10 blister strips per box (20 or 100 tablets per box for the 150 mg tablets, and 16 or 80 tablets per box for the 300 mg tablets.). Stability tests showed that the tablets are stable in both kinds of blisters.

Specifications are included for the two types of blister pack films, the aluminium foil, the primer and the heat-seal lacquer. Certificates of analysis, including IR spectra of the blister films and a safety data sheet for the heat-seal lacquer, have also been provided.

30mg and 900mg tablets
Both Ibaflin 30 mg and 900 mg tablets are dispensed in PVC/Alu (250 µm/20 µm).
- Ibaflin 30 mg: 20 tablets per blister; 1 or 5 blisters per cardboard box.
- Ibaflin 900 mg: 5 tablets per blister; 1 or 5 or 10 blisters per cardboard box.

Representative drawings of the blisters have been submitted.

The supplier specifications of the primary packaging materials, PVC 250 µm, Alu 20 µm have been presented. For both packaging materials the Applicant applies specifications for the appearance, flatness, clarity, contamination, rigidity, damage, thickness and identity. Certificates of analysis are presented and the materials fulfil the requirements.

3% and 7.5% Oral Gel
The container is a white adjustable multidose syringe consisting of HDPE (barrel, plunger, ring) and LDPE (cap, seal). Ibaflin 3% gel is filled into variable-dose (0.5-ml steps) 15-ml injectors (yellow cap) and Ibaflin 7.5% gel into variable-dose (1-ml steps) 30-ml injectors (green cap).

All immediate packaging materials (HDPE and LDPE) conform to the applicable regulations of the Food and Drug Administration for use in the manufacture of articles intended for contact in food. The plastics used are included in the list of approved plastics given in the annex of Directive 90/128/EEC. Furthermore, stability data show that the gel in its final packaging remains stable when stored at 25°C/60%RH for 36-month storage stability. Therefore, the immediate packaging materials can be safely used in the manufacture of the articles intended to come into contact with foodstuffs.

The syringes are tested on a regular basis for appearance (white adjustable dose syringe), dimensions (submitted) and identification of the plastic materials (IR). Specifications of the HDPE and LDPE parts of both injectors are presented, together with certificates of analysis and drawings of each syringe. The FTIR spectra make clearly distinction between HDPE and LDPE. The DSC analyses substantiate, via melting point and the crystallisation temperature, the LDPE character of the seal and the HDPE character of the cylinder.

Clinical trial formulations

For the clinical trials, tablets of the above composition were used. Batch results justify the proposed specifications.

30mg and 900mg tablets
Clinical trials have been performed with Ibaflin 150 mg and 300 mg tablets which have the same relative composition as these tablets.

3% and 7.5% Oral Gel
The clinical trials in cats and dogs have been performed with the same composition as mentioned above but using Carbopol 934PNF instead of Carbopol 974PNF. At that stage, no European Pharmacopoeia (Ph.Eur) monograph for carbomers was available. This monograph came into force in 1999. Both carbomers are equivalent (same apparent viscosity) but differ in the content of residual benzene. Carbopol 934PNF can contain benzene up to a level of 100 ppm and is therefore not in compliance with the current Ph.Eur. monograph for carbomers with respect to the requirement for residual benzene (2 ppm). The Carbopol 974PNF contains not more than 2 ppm benzene and is in compliance with the Ph.Eur. Carbopol 934PNF has been replaced by this carbomer.

Development Pharmaceutics

Intervet took over the development of the formulation of Ibaflin tablets in 1992 from 3M Beecham. Additional studies were performed: pharmaceutical studies (e.g. tablet divisibility, stability tests) as well as animal studies.

The tablets contain micronised ibafloxacin as the active compound. Ibafloxacin can occur in three different polymorphs with polymorphic form I predominating. One batch of an 80/20 mixture of polymorphic forms III and I was prepared for experimental purposes. Tablets containing ibafloxacin in different polymorphic ratios were then produced and their *in vitro* dissolution characteristics investigated. The different polymorphic forms showed similar dissolution characteristics.

Ibafloxacin dissolves rapidly from both strength tablets and dissolution curves for both tablet strengths are similar. The *in vitro* dissolution was tested according to the Ph.Eur. 2.9.3. A limit of ≥ 75% after 45 minutes was applied. A description of the method was provided.

The divisibility of the (double scored) tablets was tested to investigate dose accuracy for both Ibaflin 150 mg and Ibaflin 300 mg at batch release as well as at the end of the shelf life. The conclusion of the CVMP was that it is not practical to administer ¼ tablets, and therefore the products were contra-indicated for use in dogs of under 3 kg.

30mg and 900mg tablets
Two additional strengths (30 mg and 900 mg) have been added to the original range of tablet strengths (150 mg and 300 mg). Ibaflin 30 mg tablets are indicated for use in lower bodyweight dogs and Ibaflin 900 mg tablets for higher bodyweight dogs.

The relative composition and manufacturing process of all tablet strengths are identical. The information on the composition has already been evaluated in the marketing authorisation process of the Ibaflin 150mg and 300 mg tablets.

Furthermore, the *in-vitro* dissolution profile of the four tablet strengths have been compared. Three batches were tested for all tablet strengths; each batch was tested with six tablets (half tablets in case of 900 mg tablets). Justification for using half 900 mg tablets was requested from the Applicant and the Committee agreed with the justification provided.

The *in-vitro* dissolution method described in the Ph.Eur. 3rd Ed 1997 (2.9.3 (paddle apparatus)) was used. This method is identical to the method described in the current Ph.Eur. Samples were taken after predetermined intervals. The HPLC assay method used for the quality control of tablets was used.

This *in-vitro* dissolution method has already been evaluated in the authorisation of the Ibaflin 150 mg and 300 mg tablets. The data presented show that ibafloxacin is quickly released (≥ 90% within 15 minutes for all strengths) and the profiles of all strengths are comparable.

Both 30 mg and 900 mg tablets contain a single break bar. The divisibility of the tablets was tested to show dose accuracy. Tablets were divided by hand into two parts and these parts were weighed. The subdivided parts comply with the current Ph.Eur. (2.9.5) test for Uniformity of mass of single-dose preparations.

PVC/Alu (250 µm/20 µm) blisters are considered as suitable packaging material for the tablets and they are already used for the 150 mg and 300 mg tablets. During the stability tests no incompatabilities with the packaging materials in contact with the product were observed.

3% and 7.5% Oral Gel
The aim was to obtain a stable suspension for oral administration containing 3% and 7.5% ibafloxacin, easily palatable and with an adequate viscosity for the use in practice. The proposed formulations contain only well known excipients in normal concentrations. Besides, the formulations contain neither materials of animal origin nor are materials of animal origin used in the manufacturing. Therefore, the formulations can be regarded as safe with regard to any risk of transmission of TSE.

Several gelling agents have been investigated during the development of the ibafloxacin gel formulations, where viscosity was the most relevant parameter: high enough to allow prevention of sedimentation of ibafloxacin in the gel and low enough for an easy filling and expulsion of the gel from the injector. Formulations containing 2.5% carbopol appeared to have a suitable viscosity and were palatable in both dogs and cats, whereas formulations with other kinds of gelling agents were not viscous enough, difficult to produce or contained air bubbles. Therefore carbopol in a concentration of 2.5% was chosen as the gelling agent for the present gel formulation. At the start of the development of the ibafloxacin gel carbopol 934PNF was used and for reasons as mentioned above replaced by carbopol 974PNF. For the gel a pH of 6 was chosen, since this pH is well accepted for animals from a palatability standpoint.

Preservative efficacy
As the product is intended for multidose use, a preservative efficacy test according to the requirements of the Ph.Eur. for ibafloxacin gel formulations was developed and validated. During development of the method, gel formulations containing 3% ibafloxacin and no preservative have been tested and results show that ibafloxacin in the gel formulations did not inhibit the growth of *A. niger* and *C. albicans* and so the requirements of the Ph.Eur. concerning *A. niger* and *C. albicans* were not met for these formulations. Therefore a number of preservatives, which can potentially be used in oral preparations and are active at the proposed pH, have been investigated. Based on these studies, methyl parahydroxybenzoate was chosen as preservative.

A further preservative efficacy test with *P. aeruginosa*, *S. aureus*, *E. coli* according to the requirements of the Ph.Eur. for Ibafloxacin gel formulations was developed and validated. As ibafloxacin inhibits the growth of viable bacteria, it is removed from the inoculum to allow determination of the colony counts in the preservative efficacy test. The proposed preservative efficacy test is appropriate to detect a three ^{10}log reduction for *S. aureus*, *P. aeruginosa* and *E. coli* in Ibaflin oral gels formulations. Other preservative efficacy tests were performed with 3% ibafloxacin gels. In order to allow for some degradation of the preservative during shelf-life without negatively affecting the preservative efficacy of the preparation, a concentration of 0.225% was chosen.

The preservative efficacy test method with bacteria was found to be unsuitable for the 7.5% gel formulation. Ibafloxacin could not be removed sufficiently from the gel formulation after inoculation. The Committee considered that a higher concentration of ibafloxacin could only have a beneficial effect on the preservative efficacy for bacteria, and that it is very unlikely that the preservative effect of the 7.5% gel formulation is less than the 3% formulation.

A 5-month old batch of 3% ibafloxacin gel as well as a 19-month old batch 7.5% gel have been tested for preservative efficacy at the end of an 8-week in-use stability trial. Two formulations containing 90% of the nominal amount of methyl parahydroxybenzoate at pH 6.5 (upper limit), were also tested for preservative efficacy. All the preparations tested met the Ph.Eur. requirements and therefore justify the appropriate content of preservative.

Palatability
Palatability studies with gels containing various flavours or no flavour were performed in dogs and cats. It was shown that the gel was readily accepted by dogs and cats. Therefore, no flavour was included in the formulation.

Since limits for polymorphism and particle size have been established and no aggregation is observed in production, the influence in the dissolution rate can be considered to be less relevant.

Consistency of the dosing system
The consistency of the dosing system of the 15-ml and 30-ml injectors was demonstrated. An additional study was performed to demonstrate the accuracy of 2 ml increments for the 30 ml syringe. The results regarding the 1 ml, 2ml and 3 ml doses match the requirements of Ph.Eur. 2.9.27 *Uniformity of mass of delivered doses from multidose containers*, whereas the results regarding the 0.5-ml doses nearly match these requirements.

The 0.5 ml dosing of Ibaflin 3% 15 ml injectors is sufficient to treat 1 kg cats or dogs. One ml dosing of Ibaflin 7.5% 30 ml injectors is sufficient to treat 5 kg dogs or cats. Considering the size of syringe, duration of treatment and bodyweight of cats, it was concluded that the 7.5% gel formulation should only be used in dogs.

Furthermore, the accuracy of the dose delivered depends on the accuracy of the printed scale. The supplier has calculated the scale lengths on both 15 ml and 30 ml plungers so that the expected dose will be dispensed. There is no risk to have a variation on the printed scale, and consequently no risk of variation in the accuracy of the doses delivered.

Method of Manufacture

The tablets are prepared using a conventional wet-granulation method. A flow diagram of the process was provided. The batch size can vary up from 10 to 50 kg. Descriptions of the methods used during manufacturing and in process controls were submitted and were considered acceptable.

30mg and 900mg tablets
The batch size can vary from 10 kg to 300 kg and is the same as those already approved for the Ibaflin 150 mg and 300 mg tablets. The tablets are prepared using a conventional wet-granulation method.

The manufacturing process was well described in the dossier. The manufacturing steps are identical for all four tablet strengths. The tabletting step is specific for each tablet strength.

The in-process control of the intermediate granules, compression mix, during adjustment of the tablet press and during tabletting were all described in the dossier.

The methods used with the in-process controls include moisture content, ibafloxacin content, average tablet weight, hardness, disintegration time, friability. The methods are the same as used for batch release.

3% and 7.5% Oral Gel
The master formula is calculated for 100-kg batches. The master formula is in accordance with the composition of the product as mentioned under II.A. The batch size can vary from 20 kg to 1250 kg.

The applicant committed to submit the process validation of the first three consecutive production batches of maximally 1250 kg when available. The excipients are dissolved in water for injection under heating. Thereafter, the gelling agent and ibafloxacin are added. The pH is adjusted and the gel is filled into injectors. A flow diagram of the process was provided. Descriptions of the methods used during manufacturing and in-process controls were submitted and considered acceptable.

Validation of the process

Data from the production process at Intervet Labs Ltd, Dublin, Ireland, the registered production site, describes the validation of three ibafloxacin compression mix batches (20, 19 and 31 kg), two 12 kg batches of Ibaflin 150 mg and two 19 kg batches of Ibaflin 300 mg. During the granulating process, moisture content, particle size and ibafloxacin content were assessed at appropriate intervals. During the tabletting stage several relevant parameters (moisture content, tablet weight, ibafloxacin content, hardness, disintegration and *in vitro* dissolution) were also assessed. The production process yields a consistent product that meets all in process and release requirements. The final tablets all conformed to the release requirements. The powder mixtures and granulates were also shown to be homogeneous. For the 30mg tablets and 900mg tablets only the tabletting process had to be validated, this is regarded as acceptable.

In accordance with the Note for Guidance on "Investigation of chiral active substances" data, supported by validated test procedures, are provided which demonstrate there is no unacceptable change in stereochemical purity or ratio of the active substance during the manufacturing process of the finished product.

Satisfactory process validation data and a validation protocol were presented for all tablet strengths.

For batch release, the following parameters were assessed: appearance, average tablet weight, uniformity of mass, disintegration time, *in-vitro* dissolution profile, microbiological quality, ibafloxacin content and impurities, uniformity of content and enantiomeric ratio.

The validation of the tabletting was performed at Intervet Laboratories Ireland. Subsequently, Ibaflin production was moved to Vienna, where the same tablet press will be used as the one used during

validation of the tabletting. Therefore, this validation is also considered to be applicable to the Vienna plant.

3% and 7.5% Oral Gel
The production process has been validated in two separate studies. The in-process controls as well as obtained gel control data demonstrate that the production is well controlled and yields a consistent product. No differences were observed between the products prepared with the two different qualities of carbopol. The validation data demonstrate that the in-process controls are within limits and the gels produced fully comply with the release requirements. From the validation data it can be concluded that the production process is well under control resulting in a product of consistent quality.

Control of Starting Materials

Active substance

The active substance is not described in a pharmacopoeia so a specification monograph has been developed detaining specification. The Applicant refers for data concerning the active substance ibafloxacin to the Drug Master File (DMF) of Chemie Uetikon. A letter of access was submitted and the Applicant's part is included in the dossier. The active substance manufacturer's (DMF holder's) specification have been adapted to conform with the specifications used by the applicant.

As ibafloxacin is a racemic mixture of R- and S-ibafloxacin the specification, in accordance with the Note for Guidance on "Investigation of chiral active substances", includes a test and limits for optical rotation. The use of the racemate is justified.

In accordance with the CVMP/VICH guideline on impurities in new drug substances a limit for the total amount of impurities is included.

Results of batch analyses (including impurity profiles) of ibafloxacin used in the clinical and toxicological trials justify the proposed specification.

The methods of the DMF holder are also used by the Applicant with the exception of the methods for the identity and determination of ibafloxacin and related compounds. For this, the same method is used as for the determination of ibafloxacin in the finished tablets. All the methods are described and appropriately validated.

For both the named impurities, defluoro ibafloxacin and ibafloxacin ethyl ester, HPLC methods are described in the DMF. Both methods are fully validated according to the CVMP/VICH guideline and representative chromatograms are provided. For ibafloxacin ethyl ester also a TLC-method is described. This method is also fully validated according to the CVMP/VICH guideline.

For the determination of residual dimethylformamide a GC-method is described. Validation data is provided and is considered satisfactory.

The ibafloxacin assay method is identical to the method used for detection of defluoro ibafloxacin. The method is fully validated and a representative chromatogram is provided.

Synthesis:
Full details of the synthesis of the active substance are provided. Details of the batch size, specifications and control methods for the starting materials, reagents, catalysts and solvents are provided. Full details are also provided for the synthesis of the starting material, including details of the raw materials and in-process controls, and thus reassurance is provided that there is no carry over of impurities from the starting materials into the ibafloxacin final product.

Specifications and control methods are also provided for the intermediates. Impurities and residual solvents are described, and the limits applied in the specification have been justified by batch analyses data. During the synthesis methanol and xylene are used, which are class two solvents according to the

Note for Guidance on "Residual solvents". As their absence in the pure ibafloxacin was demonstrated, it is not necessary for these solvents to be limited in the ibafloxacin specification.

During the purification process ethanol, water and dimethylformamide are used. The proposed limit of 880 ppm for dimethylformamide is acceptable and in accordance with the Note for Guidance on "Residual Solvents". Residual water and ethanol are covered by the test for loss on drying.

For determination of residual palladium the Applicant relies on the test on heavy metals. A maximum limit of 1 ppm is considered acceptable, based on a daily intake of 10 g and a permitted daily exposure of 0.01 mg/day. A routine test for palladium is not included but the active substance manufacturer is currently developing a method for the determination of palladium in ibafloxacin. Details of the method, and the results from the analysis of three batches will be reported when available.

In-process controls:
During the synthesis the yield of the intermediates and the residual amount of the starting material is measured. Besides the polymorphic form, the impurity ibafloxacin ethyl ester and the loss on drying are controlled.

Structural characterisation of ibafloxacin is provided along with a detailed physico-chemical characterisation. Ibafloxacin has a chiral center at C-5, giving rise to the existence of two enantiomers S- and R-ibafloxacin). The material is racemic. The R/S enantiomeric ratio is about 0.99.

Batch data provided are in compliance with the proposed specification and demonstrate that material of the proposed specification is routinely produced.

Ibafloxacin is stable under long term testing and accelerated conditions. No degradation products have been identified. No change in enantiomeric ratio was observed. The enantiomeric ratio will continue to be determined until further experience is obtained.

The re-test period is changed from 2 years to 5 years following the submission of additional data for all ibafloxacin products during the application for the 30mg/900mg tablets and by way of a variation for those products already authorised.

Excipients

The excipients for which there is a Ph.Eur. monograph comply with the requirements described and certificates of analysis which demonstrate compliance with their respective monographs, are provided.

Yeast used for the production of the tablets is not described in any pharmacopoeia so an internal monograph was developed. Yeast is produced by Gist-brocades, Delft, The Netherlands. The Engevita Standard powder dried inactive baker's yeast is used. It is a savoury tested inactive specially selected primary grown yeast (*Saccharomyces cerevisiae*) and information on the general and chemical characteristics, production process, safety statements, release parameters, validation of production, methods of analysis and stability data are all provided. A statement is given where the supplier Gist Brocades confirms that the yeast does not contain materials from meat or animal origin. The proposed specification includes well defined limits, including those for microbial purity (total viable aerobic count plus determinations of specified micro-organisms), loss on drying and total ash and is adequate to control the quality of this excipient. A certificate of analysis is provided which demonstrates conformity with the specification.

The excipients used in the 30mg/900mg tablets are identical to the excipients used in the already approved Ibaflin tablets. The information on these constituents was therefore not re-assessed.

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

The raw materials of Ibaflin tablets/oral gels are from non-animal origin: the excipients are well known and are not from animal origin. Also the active ibafloxacin is produced by chemical synthesis and not from animal origin. The finished product complies with the current TSE-Risk assessment according to Commission Directive 1999/104/EC and Note for Guidance EMEA/410/01-Rev.1.

Control Tests on the Finished Product

Specifications and details of routine tests for control of the finished product including appearance, identity, assay, purity, related substances, microbiological tests, content uniformity (including half tablets), uniformity of mass, enantioneric ratio, disintegration and dissolution were provided. All tests were suitably validated.

Related substance limits are in line with VICH-CVMP guidelines with respect to reporting levels. Individual degradation products are limited to below the identification and qualification limits.

Certificates of analysis for all batch analysis data, from the dosage form manufacturing site, have been provided and were acceptable. The release specifications are considered acceptable.

3% and 7.5% Oral Gel
Specifications and details of routine tests for control of the oral gel finished product including appearance, identity, homogeneity, assay, purity, related substances, microbiological tests, content uniformity, pH, syringeability, dose accuracy and viscosity were provided. All tests were suitably validated.

The specifications for the viscosity of the gels are expressed with different rotation speed, because the viscosity of Ibaflin 7.5% gel is slightly higher than the viscosity of Ibaflin 3% gel, due to the higher content of ibafloxacin, and therefore the lower amount of water for injection in the formulation.

The release specifications are considered acceptable. According to the VICH Guideline *Impurities in new veterinary products* the specifications regarding the related substances of ibafloxacin do not need to be qualified.

The HPLC method for the quantitative determination ibafloxacin and its related compounds has been sufficiently described and is fully validated. The HPTLC method for the identification of ibafloxacin has been sufficiently described. The method has been validated for ruggedness (regarding small differences in eluent) and limit of detection (0.2% of the theoretical concentration). The HPLC method for the quantitative determination of methyl parahydroxybenzoate and its degradation product parahydroxybenzoic acid has been sufficiently described and is fully validated. The method is considered selective as none of the components of the (stressed) gel base or ibafloxacin and its related compounds, interfere with the peak of methyl parahydroxybenzoate and its degradation product.

Batch analyses

Certificates of analysis for all batch analysis data, from the dosage form manufacturing site, have been provided and were acceptable. The analysis results show that all batches fully comply with the release requirements.

Certificates of analysis of three consecutive full-scale batches for each tablet strength will be submitted in due time (post-approval).

Stability tests on the finished product

Several long term and accelerated stability studies have been conducted. The influence of daylight on Ibaflin 150 mg packaged in both blister types was reported. These studies show that daylight has no influence on the stability of tablets stored at ambient temperature in either packaging.

In addition to tablet hardness, dissolution and enantiomeric ratio were monitored for the stability study. Further data will be reported as further experience is gained.

During storage at 40°C/75% RH the *appearance* changed after 6 months from slightly beige to speckled and does not meet the prescribed requirement. At 25°C no change of appearance appears. The *tablet weight* and *moisture content* of the tablet slightly increase at both storage conditions but are still within the specifications. Tablet hardness decreased significantly after storage at 40°C but not at 25°C.
The *disintegration* time increased and the *dissolution* decreased at 40°C and is below the specification after 9 months. At 25°C the disintegration shows some variations but still comply with the proposed limit. The dissolution did not alter significantly at 25°C.
No change is observed in the content of ibafloxacin and related substances during the stability studies performed at both temperatures. The enantiomeric ratio did not change during the stability study performed over 24 months storage at 25°C/60% RH and 6 months at 40°C/75% RH.

No significant changes of the tested parameters occur during 3 months storage at 4°C.

The stability profiles of Ibaflin 150/300 mg packed in the two different blisters (PVC and PVC/PVDC) are similar. Therefore the stability results for the PVC blisters can be extrapolated to PVC/PVDC blisters and vice versa. It can be concluded that Ibaflin tablets are stable for 24 months at 25°C/60% RH in both the PVC and PVC/PVDC blisters.

Based on the submitted results the claimed shelf-life for the finished product of 24 months could be granted. This was subsequently increased to 48 months on submission of additional stability data by variation.

30 mg and 900mg tablets
The product specifications and routine tests for shelf-life were provided. The Applicant agreed to retain the shelf-life limits for enantiomeric ratio, microbiological quality, hardness and dissolution in the FPS until stability data to cover the 3 year shelf-life are available.

All batches of both 30 mg and 900 mg tablets stored for 6 months at 25°C/60%RH and 40°C/75%RH showed no significant changes in the organoleptic, physical or chemical characteristics. All parameters stayed well within limits. Only regarding moisture content and hardness, a slight tendency to increase and respectively decrease is noticed.

New data submitted in response to a question raised by the Committee show that the product is stable for at least 18 months when stored at 25°C/60%RH. Based on the submitted results the claimed shelf-life for the finished product of 36 months could be granted.

However, updated stability studies (three consecutive full-scale batches) were requested to support the 3 year shelf-life post-approval. The results should also monitor the enantiomeric ratio (at 24 and 36 months) of ibafloxacin, hardness and dissolution and the microbiological quality.

3% and 7.5% Oral Gel
Degradation products of well established preservatives, such as methyl parahydroxybenzoate, are normally not included in the list of specifications. The applicant has sufficiently justified not to include a limit for parahydroxybenzoic acid in the shelf-life specifications. The control methods are the same as for release of the finished product.

All batches of 3% and 7.5% gel stored at 4°C, 25°C/60%RH and 40°C/75%RH up to 36 months showed no changes in the organoleptic, physical or chemical characteristics, except for content of methyl parahydroxybenzoate and its degradation product parahydroxybenzoic acid. The decrease in content of methyl parahydroxybenzoate and the increase in content of parahydroxybenzoic acid are temperature depending: at 4°C hardly any changes could be observed, at 25°C/60%RH the content of methyl parahydroxybenzoate decreased only slightly but stayed well within limits, and at 40°C/75%RH the content of methyl parahydroxybenzoate was beyond the specific limits after 6 and up to 12 months. At all temperatures a more or less corresponding increase in the content of parahydroxybenzoic acid was observed.

From the stability studies it can be concluded that Ibaflin 3% and 7.5% gels remain stable at 4°C and 25°C/60%RH for 36 months. Therefore the proposed shelf-life for both gels of 36 months when stored below 25°C can be granted. Stability data over 36 months of three consecutive full-scale batches of maximally 1250 kg should be submitted in due time (post-approval).

In-use Stability Tests

Concerns were raised with regard to the acceptability of an in-use expiry on the grounds that a syringe should only be used to treat a single animal and should be disposed of after the course of treatment (≤ 21 days). The applicant proposed to leave the 8 weeks in-use expiry period in because otherwise owners would get the impression that they cannot use the product anymore after first dosing. The Committee concluded that an in-use expiry period was considered acceptable provided the following warning is included in the SPC: 'In order to avoid any cross contamination, the same syringe should not be used for different animals. Once a syringe is opened it should only be used to continue the treatment course in the same animal.'

Degradation at syringe tip

Relevant data of stability batches after 12 and 24 months storage at 25°C/60%RH and 40°C/75%RH were provided. These data show no difference between the three parts of the syringe, which confirm neither preferential degradation nor segregation of the active substance within the syringe during shelf life. The syringes concerned were stored horizontally. Although segregation would have been more apparent from the assay results after vertical storage, the similar assay results per syringe give no indication of segregation. Furthermore, segregation is indirectly controlled by appearance, homogeneity and viscosity and these parameters did also not change in both gels stored during the stability trial at 4°C, 25°C/60%RH and 40°C/75%RH (up to 36 months). Therefore, preferential degradation of the product at the syringe tip or segregation of the active substance within the syringe can be excluded.

Overall Conclusion on Part 2

The manufacture of the product is adequately described, validated and controlled. Methods and specifications for the active substance and excipients are acceptable. The production process has been adequately described and the control tests and specifications for finished product are adequately drawn up. The proposed shelf life of 4 years (150mg/300mg tablets) 3 years (30mg /900mg and oral gels) for the finished product can be considered acceptable. The oral gels have an in-use shelf-life of 8 weeks supported by data.

3. SAFETY ASSESSMENT

Pharmacodynamics

Ibafloxacin is a tricyclic tetrahydroquinoline derivative belonging to the group of fluorinated 4-quinolones. It is a broad spectrum antibacterial chemotherapeutic with bactericidal action against Gram-positive and Gram-negative bacteria. The mechanism of action of quinolones is the inhibition of the enzyme DNA-gyrase, an essential enzyme which maintains superhelical twists in bacterial DNA molecules.

Studies show that ibafloxacin concentrations ranging from 0.032 to 0.5 µg/ml exert an antibacterial activity against *E. coli, Staphylococci spp., Proteus mirabilis* and *Salmonella*. For *Bordetella* and *Pseudomonas*, somewhat higher concentrations are needed, i.e. 2-8 µg/ml. The metabolites 7- and 8-hydroxy-ibafloxacin also have antibacterial activity but the potency is much less than that of ibafloxacin itself (factor 4 to 10 fold less). Ibafloxacin has bactericidal activity at concentrations at or just above the growth inhibitory concentration. It also exhibits a post-antibiotic effect against Gram-positive and Gram-negative bacteria. Ibafloxacin is a racemic mixture containing equal proportions of two enantiomers (R- and S-ibafloxacin). The S-enantiomer has a much stronger antibacterial activity than the R-enantiomer (factor of up to 2000 fold). No studies were performed in relation to any potential secondary pharmacological effects of ibafloxacin.

Pharmacokinetics

This section is covered in Part 4 Pre-clinical.

Single dose toxicity

Acute toxicity studies, including lethal dose determinations, after single oral (mice) and intraperitoneal (rats, mice) administration of ibafloxacin were performed. After oral administration in mice at doses up to 5000 mg/kg no mortality, abnormal behaviour and no visible lesions after necropsy were observed. Thus, the oral LD_{50} is above 5000 mg/kg. After intraperitoneal administration, an LD_{50} of 1840 mg/kg was determined in mice and of 1010 mg/kg in rats. Animals showed hypoactivity (mice and rats) and lethargy and prostration (rats) during the 14 day observation period. Necropsy revealed no visible lesions in surviving animals. Animals that died showed haemorrhage of the gastrointestinal tract.

A pilot study for a repeated dose toxicity study in dogs was performed. In this study, ibafloxacin was administered orally to dogs in single doses of 400 to 1600 mg/kg. No mortalities were observed. In the 400 and 800 mg/kg dose groups (only 1 dog per group) no treatment related clinical signs were observed. At dose levels of 1000 mg/kg and higher, emesis was noted.

Repeated dose toxicity

The studies indicate that with an increase of dosages growth and body weight (BW) were reduced. A low palatability of medicated feed could have increased the effect. Dosages of 450 and 900 mg ibafloxacin/kg produced arthrotoxicity, mainly in male rats.

Dosages ≥195 mg/kg tended to reduce organ weight and change haematolgy parameters (lower RBC, total protein and leucocyte count). However, an increase in weights of liver and adrenals was observed in female rats. Effects were transitory and disappeared after medication was ended, except for the reduced globulin level.

In studies using dogs, dosages up to 800 mg ibafloxacin/kg for 10 days produced vomiting, pale faeces, gastro-intestinal irritation and a reduced feed intake. The frequency of symptoms increased with an increase of dosage. At dosages of 100 and 200 mg ibafloxacin/kg (56 days) pale faeces and a reduced level of total serum protein were observed.

Dosages of 200 and 400 mg/kg (for 4 weeks) reduced feed intake. At 400 mg/kg leucocyte count was reduced and blood cholesterol level was increased. Reduction of feed intake / growth and globulin level occurred at dosages of 100 and 200 mg/kg (for 26 weeks) and a reduction in erythrocyte count was observed at 200 mg/kg.

Arthrotoxicity was observed in dogs, 3 months of age, at dosages of 60 mg/kg for 14 days and 15 mg/kg for 28 days. Arthrotoxicity appeared to be present in 12-13 weeks old dogs at dosages of 20 mg/kg and more when given for 28 days. Dosages of 10 and 15 mg/kg (90 days) produced alopecia, erythema and thickening of the abdominal skin.

A number of oral repeated dose toxicity studies have been performed with ibafloxacin in the Sprague-Dawley rat. Rats used were 5 weeks of age, except for one study in which young rats of 3 weeks of age were used. It was observed that ibafloxacin has a low toxicological profile. Only at very high dosages, toxic effects such as bodyweight reduction and food intake decrease, were observed, deaths were also recorded at the highest doses used. Alopecia was the most common clinical finding. The overall No Observed Adverse Effect Level (NOAEL) can be considered to be in the region of 75 mg/kg/day. One study showed cases of alopecia, hyperactivity and hypersensitivity at this level; however, these findings were reversible.

The specific arthrogenic potential of ibafloxacin was determined in immature rats in comparison with other quinolones following oral administration at 112.5, 225, 450 and 900 mg/kg/day over 2 weeks. Histopathology evaluation showed articular cartilage lesions associated with the humerus and femur at the 2 highest dose levels; these findings were not seen following a 3 week recovery period nor at 225 mg/kg/day and below. Findings with nalidixic acid (a first generation quinolone) were more marked than with ibafloxacin and there were no findings with ciprofloxacin (a third generation 4-quinolone). Overall, the no effect level of ibafloxacin for arthropathy was considered to be 225 mg/kg/day in the young rat.

The repeated dose toxicity of ibafloxacin after oral administration has also been investigated in the target animal, the dog. Beagle dogs used were 5-18 months of age, except for two studies in which immature dogs of 3 months of age were used. Ibafloxacin has a low toxicological profile in dogs. Only at high dosages, toxic effects such as nausea, body weight reduction and food intake decrease were noted along with an inconsistent pattern of pale faeces and effects on erythrocyte/leucocyte and blood protein values. Based on these findings, the NOAEL in dogs of 5 months and older is above 50 mg/kg/day. In studies with younger dogs of 3 months of age, the NOAEL can be considered to be in the region of 10 mg/kg/day based on infrequent clinical signs (a maximum of 2/4 dogs and usually in one sex only) of gait abnormalities and alopecia/erythema/skin thickening of the ventral surface. The latter finding may even be related to impetigo in the young dogs used.

The arthrogenic potential of ibafloxacin was examined in 3 studies with immature dogs. In the most recent, 90 day study, only minor isolated findings in the joints were observed in the 15 mg/kg/day group (but not at 10 and 5 mg/kg/day) and were considered to be of a nature usually seen and not to be signs of toxicity. In an older arthrotoxicity study, clinical signs of arthrotoxicity were reported in the 15 mg/kg/day dose group when ibafloxacin was given for a period of 28 days but not when given for a period of 14 days. Therefore, it cannot be fully excluded that the observed minor effects in the joints in the 90 day study are not treatment related. In one study, histopathological examination was performed on young dogs following treatment for 28 days with 0, 20, 60 and 100 mg ibafloxacin/kg. Lesions on joint surfaces were observed in some animals of all ibafloxacin treated groups. Overall, the no effect level for arthropathy was considered to be 10 mg/kg/day in the immature dog.

It was concluded that the use of ibafloxacin in skeletally immature dogs should be contraindicated. A warning was added under point 5.2 contra-indications; *'Do not use in dogs during the period of growth as articular cartilage may be affected. This period depends on the breed. For the majority of breeds the use of ibafloxacin is contra-indicated in dogs less than 8 months of age; in giant breeds less than 18 months.'*

The mild skin changes observed occasionally in some studies are most likely not related to ibafloxacin treatment. In none of the toxicological studies performed in the adult dog given the clinically

recommended dose, were skin changes or alopecia observed. This is confirmed by the pre-clinical model studies and the field trials. In these studies more than 400 dogs have been treated with Ibaflin and no signs of alopecia or other skin related side effects were reported. The skin effects were not observed in the target species of the minimum age regardless of dose.

The underlying mechanism of the skin changes observed at extremely high ibafloxin dosages in rats is unknown. Potentially, the skin changes observed in the repeated dose toxicity studies in the rats are secondary to the general signs of toxicity observed in these studies and resulting from the extremely high ibafloxacin dosages administered.

Warnings about possible adverse effects on GI tract were considered justified and were consequently introduced under point 5.3 Undesirable effects of the SPC; '*Diarrhoea, soft faeces, vomiting, dullness and anorexia have been observed with low frequency. These effects were mild and transient.*'

Tolerance in the target species

This section is covered in Part 4 Pre-clinical studies.

Reproductive toxicity, including teratogenicity

Study of the effects on reproduction

A two generation reproductive toxicity study and a peri- and postnatal toxicity study with ibafloxacin have been performed in rats.

Ibafloxacin was administered orally at dose levels of 0 (control), 75, 195 and 500 mg/kg/day to groups of 24 male and 24 female rats in the parental (F0) generation. Males were dosed for 9 weeks before pairing with females from the same group which had been treated for 2 weeks. Half of the females were subsequently killed for a caesarean examination on Day 20 of gestation and half were allowed to litter and rear their offspring (F1 generation) until weaning (Days 21-23 post partum). Dosing of the females continued throughout the pairing, gestation and lactation periods as appropriate. Treatment of the males continued until necropsy following weaning of the F1 offspring. Following weaning, 12 male and 12 female offspring of the F1 generation were maintained untreated for 10 weeks before pairing. All females were allowed to litter and rear their offspring (F2 generation) to weaning.

F0 generation: Hair loss was evident in the majority of males and in some females in the 500 mg/kg/day group from the first week of treatment. Hyperactivity and hypersalivation was observed in both sexes during the pre-pairing gestation and lactation periods in the 195 and 500 mg/kg/day groups. Hyperactivity was also seen in the 75 mg/kg/day group. Body weight gain of the males was slightly reduced throughout the treatment period in the intermediate and high dose groups: the high dose females were similarly affected. There were no effects on reproductive performance as assessed by pre-coital interval, insemination, fecundity and fertility indices. At Day 20 of gestation there were no effects on the caesarian data at 75 or 195 mg/kg/day but at 500 mg/kg/day, foetal weight was reduced and resorption rate increased as compared to the controls. There were no treatment-related effects on major or minor abnormalities. A dose-related increase in the number of foetuses with retarded ossification was reported in all treatment groups.

F1 generation: The duration of gestation and parturition were unaffected by treatment. The viability, growth and functional, behavioural and reproductive performance of the 75 and 195 mg/kg/day groups was unaffected by treatment. In the 500 mg/kg/day group the live birth index was unaffected by treatment but the mean offspring body weight at Day 0 of lactation was lower than the controls, reflecting the lower foetal weights described above. The subsequent pre-weaning growth and viability of the offspring in this group was decreased compared to the controls but there were no effects on functional, behavioral or reproductive performance.

F2 generation: There were no effects observed in the F2 animals.

It was concluded that the vast majority of the adverse events reported above were likely to be the result of parental toxicity rather than a specific toxic effect on reproductive function. The findings such as reduced birth weights and retarded skeletal ossification are common manifestations of such parental toxicity. The reproductive parameters measured in this study were largely unaffected by treatment, especially at the low and mid-dose treatment levels. Occasional litter loss was reported in this study, but no dose-effect was evident. The only areas of concern were the reduced viability of the F1 progeny to weaning at the highest dosage level (but this could be related to maternal toxicity as their weights were slightly reduced) and the anasarca/dilated brain ventricles seen in some progeny from the same group. Some reflexes, such as the righting reflex, had a delayed time of onset in high-dose F1 progeny. Systemic signs of toxicity similar to those previously reported were again recorded (CNS effects, alopecia). Overall, it is felt that significant effects on reproductive performance were only present at the highest dosage level of 500 mg/kg/day.

In a second study ibafloxacin was given orally to groups of 25 pre-mated rats from day 15 of gestation to weaning (Days 21-23 post partum) at dose levels of 0 (control), 75, 195 and 500 mg/kg/day. Hyperactivity occurred at 500 mg/kg/day and hypersalivation was seen after treatment at 195 and 500 mg/kg/day. In the 500 mg/kg/day group, body weight gain and food intake was decreased during the gestation period. This effect was reflected in the mean body weight at Day 0 of lactation but growth during lactation was unaffected by treatment. Food intake was slightly reduced at 195 mg/kg/day at the end of gestation but there were no effects on body weight. There was a dose-related increase in the number of stillborn offspring in the 195 and 500 mg/kg/day groups.

The subsequent growth, development and viability of the offspring in the 195 mg/kg/day group was unaffected by treatment though a delayed onset of auditory startle response was reported at weaning. At 500 mg/kg/day the viability of the offspring was reduced and the growth and time of onset of pinna unfolding, incisor eruption and auditory startle response was retarded compared to the controls. There were no effects at 75 mg/kg/day. The presence of ibafloxacin in the maternal milk could only be detected in the 500 mg/kg/day group with mean levels of 0.27 ± 0.21 µg/ml being recorded.

Conclusion: Oral treatment of iblafloxacin at 75 mg/kg/day produced no maternal toxicity nor effects on peri- and post natal development. Retarded development of the offspring was observed at dose levels of 195 and 500 mg/kg/day which produced maternal toxicity.

From the studies in rats, a dose rate of 75 mg/kg/day can be accepted as a NOEL for reproductive toxicity.

In a dog study using oral administration by tablets, the safety of ibafloxacin in female breeding dogs was investigated at a dose rate of approximately 15 or 45 mg ibafloxin per kg body weight per day (i.e. 1 x and 3 x the recommended clinical dose) during 90 to 98 consecutive days. Treatment started in the pro-oestrus phase until three weeks (21 days) of lactation (covering all stages of reproduction: pro-oestrus phase, early-, mid- and late-pregnancy, parturition and lactation). In this study 3 groups of 6 female dogs each, were used. Two groups were treated orally with Ibafloxacin tablets: Group I at a dose rate of approximately 15 mg ibafloxacin kg body weight per day and Group II at a dose rate of approximately 45 mg ibafloxacin (i.e. x1 and x3 the recommended daily dose). Group III served as the non-treated control group. Ibafloxacin did not affect the oestrus rate, pregnancy rate, whelping rate, litter size and survival rate of litter. Ibafloxacin did not produce congenital defects in puppies. It is concluded that Ibaflin had no effects on pregnancy and lactation at levels up to 45 mg/kg/day.

Embryotoxicity including teratogenicity

Studies were conducted in rats and rabbits, with the main rabbit study being preceded by a pilot study.

Ibafloxacin was administered orally to groups of 25 pre-mated rats at dose levels of 0 (control), 75, 195 and 500 mg/kg/day from Days 6 to 15 of gestation inclusive. All animals were killed on Day 20 of gestation. There were no adverse clinical observations. There was a dose-related reduction in food

consumption in the 195 and 500 mg/kg/day groups. Body weight gain was also slightly decreased in the 500 mg/kg/day group. At the caesarean examination there was a dose-related reduction in mean foetal weight at the 195 and 500 mg/kg/day groups. There were no treatment-related major or minor foetal abnormalities. A dose-related retardation in ossification of the foetal skeleton was reported in all treatment groups: at 75 mg/kg/day these effects were particularly associated with two litters of atypically small foetuses. Maternal toxicity was evident at 195 and 500 mg/kg/day but there was no embryotoxicity nor teratogenicity. Retarded ossification was reported at 75 mg/kg/day in the absence of maternal toxicity, but these effects were particularly associated with two litters of atypically small foetuses. There was no evidence for any teratogenic effect of the test article.

In a pilot rabbit study ibafloxacin was administered orally to groups of pre-mated rabbits at dose levels of 100, 300 and 1000 mg/kg/day from Days 6 to 18 of gestation inclusive. Surviving animals were killed on Day 29 of gestation. In the 1000 mg/kg/day group two females died and two aborted their pregnancies following marked reductions in food consumption. In the surviving animals there were no maternal effects. An increased number of late resorptions and a reduced foetal weight were seen in the 1000 mg/kg/day group at the caesarean examination. There were no foetal abnormalities.

In a larger rabbit study, ibafloxacin was administered orally to groups of pre-mated rabbits at dose levels of 0 (control), 100, 275 and 750 mg/kg/day from Days 6 to 15 of gestation inclusive. Surviving animals were killed on Day 29 of gestation. In the 750 mg/kg/day group one animal died and five animals aborted their pregnancies following marked effects on food consumption. One animal in the 275 mg/kg/day group also aborted without prior clinical signs. There was a dose-related reduction in food consumption in all dose groups during the treatment period and a slight reduction in weight gain in the 750 mg/kg/day group. No treatment-related effects were observed at the caesarian examination on Day 29 of gestation. In conclusion, treatment at 275 and 750 mg/kg/day produced dose-related maternal toxicity and abortion. In pregnancies which survived to Day 29 of gestation, there were no adverse effects. No embryo/foetotoxicity occurred in the ibafloxacin treated animals.

Overall, whilst maternotoxicity and embryo/foetotoxicity can be induced with high dosage levels, and can lead to reproductive failure, there is no evidence of any specific reproductive toxic potential at low dose levels, and the compound shows no evidence of teratogenicity.

No information is provided with regard to the safe use of the oral gel product in pregnant and lactating cats and lactating dogs, therefore it was agreed to introduce the following standard warning in the SPC: 'The safety of the veterinary medicinal product has not been established in pregnant cats and in lactating dogs and cats.'

Mutagenicity

In total 7 mutagenicity studies have been done with ibafloxacin. Negative results were concluded for ibafloxacin in each of the mutagenicity systems. However, these tests were conducted in the mid-late 1980s, and the protocol designs used in the *in vitro* studies generally would now not be considered entirely adequate according to current protocol guidelines for assessment of the mutagenic potential of compounds. In addition, the numbers of cells scored in the rodent bone marrow cytogenetic studies would now not be considered to provide an adequate statistical power. However, no clear indication of positive responses were reported across seven different assay systems, which may be considered to provide some evidence for a lack of mutagenic potential.

Ibafloxacin had no genotoxic activity in the unscheduled DNA synthesis rat hepatocyte test and in HeLA cells, although a small rise in repair activity was observed in the presence of S-9. Ibafloxacin was unable to induce chromosomal aberrations in CHO cells and was non-mutagenic in the mouse lymphoma assay. No significant effect in the micronucleus test was observed and chromosomal aberrations were absent in bone marrow cells in the rat *in vivo*. No potential for genotoxicity was observed in the sex-linked recessive lethal test in *Drosophila melanogaster*. Finally, the sensitivity of bacterial DNA gyrase was a 100,000-fold that of human topoisomerase.

Unscheduled DNA synthesis in rat hepatocytes
The study comprised two independent experiments. Cultures were exposed to concentrations of up to 500 µg/ml ibafloxacin and UDS activity monitored by autoradiography following incubation with ^{3}H thymidine. No clear effect on net nuclear grain count or percentage of cell in repair was reported.

Unscheduled DNA synthesis in HeLa cells
Induction of UDS was determined by extraction and scintillography of cellular DNA following exposure to ibafloxacin in the presence of ^{3}H-thymidine in a single experiment. Cultures were exposed to concentrations of up to 500 µg/ml ibafloxacin both in the presence and absence of a rat liver post-mitochondrial supernatant (S9 mix). Cultures exposed in the presence of S9 showed a statistically significant, dose-related increase in DNA repair. However, the maximal increase in repair was small (approximately 1.3 times background) and therefore the biological significance of this response is not clear.

Induction of chromosomal aberrations in CHO cells
A single experiment was conducted to assess the clastogenic potential of the compound in vitro. Cultures of CHO cells were exposed to concentrations of up to 700 µg/ml ibafloxacin for 2 hours in the presence or absence of an S9 mix and harvested for metaphase analysis after a further 19 hours incubation. The highest exposure level was at or close to the limit of solubility and toxicity in the test system. Lower concentrations were obtained by 2-fold dilution from the maximum. Similar frequencies of cells with aberrations were seen in both treated and control cultures.

Mammalian cell gene mutation in mouse lymphoma cells
The potential of ibafloxacin to induce 6-thioguanine resistance in mouse lymphoma L5178Y cells was investigated in two independent experiments in the presence and absence of metabolic activation (S9 mix). A series of widely-spaced concentrations was used in the first experiment, and no positive responses were reported. In the second experiment, six treatment concentrations covering the range of 50-500 µg/ml were used. Statistically significant increases in 6-thioguanine resistant cells were reported at 300 and 500 µg/ml in the absence of S9 mix only. However, these responses did not exceed the historical control range for the testing laboratory, and therefore the biological significance of these effects is not clear.

Rodent bone marrow micronucleus test
A mouse bone marrow micronucleus test was conducted, following oral administration of ibafloxacin at 1000, 2000 or 4000 mg/kg to groups of five male and five female mice. Some mortalities were recorded in female animals at the highest dose level. No effects were noted on the ratio of polychromatic to normochromatic erythrocytes (PCE:NCE) at any dose level. One thousand PCE were analysed per animal for micronuclei and a negative response was concluded.

Induction of chromosomal aberrations in rat bone marrow in vivo

The in vivo clastogenic potential of ibafloxacin was also assessed in a rat bone marrow metaphase study. The compound was administered orally at 1250, 2500 and 5000 mg/kg, and groups of 5 male and 5 female rats were killed at 6, 24 and 48 hours after treatment. Up to 50 metaphases were analysed from each animal and a negative response was concluded.

Sex-linked recessive lethal test in *Drosophila melanogaster*
Ibafloxacin showed no genotoxic potential in the sex-linked recessive lethal test in *Drosophila melanogaster* when tested at concentrations of 0.1 and 0.2%.

Effects on bacterial DNA gyrase and mammalian cell topoisomerase

The antibacterial activity of ibafloxacin is due to its inhibition of bacterial DNA gyrase. Therefore a comparison of the inhibitory activity of ibafloxacin and another quinolone antibacterial (enrofloxacin) on both bacterial DNA gyrase and mammalian cell topoisomerase II was made. Both antibiotics were potent inhibitors of DNA gyrase (minimum inhibitory concentration of $\leq$0.01 µg/ml in each case). However, ibafloxacin was a less potent inhibitor of human topoisomerase II than enrofloxacin (minimum inhibitory concentrations of 2400 µg/ml and 1400 µg/ml respectively). The results of this

study indicate that ibafloxacin would be expected to inhibit DNA gyrase at concentrations >200 000-fold lower than those which inhibit human topoisomerase II activity.

Conclusion
Despite some deficiencies in the protocol designs, negative responses were obtained in seven different mutagenicity assays with ibafloxacin, and a significant safety margin was demonstrated between inhibition of bacterial DNA gyrase and mammalian cell topoisomerase II. In the mutagenicity assays it was generally not possible to test to concentrations significantly greater than 500 µg/ml *in vitro*, due to limitations of solubility and toxicity. Therefore the test systems were not exposed to concentrations likely to be associated with inhibition of topoisomerase II (2400 µg/ml). Even at the g/kg dose levels employed in the in vivo test systems, it is considered unlikely that plasma/tissue concentrations would approach the levels required for inhibition of topoisomerase II.

Carcinogenicity

Equivocal results were reported in at least one, if not two mutagenicity studies. However, in view of the general conclusions from the mutagenicity studies, the absence of structural alerts and the absence of a tumorigenic potential in quinolones, it was decided not to request for further studies on carcinogenicity.

Immunotoxicity

No specific studies were performed in the field of immunotoxicity. A literature study shows that skin and hypersensitivity reactions of quinolones appear to be rare. In the single and repeated dose toxicity studies, no signs of toxicity of the immune system were observed. It is considered that further specific studies on immunotoxicity are not justified.

Microbiological properties of residues

Ibafloxacin has clear antimicrobiological properties, as described in the pharmacodynamic section of the dossier. However, because Ibaflin is indicated for cats and dogs, residues are considered not relevant.

Observations in humans

In a pharmacokinetic study the metabolism of ibafloxacin in humans was investigated. It appeared that, in comparison to the other species, the metabolic pattern of ibafloxacin in humans was similar.

As ibafloxacin is not intended for use in humans, only limited data are available in humans. In a metabolism study, the metabolism of ibafloxacin in humans after oral administration of 600 mg ibafloxacin per person was investigated. As compared to the other species, dog, mice, rabbit, monkey, the metabolic pattern of ibafloxacin in humans was similar.

User safety

The tablet is for oral administration of dogs by the animal owner. The gel formulation is for oral administration to dogs and cats by the animal owner. Given these formulations and the toxicity profile, Ibaflin is unlikely to cause toxicity for the user. In order to further reduce any potential risk for children, a warning is included on the product information; '*Keep out of reach and sight of children*'. Furthermore, a warning is given for quinolone hypersensitive persons to avoid contact with the product.

Studies on metabolites, impurities, other substances and formulation

As ibafloxacin is a new quinolone, no interactions with other drugs are known. However, literature information is available for fluoroquinolones which are marketed already. It is likely that interactions described for these older fluoroquinolones will also occur with ibafloxacin . Fluoroquinolones appear to interact with antacids containing cations (aluminium, magnesium, calcium) or sucralfate by binding to the

quinolone and thereby preventing its absorption. The clearance of theophylline and caffeine may be interfered with by quinolones . Probenecid blocks tubular secretion of quinolones and may increase their blood level and half life; synergism may occur with aminoglycosides, 3rd generation cephalosporins and extended-spectrum penicillins; antagonism may be observed with nitrofurantoin; fluoroquinolones may exacerbate the nephrotoxicity of cyclosporines used systematically. Concurrent administration with NSAIDs might enhance the possibility of convulsions following the use of quinolones.

Ecotoxicity

The tablet formulations are intended for individual treatment of dogs. The oral gel formulations are intended for individual treatment of dogs and cats. The exposure of the product, its active ingredient or relevant metabolites to the environment will therefore be very limited. In line with VICH Topic GL6 (Ecotoxicity Phase I) Step 7 Guideline on Environmental Impact Assessment (EIAS) for Veterinary Medicinal Products - Phase I (CVMP/VICH/592/98-FINAL), further studies on the issue of ecotoxicity were, therefore, not considered necessary.

CONCLUSIONS ON TOXICITY

From the toxicological data it can be concluded that the single dose toxicity of ibafloxacin is low, especially after oral administration. Overall, the toxicological assessment largely refers to the tablets dossier. As can be seen from the repeated dose studies, the toxicity of ibafloxacin increases when given for a longer period. However, ibafloxacin can be administered to the mature dog for 90 days at the recommended dose level of 15 mg/kg body weight, without adverse effects becoming apparent. According to the studies the safety margin for the mature dog is 3.

Vomiting, a reduced feed intake, a reduction in RBC, leucocyte count and total plasma protein, pale faeces and changes in organ weight have been observed in the dog. These effects are transient and only appear at dose rates, much higher than the dosage recommended for therapeutic use.

The only relevant toxic effect is the induction of lesions in articular cartilage of immature animals. The tolerance study confirms the potential of ibafloxacin for the induction of cartilage lesions. Immature and growing animals appear to be more sensitive to the damaging effect and are to be excluded from treatment, which is stated in the SPC (5.2) accordingly. A dose level of 15 mg ibafloxacin/kg body weight is considered to be safe in the mature dog.

From the reproduction studies ibafloxacin appears to be safe when given to male and female rats and female rabbits during pregnancy. Reproduction safety in the female breeding dog is confirmed by the tolerance study. Additionally, ibafloxacin can be safely administered to dogs during lactation as well. A statement is included on the SPC (5.5) concerning the safe use during pregnancy and lactation in the female dog. On the basis of information on the male rat ibafloxacin can be considered safe when given to male breeding dogs.

The oral gel product is intended for oral administration to dogs and cats by the animal owner. Given the formulation and the toxicity profile, Ibaflin oral gel is unlikely to cause toxicity for the user. In order to further reduce any potential risk for children, a warning is included on the product information ‘Keep out of reach and sight of children’. Furthermore, a warning is given for quinolone hypersensitive persons to avoid contact with the product.

Also, the exposure of the product, its active substance or relevant metabolites to the environment will be very limited and further studies on the issue of ecotoxicity are, therefore, not requested. It is concluded that ibafloxacin is safe when used according to the recommendations included in the SPC.

B. RESIDUE DOCUMENTATION

The application is for a non-food producing species, and therefore residue documentation is not applicable.

MICs of ibafloxacin, enrofloxacin, marbofloxacin and amoxicillin / clavulanate (ratio 1:4) against bacterial strains isolated from diseased cats

MICs of 330 strains were determined using an IST agar dilution method. Pathogens were isolated from cases of dermatitis and urinary or respiratory tract infections in cats from Germany, the Netherlands and Italy. The following values for the MIC_{90} were calculated (µg/ml).

	ibafloxacin	**enrofloxacin**	**marbofloxacin**	**amoxicillin**
Escherichia coli	0.5	0.128	0.128	8
Staph. aureus	0.5	0.5	2	1
all staphylococci	1	0.5	1	1
Pasteurella	0.064	0.032	0.064	0.128
Streptococcus	8	2	4	1
Proteus mirabilis	>32	8	2	8
Pseudomonas	16	4	2	>32
Klebsiella	0.5	0.128	0.128	16

MICs of racemic ibafloxacin, R and S-ibafloxacin, 7-hydroxy- and 8-hydroxy-ibafloxacin against feline bacterial pathogens

MICs were determined using an agar dilution method. Pathogens were isolated from cases of soft tissue infections and urinary or respiratory tract infections in cats from Germany and the Netherlands. Aslo reference strains were included. The following MIC-ranges were observed (µg/ml).

	R-IBA	**S-IBA**	**R/S-IBA**	**7-OH-IBA**	**8-OH-IBA**
Escherichia coli	4-16	0.128-0.25	0.128-0.25	1-2	2-4
Staph. aureus	16-128	0.064-0.25	0.128-1	2-8	4->64
Staph. intermedius	>128	0.128-0.25	0.128-1	4-8	8->64
Klebsiella	16-32	0.25	0.25-0.5	2-4	2-4
E. coli (ref.)	0.25-4	<0.008-0.128	<0.016-0.128	0.128-1	0.25-8
S. aureus (ref.)	>128	0.128	0.128	4	2

The study confirms the conclusions made for the tabet formulation i.e. that the S-enantiomer is the active one. *In vivo*, the antibacterial effect is based on ibafloxacin and/or 8-OH-ibafloxacin. MIC data for the separate compounds do not properly reflect the antibacterial potential of ibafloxacin *in vivo*, as efficacy is based on interaction. Therefore, susceptibility testing should be based on both ibafloxacin and 8-OH-ibafloxacin (as the predominant metabolite), with concentrations at various time points resembling their *in vivo* plasma or tissue level profiles.

Additional data were provided on MICs for relevant pathogens from dogs and cats sampled during clinical trials

MICs were determined for mixtures of ibafloxacin, 8-OH-ibafloxacin and 7-OH-ibafloxacin using ratios' in which substances appear *in vivo* in plasma (Ratio's A-F) and urine (Ratio G) at different time points. Kill curves were produced, also using mixtures of ibafloxacin and 8-OH-ibafloxacin in ratios in which substances appear *in vivo* in plasma. Time intervals used were 0-2, 2-8 and 8-24 hours and the levels and ratios used were based on averages for these intervals. Results indicate that a kill effect is obtained rapidly.

For dog pathogens MIC_{90}s were $\geq$1 mcg/ml for *E. coli* and *S. intermedius* and $\geq$ 0.5 mcg/ml for *Proteus mirabilis* and *S. aureus*. For cat pathogens MIC_{90}s were $\geq$ 0.032 mcg/ml for *Pasteurella multocida*, $\geq$ 0.5 mcg/ml for *S. aureus* and *S. intermedius* and $\geq$ 1 mcg/ml for *E. coli*. The highest ibafloxacin/8-OH-ibafloxacin ratio (60/40 = 1.5) resulted in the lowest MICs and MICs increased as

ratio's decreased. MICs for urine at an ibafloxacin/8-OH-ibafloxacin ratio of 5/95 were above 2-4 mcg/ml for all isolates, except for *Pasteurella* (cat), being 0.128 mcg/ml.

Regarding the MICs of the 3 substances it is observed that these data confirm the conclusions on the mode of action as made for the tablet. Ibafloxacin is the most effective. As it is replaced by its predominant metabolite efficacy decreases, resulting in a gradual increase of MICs, however this is not the same for different bacterial species. When compared to the actual plasma levels of ibafloxacin and 8-OH-ibafloxacin, results also indicate that in the dog, efficacy is unlikely to depend on levels exceeding MICs, as from 12 hours and on MICs tend to be $\geq$1 mcg/ml, but levels $\leq$ 1mcg/ml. As elimination in the cat is relatively low, plasma levels tend to persist. The possibility that efficacy is also based on levels exceeding MIC cannot be excluded. However, it should be kept in mind that tissue levels are about 1/3 of those in plasma.
Ibafloxacin/8-OH-ibafloxacin ratios used were based on plasma levels for the gel and the tablet for the dog and for the gel only for the cat. Isolates used were *E. coli, S. aureus, S. intermedius, Proteus mirabilis* and *Bordetella bronchiseptica* from the dog and *E. coli, S. aureus, S. intermedius* and *Pasteurella multocida* from the cat. All isolates had MICs $\leq$ 1 mcg/ml except for *Bordetella* (2 mcg/ml). Inoculation size used was 5.10^{4-5} CFU.

The study indicates that subsequent exposure of bacteria to ibafloxacin and 8-OH-ibafloxacin results in kill effect. Kill effect is obtained more rapidly for *Pasteurella* and *S. aureus,* compared to kill effect of *S. intermedius* and *E. coli,* indicating that kill effect occurs more rapidly in isolates having lower MICs.

Both studies indicate that rapid kill effect can be obtained if isolates are exposed to ibafloxacin and subsequently to ibafloxacin and 8-OH-ibafloxacin in different ratios. In the dog levels of ibafloxacin and 8-OH-ibafloxacin separately do not persist for the full dosing interval and do not exceed MICs at tissue level to explain efficacy. Therefore $T_{>0.5\ mcg/ml}$ is not considered to be relevant as a measure of the mode of action in the dog. Furthermore the distribution of ibafloxacin in tissues and body fluids from dogs indicates that persistence over in time of tissue levels is low and does not cover an interval of 24 hours, which is needed if efficacy is to be based on inhibition, as assumed by referring to $T_{>0.5\ mcg/ml}$.

OVERALL CONCLUSIONS ON MIC STUDIES

As was already observed from the data submitted for the tablet formulation, the values for MICs found depend on the method used. Prediction of clinical efficacy on the basis of extrapolation from pharmacokinetic and MIC data for ibafloxacin only is considered to be of minor importance, as the response to various levels of ibafloxacin and/or 8-OH-ibafloxacin is different for different strains of bacteria. In accordance with the probable mode of action of ibafloxacin, susceptibility testing should be based on both ibafloxacin and 8-OH-ibafloxacin (as the predominant metabolite). Data also indicate that, if efficacy was to be based on a level of 0.5 µg/ml, as done by the applicant, the antimicrobial spectrum appears to be smaller than claimed.

In the cat levels do persist and the mode of action is likely to be a combination of persistence in plasma (post-kill effect) and $T_{>MIC}$. Incomplete kill effect can be compensated for by levels exceeding MICs, especially for the 12-24 hours interval. Consequently, justification of dosage and efficacy in the cat cannot fully be extrapolated from dog data. The persistence of plasma concentrations above the relevant MICs in the cat is noted.

Pharmacokinetics

A total of five basic pharmacokinetic studies were performed as follows:

a. Plasma, urine, faeces and tissue analysis after single oral or iv administration of 25 mg/kg to dogs.
b. Plasma and tissue distribution after oral administration of 10 mg/kg for 5 treatments.
c. Metabolism in dog, mice, rabbit, monkey and humans after oral administration of 30-600 mg.
d. Plasma, urine and faeces analysis after single iv or oral administration of 10 mg/kg to dogs.
e. Metabolism in the dog after oral administration of 10 mg/kg.

These initial studies have certain deficiencies when it comes to drawing firm conclusions on the ADME characteristics of ibafloxacin. The analytical methods employed were not properly validated at the time the studies were performed. The formulations used were not the final commercial one and the dosages employed were not the Recommended Therapeutic Dosage (RTD). The route of exposure was not always oral. Some general features of the above studies were the 3-4 hours generally taken for C_{max} following oral dosing and the extensive metabolism of the parent compound, particularly in urine.

In addition to the basic pharmacokinetic studies, a full range of kinetic studies with ibafloxacin in the dog have been performed. Although the tablet formulation was used throughout, in some cases, ibafloxacin was also administered intravenously as a solution. Two analytical methods were used in the kinetic studies: a microbiological method and a HPLC assay. Both assays have been properly validated for analysis of plasma, urine and faeces. Using the microbiological assay, the total concentration of microbiologically active compounds was determined.
The following studies were performed:

1) Pharmacokinetics of Ibafloxacin in Plasma after a Single Intravenous (5mg/kg) or Oral Administration (5, 10 and 15 mg/Kg) to Beagle Dogs; a Four-Way Cross-Over Study.

After oral administration of Ibafloxacin tablets the maximum plasma concentration was reached within 2 hours irrespective of the dose. The mean maximum plasma concentration measured with the microbiological assay increased with dose and was 3.83, 5.17 and 8.64 μg/ml for the 5, 10 and 15 mg/kg dose, respectively. The AUC also increased with dose from 14.36 μg.h/ml for the 5, 18.80 μg.h/ml for the 10mg/kg dose, and 32.07 μg.h/ml for the 15 mg/kg dose. The bioavailability of microbiological active compounds was high (85%) for the lowest dose and decreased to about 60% for the higher doses. The time during which the concentration of microbiologically active drug was above 0.5 μg/ml was almost 7 hours for the 5 mg/kg dose and 8 and 10 hours for the 10 and 15 mg/kg dose. A distribution volume higher than the plasma volume indicates a good penetration of the compound into tissues.

2) Concentration of Ibafloxacin and Metabolites in Plasma and Urine in Dogs after a Single Oral Administration of 15 mg Ibafloxacin /Kg Body Weight.

After administration of Ibafloxacin tablets at a dose of 15 mg/kg to dogs (two males and two females) who were involved in an *Escherichia coli* cystitis infection model at 5 - 6 weeks before dosing of ibafloxacin, microbiological activity in plasma was high (15-20 μg/ml at 2 hours after dosing). Once absorbed, ibafloxacin is metabolized to 7-OH and mainly 8-OH-ibafloxacin and excreted into the urine as such and as glucuronide. 8-OH ibafloxacin (and glucuronide) is the main metabolite and contributes to 95 - 98% of the total amount of the drug that is excreted in the urine. Ibafloxacin and metabolites ensure high microbiological activity in the urine at least up to 24 hours after dosing.

3) Pharmacokinetics of Ibafloxacin in Plasma after a Single Oral Administration of Ibafloxacin Tablets at a Dose of 15 mg/Kg to Male and Female Beagle Dogs.

A mean dose of 14.5 mg/kg ibafloxacin, given as tablets to healthy male and female Beagle dogs, resulted in high plasma drug levels with a mean individual animal peak concentration of 12.1 $\pm$ 1.6 μg/ml (microbiological assay) which was reached in 1.4 $\pm$ 0.4 hours. The plasma concentration of microbiologically active compounds remained above the MIC of many important pathogens for at least 12 hours and in some dogs even for 24 hours (mean plasma concentrations were 0.56 $\pm$ 0.34 and 0.27 $\pm$ 0.39 μg/ml at 12.3 and 24 hours respectively). This justifies once daily administration of ibafloxacin tablets for the treatment of infections caused by susceptible micro-organisms.

4) Pharmacokinetic Study of ibafloxacin Excretion into Urine and Faeces after a Single Oral Administration (15mg/Kg) to Beagle Dogs.

The microbiological activity in urine (as determined with the microbiological assay and expressed as μg ibafloxacin/ml) generally was between 43 μg/ml and 62 μg/ml at 3 to 6 hours after dosing. At 24 - 27 hours after dosing the concentration in the urine ranged from 1.86 μg/ml to 16.28 μg/ml (well above the MIC of many important urinary pathogens). At 48 hours, the concentrations in urine of 50% of the dogs were above 2 μg/ml. 8-OH-ibafloxacin contributed highly to the activity in the urine. In faeces also high concentrations of ibafloxacin, 7-OH- and 8-OH-ibafloxacin were found. The total recovery of ibafloxacin, 7-OH- and 8-OH-ibafloxacin and conjugates in urine and faeces was 61.8% to 99.90% of the dose.

5) Pharmacokinetic Study of ibafloxacin in Plasma after a Single Intravenous (Dose: 15mg/Kg) or oral (Dose : 7.5, 15, 30 mg/Kg) Administration to Beagle Dogs.

Over the oral dose range tested there were no consistent changes apparent in terms of T1/2 total plasma clearance and volume of distribution. Non-parametric comparison (Kruskal-Wallis) of T_{max} data did not show any statistically significant differences between the oral dose levels tested. These findings are in support of linear pharmacokinetics and dose proportionality over the oral dose range tested. On average, absolute oral bioavailability calculated from the HPLC and microbiological data, was 75%.

The data revealed that ibafloxacin is subject to substantial metabolic conversion both after oral and intravenous dosing and that 8-OH ibafloxacin is the major metabolite of ibafloxacin. Proportions of the produced OH-metabolites were very similar after intravenous and oral dosing indicating that pre-systemic conversion in the GI-tract is negligible.

Oral C_{max} averaged 3.718 μg/ml, 6.043 μg/ml and 12.149 μg/ml at the respective oral dose levels tested. The time interval during which the concentration of ibafloxacin exceeded the minimal inhibitory concentration of most relevant pathogens (0.5 μg/ml) ranged from 7.47 $\pm$ 2.30 h at the dose level of 7.5 mg/kg to 13.59 $\pm$ 3.53 h at the dose level of 30 mg/kg.

6) The Pharmacokinetics of ibafloxacin in Plasma after Once Daily Oral Administration of Ibafloxacin Tablets at a Dose of 15mg/kg to Male and Female Beagle Dogs during 10 Consecutive Days.

Based on comparable pharmacokinetic parameters at day 1, 5 and 10, and similar plasma levels at t = 0 and t = 1.5 hours after tablet administration throughout the 10 days of tablet administration, it can be concluded that the results show that no accumulation of ibafloxacin or metabolites occurred in plasma during the 10 days treatment course at the recommended dosage of ibafloxacin tablets (15 mg/kg body weight). No significant differences (pared t-test, $p < 0.05$) were observed when C_{max}, C_{maxd}, t_{max}, AUC_{0-24} or AUC_{0-24d} of ibafloxacin at days 1, 5 and 10 were compared, except for AUC_{0-24d} which was significantly higher at day 10 than at day 1 (only when determined with a microbiological method, not with HPLC). However since the pharmacokinetics at day 5 and 10 were found fully comparable it was accepted that there is no risk for accumulation after multi-day dosing.

7) Influence of Food on the Absorption Kinetics of ibafloxacin after a Single Oral Administration to Beagle Dogs.

Food was supplied 15 minutes prior to tablet administration or 4 hr thereafter. The drug concentration was measured using a microbiological assay (m.b.) and HPLC. The following pharmacokinetic values were calculated (n=8):

Assay		**T_{max} (h)**	**C_{max} (μg/ml)**	**AUC (μg.h/ml)**	**t > 0.5 μg/ml**
m.b.	-food	2.13 $\pm$ 0.74	7.49 $\pm$ 2.50	27.63 $\pm$ 5.16	12.36 $\pm$ 5.28
HPLC	-food	2.13 $\pm$ 0.74	3.82 $\pm$ 1.00	12.42 $\pm$ 2.33	5.74 $\pm$ 1.88
m.b.	+food	2.13 $\pm$ 1.87	11.29 $\pm$ 5.40	34.74 $\pm$ 7.23	12.64 $\pm$ 4.01

HPLC	+food	2.13 ± 1.87	5.49 ± 3.58	16.20 ± 3.71	7.28 ± 2.45

Food intake prior to administration of drug did not change Tmax but had a positive effect on the Cmax and AUC. The time during which plasma drug concentration, measured as microbiological activity, was higher than 0.5 g/ml was > 12 h irrespective of the presence or absence of food during administration.

These results show that timing of food intake positively influences ibafloxacin absorption. Thus, it may be recommended to administer ibafloxacin tablets simultaneously with food. Furthermore, a once daily administration of 10 mg ibafloxacin/kg body weight results in microbiologically active plasma levels which are above the MIC or relevant micro-organisms (0.5 g/ml) for about 12 h.

8) Pharmacokinetic study of the R/S Enantiomers of ibafloxacin in Plasma and Excretion into Urine and Faeces after a Single Oral or Intravenous Administration to Beagle Dogs.

In this study, 2 groups of 1 male and 1 female adult, healthy Beagle dogs each were used. They were housed in 4 separate metabolism cages during 72 hours after administration. In the first week, they were given ibafloxacin orally as capsules (group 1: 7.5 mg ibafloxacin R-enantiomer per kg and group 2 : 7.5 mg ibafloxacin S-enantiomer per kg) followed two weeks later by intravenous ibafloxacin as a solution (group 1 : 7.5mg ibafloxacin R-enantiomer per kg and group 2 : 7.5 mg ibafloxacin S-enantiomer per kg).

It was concluded that R and S-ibafloxacin follow different pharmacokinetics after i.v. and oral administration to dogs: S-ibafloxacin has a longer elimination half-live, higher AUC, C_{max}, and MRT and a lower C1 than R-ibafloxacin. The bioavailability of S-ibafloxacin is complete (115%) and higher than R-ibafloxacin (30%). The low bioavailability of R-ibafloxacin is probably caused by an extensive first pass metabolism to R-8-OH-ibafloxacin. R and S-ibafloxacin, and its metabolites were found in the faeces after i.v. administration which indicates that they are subject to biliary excretion (and entero-hepatic recycling). High microbiological activity was measured in plasma, urine and faeces only when the S-enantiomer was given. The R-enantiomer has less microbiological activity than the S-enantiomer. No conversion of one enantiomer into the other was observed.

General conclusions on pharmacokinetics

Absorption
After oral administration of Ibaflin to dogs, absorption occurs rapidly with maximum plasma levels observed at 1-2 hours after administration. The oral bioavailability is about 50-80% when given without food. Separate enantiomer studies have shown that for S-ibafloxacin, the bioavailability is complete, while for R-ibafloxacin it is relatively low (30%). The AUC of S-ibafloxacin is approximately 20 fold higher than that of the R-ibafloxacin.

When administered with food, T_{max} is unchanged, whereas C_{max} and AUC are somewhat increased. It is concluded that food intake does not influence the rate of absorption, but causes some increase in the extent of the absorption. The presence or absence of food has no influence on the time period for which microbiologically active plasma levels persist. However, bioavailability does appear to be improved by feeding, and as this is also likely to reduce GI tract side-effects, administration with food is therefore recommended.

Distribution
The basic pharmacokinetic studies performed with ibafloxacin show that ibafloxacin is distributed into tissues. Shortly after administration (2-4 hours), levels can be observed in kidney, liver, muscle and fat. The concentrations in tissues are lower than those observed in plasma (50%-90%). In urine, bile and throughout the gut, high concentrations of microbiologically active compounds are observed as compared to plasma levels.

Metabolism and elimination

Terminal plasma half-life is about 4-5 hours. The main excretion route is the urine and faeces. The most abundant metabolite is 8-hydroxy-ibafloxacin. In urine, this compound is the main contributor to the microbiological activity observed.

After multiple oral administration, maximal, minimal and average plasma concentrations on day 1, 5 and 10 are comparable indicating that steady state is reached within one day after the first oral administration and that no accumulation occurs.

Kinetics are linear in the dose range of 7.5 - 30 mg/kg. The basic pharmacokinetic data indicate biliary excretion and enterohepatic circulation.

Ibafloxacin shows enantioselective pharmacokinetics. After administration of ibafloxacin as racemate, the R-enantiomer is rapidly removed from the blood and metabolised such that practically all circulating ibafloxacin is the more active S-enantiomer.

A general and consistent concern, however, throughout most of pharmacokinetic studies is the time period where ibafloxacin, or even its microbiologically active metabolites, are present at a concentration above 0.5 µg/ml in the plasma. The data presented cover a variety of dose levels, but even at dose levels above the RTD, effective plasma levels seem to be present only for a period of approximately 12 hours. Mean values at 24 hours were 0.27 ± 0.39 µg/ml. This is a further concern that the MIC_{90} data, which may lead to the conclusion that 0.5 µg/ml may not even be a suitably high baseline concentration to aim for. Furthermore, many of the studies which investigated the time for which drug levels were greater than 0.5 µg/ml, were based on a microbiological assay, that measured all microbiologically active components, not just parent compound and major metabolites. In virtually all the studies, total drug concentrations were significantly higher by the microbiological method than by the HPLC assay.

Whilst the data clearly show that once daily dosing at the RTD is suitable for treatment of acute urinary tract infections, levels of ibafloxacin in plasma and tissues are likely to be at or below 0.5 µg/ml within 12 hours of dosing. In general the kinetical studies indicate that this plasma value is too low to be efficacious against several common bacterial species in the dog, in comparison to the MIC values found for these species. The post-antibiotic effect is generally of short duration. Therefore in theory a twice daily dosing should be considered for dermal and respiratory tract infections. However it became clear from the model studies and field trials that the common scientific approach to evaluate efficacy based on MIC values and plasma concentration is not consistent with the findings of the clinical field trials where a once daily dose proved to be efficacious and this has finally been approved by the Committee.

<u>Oral Gel Formulations</u>

New pharmacokinetic studies for the dog and the cat, using both strengths of the gel formulation were submitted.

Dog pharmacokinetic studies

***In vitro* plasma protein binding of the R/S enantiomers of ibafloxacin in Dogs**

Plasma from untreated dogs was spiked with ibafloxacin, either as the racemic mixture or as the seperate enantiomers. Protein free plasma was prepared by ultrafiltration. Within the range from 3 to 50 µg/ml plasma protein binding appeared to be concentration dependent, varying from 84 to 96%. The unbound fraction was 3 times higher for the R-enantiomer, compared to the S-enantiomer. Difference in binding adds to the explanation for the greater mobility of the R-enantiomer, as appeared from the kinetic studies.

Bioequivalence of ibafloxacin gel preparation and tablets in healthy Beagle dogs after a single oral adminsitration of approximately 15 mg ibafloxacin per kg bodyweight in a two-way cross-over design

From the Ibaflin tablet dossier it was concluded that efficacy of ibafloxacin was based on the combined effect of S-ibafloxacin and its predominant metabolite 8-OH-ibafloxacin. Furthermore, efficacy is not likely to depend on the total amount of active ingredients (ibafloxacin and 8-OH-ibafloxacin) only, but also on their ratio. Three "mode of actions" were distinguished: 1) a direct effect of S-ibafloxacin (and to a lesser extent of the metabolite); 2) a Post Antibiotic Effect (PAE) (initially an exposure to high levels of active ingredient, followed by an exposure to lower levels), and; 3) synergy between S-ibafloxacin and 8-OH-ibafloxacin.

The aforementioned observations led to the following conclusions. The difference in C_{max} between the gel formulation and the tablet results in different plasma level profiles for ibafloxacin and its metabolites. In view of the mode of action this is likely to result in differences in antimicrobial activity between both formulations, the tablet being the more effective one. Similarity in AUC is insufficient ground for the assumption of equivalence in efficacy, as variation in AUC cannot be directly related to a variation in antimicrobial activity. If $T_{> 0.5\ \mu/ml}$ was decisive for the mode of action of ibafloxacin a twice daily treatment had to be recommended.

However, considering that the C_{max} after administration of the gel formulation is well above the MIC of relevant pathogens and that both AUCs are comparable, the applicant claimed that differences in C_{max} will not result in a difference in clinical efficacy.

Bioequivalence of two gel preparations containing 3 and 7.5% ibafloxacin and tablets (reference product) in healthy Beagle dogs after a single oral administration of approximately 15 mg ibafloxacin per kg body weight in a three-way cross-over design

Animals were treated either with the 3% and 7.5% gel formulation or the 300 mg tablets. The concentration of ibafloxacin in plasma was determined by using HPLC and microbiological methods. C_{max}, AUC, T_{max}, and $T_{>0.5\ mcg/ml}$ were calculated. The Committee agreed that both gel formulations are bioequivalent, but tablets and gel formulations were not considered bioequivalent. The applicant considered the differences in C_{max} between the gel formulations and the tablet as clinically irrelevant. However, the Committee felt that such conclusion would disregard the knowledge on the mode of action of ibafloxacin.

Plasma kinetics of ibafloxacin and metabolites in dogs after single oral administrations of two different gel formulations (given with or without food) or tablets at a dose of 15 mg ibafloxacin/kg body weight (pilot study)

Formulations used were the 150 mg Ibaflin tablet, a 3% ibafloxacin gel (Ibaflin), a 2% (A) and a 2.5% gel (B), both containing Carbopol as a thickener. Concentrations of ibafloxacin and metabolites were determined by HPLC and a microbiological assay.

8-OH-ibafloxacin was the major metabolite and concentrations in plasma were higher than for ibafloxacin between 4 to 24 hours after administration. The applicant concluded that bioavailability of ibafloxacin (expressed as AUC) was higher when given with food. Dry food was given 6 hours after medication.

Plasma pharmacokinetics of ibafloxacin after a single intravenous (dose: 6 mg/kg) or oral administration to Beagle dogs (dose: ibafloxacin gel formulation 6 and 15 mg/kg and ibafloxacin tablets 6 mg/kg); influence of food on ibafloxacin kinetics

Adult dogs received a single dose of ibafloxacin on the same day every week for 4 weeks, using a modified 4-way cross-over design.

It was concluded that administration of ibafloxacin together with food increased the bioavailability. It was, however, noted with 47.8% (HPLC) bioavailability was lowest in dogs receiving food 6 hours after gel-treatment (6 mg/kg). With 69.2% (HPLC) bioavailability was highest for tablets (6 mg/kg), when followed directly by offering food.

A pharmacokinetic study of ibafloxacin in plasma after a single oral administration of a 7.5% w/w/ gel formulation to Beagle dogs at a dose of 15 mg/kg

Dogs (male and female) were treated with ibafloxacin gel, given directly into the mouth, directly followed by food. Concentrations of ibafloxacin and metabolites were determined using a microbiological assay.

Values for kinetic parameters were as follows (means): a T_{max} of 4 hours, a C_{max} of 6.81 µg/ml, an AUC of 49.92 µg.h/ml and a $T_{>0.5\ mcg/ml}$ of 18 hours. It was concluded that after a single administration of 15 mg ibafloxacin/kg BW as a 7.5% gel formulation, high plasma levels of microbiological active compounds are reached and remain above the MIC of many pathogens for more than 18 hours.

OVERALL CONCLUSION ON THE PHARMACOKINETIC STUDIES FOR THE DOG

All studies show that there is a difference in ibafloxacin plasma level profiles for tablet and gel formulations, when given at the same dose. The most obvious difference is a considerably lower C_{max} for the gel formulations. As ibafloxacin is transformed into the microbiologically active metabolite 8-OH-ibafloxacin, a difference in C_{max} will result in a difference in the 8-OH-ibafloxacin profile as well. Comparison of ratios at different time points for ibafloxacin and 8-OH-ibafloxacin plasma levels reveals no major difference between the tablet and the gel formulations. This leaves the absolute levels of ibafloxacin and 8-OH-ibafloxacin to be the major determining factors for efficacy. A lower C_{max} for ibafloxacin means lower levels for 8-OH-ibafloxacin. Lower plasma levels are likely to affect barrier crossing; this will lead to lower tissue levels. This means that the upper limit of 0.5 µg/ml for the MIC_{90} of relevant pathogens, as based on levels for the tablet formulation, cannot be used for the gel formulation.

In strictly applying the bioequivalence guideline it was concluded for the dog that, although the AUC levels are comparable between the gel and the tablet formulations, both formulations are not considered bioequivalent, because of the consistent lower C_{max} levels in the gel formulation compared to the tablet formulation (approximately 60% of the corresponding value for the tablets in some cases).

Nevertheless, a dosage of 15 mg/kg once daily was considered justifiable based on the knowledge that the absolute levels of the active substance are well over the MICs for relevant pathogens and based on the knowledge that ibafloxacin exerts a post antibiotic effect (PAE), has a $T_{1/2}$ elim of about 5 hours and has good tissue distribution although levels are about 1/3 of those in plasma.

Cat pharmacokinetic studies

Plasma kinetics of ibafloxacin and metabolites in cats after a single oral administration of a gel fromulation containing 2.5% w/w/ Carbopol and 3% w/w/ ibafloxacin at a dose of 15 mg/kg ibafloxacin/kg body weight (pilot study)

One cat was given a single dose on two occasions and 2 cats were given ibafloxacin gel, mixed with tin food. C_{max} in plasma varied from 3.20 to 4.60 µg/ml for the microbiological assay or 2.19 to 4.20 µg/ml for HPLC. T_{max} varied from 2-4 hours. Levels in plasma at 8 and 24 hours p.a. varied from 0.95-1.4 or 0.12-0.49 µg/ml.

For the cat that was treated twice, a considerable difference in plasma profiles was established between the first and the second treatment. The plasma profile could not be properly established because the number of samplings shortly after administration was rather low. T_{max} is to be expected somewhere between 2 and 4 hours p.a. The presence of food does not seem to affect the absorption.

Compared to the dog, ibafloxacin plasma levels are less, but persist over a longer period. The plasma profile for the metabolites is comparable to that of the dog, but at a lower level.

Plasma kinetics of ibafloxacin and metabolites in cats after a single oral administration of a gel formulation at a dose of 15 mg ibafloxacin/kg body weight (pilot study)

Ibafloxacin gel was given to cats (male and female) directly into the mouth. C_{max} ranged from 2.05 to 3.98 µg/ml (microbiological method) or 1.24 to 3.66 µg/ml by HPLC. 8-OH-ibafloxacin was the major metabolite and was found in higher concentrations, compared to ibafloxacin. C_{max} for 8-OH-ibafloxacin ranged from 7.64 to 9.92 µg/ml (HPLC) and T_{max} varied from 3-6 hours. It was noted that from 1 hour after administration plasma levels for 8-OH-ibafloxacin are considerably higher than for ibafloxacin.

Pilot pharmacokinetic study of ibafloxacin (37.5 mg/kg) after a single oral dose of a 7.5% ibafloxacin gel formulation

The ibafloxacin gel formulation was given to cats (male and female) as a single dose directly into the mouth. Food was made available directly after.

A higher dose of ibafloxacin produced higher levels, but does not seem to result in a considerable higher persistence of levels. Two thirds of cats showed levels > 0.5 µg/ml at 8 hours post administration and less than one third at 12 hours post administration.

Pharmacokinetic study of ibafloxacin after a single oral dose (5 mg/kg) of a gel formulation and after a single intravenous dose (5 mg/kg) of an aqueous solution to cats

Ibaflin as a 3% gel formulation or as a 2.5% aqueous solution was administered to cats (males and females) in a two period cross-over study design.

METHOD	**HPLC**		**microbiological**	
PARAMETERS	i.v.	oral	i.v.	oral
T_{max} (h)	-	2.07	-	2.14
C_{max} (µg/ml)	-	1.93	-	1.10
Cl_b (ml/min/kg)	6.85	-	6.07	-
AUC_t (µg.h/ml)	12.13	4.79	13.11	6.45
$t_{1/2}$elim (h)	2.84	3.50	3.31	4.84
V_{dss} (l/kg)	0.85	-	1.09	-
V_{darea} (l/kg)	1.64	-	1.66	-
MRT (h)	13.65	6.06	3.21	8.01
Bioavailabilty (%)	-	36.6	-	46.0

Pharmacokinetic study of ibafloxacin after a single oral dose (15 mg/kg body weight) of a 3% gel formulation to cats - influence of food intake on ibafloxacin kinetics

Healthy cats (males and females) were randomly allotted to three treatment groups. Ibafloxacin gel was given at 3 separate occasions and at 3 different modes of administration. A three-period cross-over study design was used. Pharmacokinetic parameters were determined.

As for the dog, higher levels are achieved in the cat when ibafloxacin is given with food.

Pharmacokinetic study of ibafloxacin in plasma after a single oral dose (7.5, 15 and 30 mg/kg body weight) of a 3% gel formulation to cats (dose linearity)

Healthy cats (males and females) were randomly allotted to three treatment groups. Ibafloxacin gel was given as a single oral treatment on 3 separate occasions in three different doses, using a three period cross-over study design. Pharmacokinetic parameters were determined.

Ibafloxacin levels and related parameters were measured. Plasma concentrations increased with dose. When normalized for dose, relatively high values for C_{max}, AUC and T_{max} were seen for the 15 mg/kg dose. Therefore, at a dose of 7.5 mg/kg the available absorption capacity was not completely used; at a dose of 30 mg/kg the absorption capacity is somewhat exceeded. Values for C_{max} and AUC indicate that the total amount absorbed still increases with dose; the rise in T_{max} indicates that the absorption rate is rather constant. This can also be seen from the graphical depiction of plasma levels; the absorption phase is similar for all three doses. For 8-OH-ibafloxacin values were also measured (HPLC only).

Pharmacokinetic study of ibafloxacin after repeated administration of ibafloxacin 3% gel to cats at a dose rate of 15 mg/kg body weight once daily

Multiple dose pharmacokinetics of ibafloxacin, administered daily for 10 consecutive days, were studied inmale and female cats. Results for plasma were as follows (for ibafloxacin only, by HPLC).

Time →	**D1**		**D5**		**D10**	
PARAMETERS ↓	**HPLC**	**microbiol.**	**HPLC**	**microbiol.**	**HPLC**	**microbiol.**
C_{max} (µg/ml)	3.26	3.79	4.11	4.51	5.24	6.03
C_{min} (µg/ml)	0.03	0.08	0.06	0.12	0.14	0.36
T_{max} (h)	2.92	2.92	3.25	3.00	3.25	2.94
AUC_{0-24} (µg.h/ml)	19.16	22.76	27.70	32.87	36.94	46.87
$T_{>0.5\ mcgml}$ (h)	-	9.67	-	11.50	-	13.00
MRT_{inf} (h)	5.43	6.34	6.09	6.86	6.66	8.14

Over the 10-day period levels of metabolites tend to show an increase. Between 18 and 59% of the administered daily dose was excreted in the urine over a 24 hour period. Repeated administration of ibafloxacin to the cat resulted in a modest accumulation of ibafloxacin and its metabolites. However, it was observed from the graphical depiction that metabolite levels in urine do not show an increase over time. Therefore, the increase of plasma levels for ibafloxacin in time may be caused by exceeding the metabolic capacity. Moreover, the increase of levels for the metabolites indicates that clearing capacity of the kidneys is exceeded as well. It is unclear whether this is due to conjugation or/and metabolism (ibafloxacin is not only metabolised in the liver, but in other tissues / organs as well).

VALIDATION STUDIES FOR THE CAT

Validation of ibafloxacin microbiological assay in cat plasma

The method is based on a microbiological agar diffusion assay for cat plasma, using *E. coli* ISF 432 as a test organism. Values for LOD and LOQ as found, were 50.8 ng/ml and 62.5 ng/ml respectively. A linear relationship between ^{e}log. concentration and inhibition zone was found within the range of 62.5-2000 ng/ml. The precision was between 7.9% and 16.5% and mean accuracy was between 0.0% and 15.18%. The validation was based on ibafloxacin only. However, *in vivo*, the antimicrobial activity is based on ibafloxacin and 8-OH-ibafloxacin. The FIC index for E. coli strains is estimated at about 0.3 for a 1:1 ratio (see study PD9 form the tablet dossier). Therefore, the test will not indicate the proper ibafloxacin levels, but will give an overestimation. This can also be seen from the comparisons of values from the HPLC and the microbiological method.

Validation of ibafloxacin microbioligical assay in cat urine

The method is based on a microbiological agar diffusion assay for cat urine, using *E. coli* ISF 432 as a test organism. The method was validated with and without beta-glucuronidase. The LOD and LOQ were 0.03 µg/ml and 0.4 µg/ml respectively. A linear relationship between ^{e}log concentration and inhibition zone was found within the range of 0.4-10 µg/ml. The precision was between 10.8% and 20.3% and mean accuracy was between -23.32% and -3.70%. The relevance of this validation study is

not clear. *In vivo*, nearly all active substance in the urine is present as metabolites. Ibafloxacin is not present in the urine in such quantities that it is of antimicrobial significance.

Validation of the method for the quantification of ibafloxacin, 7-OH- and 8-OH-ibafloxacin in cat plasma by positive electrospray tandem mass spectrometry

Concentration ranges for calibration lines were 16-2000 ng/ml for ibafloxacin, 8-1600 ng/ml for 7-OH-ibafloxacin and 9-1700 ng/ml for 8-OH-ibafloxacin. Nalidixic acid was used as an internal standard. Also stability in plasma was investigated. Concentrations in plasma samples appeared to correlate well to a log. linear model. Overall mean recoveries were 90.4% for ibafloxacin, 101.7% for 7-OH- and 92% for 8-OH-ibafloxacin. LOQs were 15.9 ng/ml, 8.2 ng/ml and 8.7 ng/ml respectively. Stability in plasma was at least one month.

Validation of the liquid chromatography tandem mass spectrometry method used for the quantification of ibafloxacin and its metabolites in cat urine

Concentrations from the urine samples appeared to correlate well to a log. linear model, with no difference caused by the presence of beta-glucuronidase. Stability in urine was at least one month. However, the relevance for the validation of ibafloxacin is not clear. *In vivo* nearly all active substance in the urine is present as metabolites.

Validation of ibafloxacin and 8-OH-ibafloxacin enantiomer determination in cat plasma by capillary zone electrophoresis after solid phase extraction
Concentrations in spiked plasma samples were comparable to those in dilution solvents.

Validation of the capillary zone electrophoresis method used for the determination of ibafloxacin enantiomer ratio and quantification of 8-OH-ibafloxacin enantiomers in cat urine
The concentration ranges used were 5.2-100 µg/ml. Using a log-log model, the response function was linear for these ranges. The presence of beta-glucuronidase did not affect the results.

OVERALL CONCLUSION ON VALIDATION STUDIES FOR THE CAT

Study results indicate that ibafloxacin and metabolites can be determined in relevant body fluids. The level of precision and accuracy is satisfactory.

OVERALL CONCLUSION ON PHARMACOKINETIC STUDIES FOR THE CAT

From the pharmacokinetic studies it can be concluded that the plasma level profile in the cat after the administration of the gel formulation in the same dose is different from the plasma level profile in the dog. Maximum levels are lower and the plasma level profile for 8-OH-ibafloxacin is also different from that in the dog. Consequently ratios in time for ibafloxacin and 8-OH-ibafloxacin are also different, leading to a difference in bacterial kill effect compared to the dog.

The clinical dosage as recommended by the applicant is 15 mg ibafloxacin/kg once daily for 10 days. However, only one study has been submitted in which 3 different doses were compared for their pharmacokinetic qualities.

According to the applicant the literature indicates that Cmax/MIC and AUC/MIC (= AUIC) ratio can be used as predictors for clinical response to antimicrobial therapy. A ratio of > 8 for Cmax/MIC and a value of about 30 to 125 for AUIC have been indicated as breakpoints. In fact, it is suggested that AUIC gives a better indication of both the clinical and microbiological outcome for the fluoroquinolones and a means of comparing the effects of different fluoroquinolones. By using the MIC_{90} value obtained for ibafloxacin against most relevant feline pathogens (i.e. ≤ 0.5 µg/ml) and the C_{max} and AUC determined by the microbiological assay, a single oral dose of ibafloxacin (15 mg/kg)

in cats yields a C_{max}/MIC of around 8 (1 day of treatment) to 12 (10 days of treatment) and an AUIC of around 50 (1 day of treatment) to 100 (10 days of treatment) in cats. The applicant concluded that the C_{max}/MIC and AUIC obtained with Ibaflin oral gel in cats are sufficiently high to predict likely bacteriological and clinical efficacy.

The reasoning given for the deduction of a dosage in cats from dog data was submitted but not accepted by the Committee. The assumption that the dosage for ibafloxacin can be based on the dosages for enrofloxacin, norfloxacin and ciprofloxacin had not been adequately verified. The clearance concept has not been accepted as a basis for dosage substantiation.

On the basis of the dossier for the tablet formulation it was concluded that the antibacterial activity of ibafloxacin was most likely to be produced by synergy of ibafloxacin and 8-OH-ibafloxacin, firstly exposing bacteria to levels of ibafloxacin, exceeding MIC or MBC manifold, and sequentially to a persistent level of 8-OH-ibafloxacin. It is known that for quinolones, like ibafloxacin, the antibacterial activity can be increased considerably this way (in agreement with PK/PD principles), compared to maintaining levels above the MIC in time.

The applicant based the antibacterial activity upon maintaining ibafloxacin levels above the MIC of relevant pathogens. A value of 0.5 µg/ml is indicated as the level to be aimed at. Additionally, it is based on plasma levels, not tissue levels. Information on tissue levels for the cat is absent. It is not unlikely that lower maximum plasma levels as observed for the cat compared to the dog and for the tablet formulation, will lead to a lower level of tissue concentration and less persistence.

Kill curves showed that when bacteria were exposed to either concentrations of ibafloxacin or/and 8-OH-ibafloxacin, representative for plasma and the gel formulation in the cat, kill effect was rapid and nearly complete. Results were comparable to those obtained for the gel and the tablet in the dog.

The Committee concluded that although C_{max}/MIC and AUC/MIC ratios may be applicable as predictors for the results of clinical efficacy of fluoroquinolones in general, differences between the different types of fluoroquinolones are such that assumptions have to be verified. Without verification this assumption remains hypothetical. Nevertheless, the Committee agreed on the basis of the kill curves and clinical trials submitted that the applied dosage and duration of treatment for the clinical trials was acceptable.

TOLERANCE IN THE TARGET SPECIES

Two studies on target animal tolerance have been submitted.

Ibafloxacin was administered as tablets in dosages of 0, 15, 45 and 75 mg ibafloxacin/kg BW to 4 goups of 8 Beagle dogs during 90 days. At the start of the study, animals were 8 months of age. Necropsy was performed at the end of the study and the left and right shoulder, elbow, hip and knee joints were examined. Treatment resulted in a dose dependent increase in the number of animals showing lesions of the articular cartilage: 1/8 in the 45-mg-group (1/64 joints affected) and 5/8 in the 75-mg-group (5/64 joints affected). It was concluded that 15 mg ibafloxacin/kg BW was the NOAEL for the dog.

Dogs (8 months of age, 4 males and 4 females per group) were treated orally with ibafloxacin for 90 days, once daily, on an empty stomach. Food was given directly after administration. It was concluded that the test article was safe when given during 90 days in the clinical dose of 15 mg/kg to Beagle dogs, which were about 8 months of age at the start of the study. The only symptom of toxicity in the higher dose group was a moderate quinolone-induced type of lesion of the cartilage in 1 joint out of 64 examined joints in 1 of the 8 animals in the 45 mg/kg group, and in 5 joints out of 64 examined joints in 3 of the 8 animals in the 75 mg/kg group. Additionally, at gross pathology, lesions in 4 joints of 3 animals in the high dose group were seen without microscopic changes.

Although in this study articular changes were recorded only at the higher dose levels, it was decided that the use of ibafloxacin should be contraindicated in all skeletally immature animals, even at the RTD.

A study of the potential of phototoxicity of ibafloxacin has been assayed by uptake of neutral red in Balb/c 3T3 fibroblast cells. The results show that ibafloxacin was not phototoxic in the *in vitro* test system, according to the proposed OECD guideline evaluation criteria. Also the metabolites of ibafloxacin, 7-OH and 8-OH were assayed. Both fulfilled the criteria for a test article to be considered phototoxic in this system. However, the concentrations at which phototoxicity was observed were high, above 10 μg/ml for 7-OH and above 18 μg/ml for 8-OH. In pharmacokinetic studies it is observed that maximal plasma levels of 7-OH and 8-OH are below these concentrations, i.e. less than 1 μg/ml for 7-OH and less than 7.66 μg/ml for 8-OH. Thus, plasma concentrations of 7-OH and 8-OH observed after oral Ibaflin administration to dogs, are well below the concentrations which were shown to be phototoxic *in vitro*. Furthermore, in preclinical studies it is observed that ibafloxacin levels in skin are not higher than levels observed in plasma. Therefore, the levels of metabolites present in skin and which are potentially exposed to Ultra Violet light, are expected to be below levels observed to be active in the *in vitro* test system. Furthermore, preclinical target animal safety studies and the clinical studies indicate that Ibafloxacin causes no risk for phototoxicity. The only side effects observed were diarrhoea, vomiting, dullness and anorexia.

Vomiting, a reduced feed intake, reduction of RBC, leucocyte count and total plasma protein, pale faeces and changes in organ weight have been observed in the dog. These effects are transient and only appear at dose rates, much higher than the recommended therapeutic dose. A warning statement on adverse effects is included in section 5.3 of the SPC.

In one study ibafloxacin tablets were administered to 4 groups of 6 female dogs in dosages of 0, 15 and 45 mg ibafloxacin/kg BW, during 90-98 days, beginning in the pro-estrus phase until the end of the 3rd week of lactation. A total of 113 pups were born. No adverse effects on fertility and pregnancy, and no differences between groups in still-birth, mortality or congenital defects were observed. Appetite was reduced around parturition. One pup from the 15-mg-group and 2 from the 45-mg-group showed an abnormality of the hair coat. Blood samples from pups at 3 weeks of age did not reveal ibafloxacin to be present in plasma. It was concluded that ibafloxacin at a dose rate of 15 mg/kg could be safely administered to female breeding dogs during pregnancy and lactation.

No information is present on the safe use of ibafloxacin in the male breeding dog, but in view of the absence of adverse effects in the male rat no adverse effects in male breeding dogs are to be expected.

Oral Gel formulations

New studies for the dog and the cat, performed with the gel formulation, were submitted.

Pilot safety study of a gel formulation containing 3% ibafloxacin and 2.5% carbopol in male and female dogs

Ibafloxacin gel was given to male and female Beagle dogs for 30 days at a dose rate of 45 mg/kg/day (3 times the recommended dose), directly into the mouth. It was concluded that ibafloxacin gel is well tolerated by the dog when given at a dose of 45 mg/kg/day for 30 days.

90-day safety study in adult Beagle dogs after once daily oral administration of 1.3 or 5 times the recommended clinical dose of INT-5926

Ibafloxacin was administered as a gel formulation to male and female dogs for 90 days at doses of 15, 45 or 75 mg/kg daily. According to the applicant the observed NOEL was 75 mg/kg/day.

Similar studies have been performed for ibafloxacin, administered in capsules (90-day safety study with doses of 5, 10 or 15 mg/kg/day), or as tablets (90 day oral safety study with doses of 15, 45 or 75 mg/kg/day). In the last study treatment resulted in a change of haematological parameters as well as joint abnormalities (5/8 animals in the 75 mg/kg-group). The observed NOEL was 15 mg/kg.

In view of the pharmacokinetic characteristics of the gel and tablet formulations, differences between studies are likely to be related to differences in C_{max}, as AUCs are comparable (even higher for the gel

formulation).

Pilot safety study of a gel formulation containing 3% ibafloxacin and 2.5% carbopol in male and female cats

Ibafloxacin gel was given to male and female cats, 1-1.5 years of age, at a dose rate of 45 mg/kg/day for 30 days. The gel was well accepted and did not cause any local adverse effect. It was concluded that ibafloxacin gel is well tolerated by the cat when given at a dose of 45 mg/kg/day for 30 days.

30-day safety study in adult cats after once daily oral administration of 0, 1, 3 or 5 times the recommended clinical dose (15 mg/kg body weight) of ibafloxacin (INT-5926) 3% gel

Ibafloxacin gel was given to cats male and female 8-11 months of age, at a dose rate of 15, 45 or 75 mg/kg/day for 30 days. All animals were subjected to a *post mortem* examination. It was concluded that ibafloxacin gel is safe when given at a dose of 15 mg/kg/day for 30 days. The frequency of observed adverse effects (vomiting and salivation) was low.

Evaluation of *in vitro* phototoxicity of ibafloxacin on BALB/c 3T3 fibroblasts using the neutral red uptake assay

Ibafloxacin did not appear to be phototoxic *in vitro*, but the metabolites were.

OVERALL CONCLUSION ON TOLERANCE STUDIES FOR THE DOG AND THE CAT

The studies indicate that ibafloxacin gel is well tolerated by the dog and the cat, when given at the recommended treatment dose as well as at a 5-times overdose. The maximum treatment period was 90 days for the dog and 30 days for the cat. No treatment-related adverse effects were observed in both species.

The results for the dog are in agreement with those submitted for the tablet formulation, although the safety margin for the gel appears to be much wider than for the tablet. This can be accounted for by the differences in pharmacokinetics between both formulations. It is concluded that Ibaflin oral gel is well tolerated by the dog and the cat.

RESISTANCE

MIC values of ibafloxacin against pathogens isolated from diseased dogs have been determined. The report gives an overview of MIC values of ibafloxacin against bacteria isolated from dogs with dermatitis or pyoderma (n=435), and urinary (n=251) or respiratory tract infections (n=155) in France, the United Kingdom, Germany, Slovakia and the Netherlands. MICs of ibafloxacin were determined for strains isolated between 1987 and 1998. Data show that over the different indications and countries, *Escherichia coli*, *Pasteurella* spp., *Klebsiella* spp, *Proteus* spp, *Staphylococcus aureus* and *Staphylococcus intermedius* are sensitive for ibafloxacin. For the pathogens on which sufficient data were available, the possible change of MIC values over time was studied. For each pathogen, data were pooled for all indications per country per year to obtain groups sufficiently large for evaluation. MIC calculations show that over the years, there is no increase in the MIC concentrations of ibafloxacin for the sensitive pathogens. Especially for *E. coli*, *S. aureus* and *S. intermedius*, where most data were available, MIC_{50} and MIC_{90} values for strains isolated between 1987 and 1998 are comparable and within the range of 0.128-0.5 µg/ml. No substantial differences in sensitivity for ibafloxacin between different countries was observed. It should be noted that species such as Streptococcus, Pseudomonas and Bordetella were not included in this list of sensitive species.

Although plasma mediated quinolone resistance is possible, it is not a common route. Mutation in genes that code for GyrA or GyrB or changes in membrane characteristics, reducing the uptake of quinolones are more likely to be a cause of resistance.

It was concluded that as with all other antibiotics, the use of ibafloxacin is likely to result in an increase in prevalence of resistant strains although this risk may be less due to the treatment of individual animals for this product. Due to known problems with increasing fluroquinolone resistance the SPC includes under section 5.4 the following statement: *'Ibaflin should only be used based on susceptibility testing.'*

According to the applicant the occurrence of strains, resistant to quinolones, is low for the dog. No data are available for ibafloxacin, but for other quinolones used in small animal veterinary practice no increase has been observed.

CLINICAL STUDIES

Wound infection model

A wound infection model was developed to investigate the activity of ibafloxacin. In healthy Beagle dogs an incision was made in the dorsal neck region and inoculated with a suspension containing microbeads and *E. coli* or *E.coli* and *Proteus mirabilis*. Thereafter, dogs were treated daily with ibafloxacin for 10 consecutive days (directly after administration, food was made available) or were left untreated. The dogs were monitored daily for appetite, general clinical appearance and rectal temperature. The appearance of the wound was scored (severe swelling, redness, temperature, pain, pus formation) and the size of the swelling was measured. The wound lesions were aspirated at several days after infection and the exudate samples were cultured for bacterial count of the challenge strain. At the site of the incision and bacterial inoculation an infection process developed characterised by swelling, pus/exudate formation and sometimes accompanied by redness and heat. Three trials were performed. In the first two trials, 15 mg ibafloxacin per kg bodyweight (BW) was given daily. The third trial was a dose titration experiment in which ibafloxacin dosages of 7.5, 15 and 30 mg/kg were investigated.

All three studies performed show that an oral once daily dose of 15 mg ibafloxacin per kg bodyweight given for 10 consecutive days is effective in reducing the clinical signs of the induced wound infection and in reducing the bacteriological infection as compared to untreated animals. It was noted that self-cure was also present, which is not uncommon. The dose titration study demonstrates that dosages of 7.5, 15 and 30 mg/kg all are effective. However, increasing the dosage results in an earlier onset of effect. No statistically significant differences were observed at all time points examined between the three dose groups on the general wound appearance and swelling. On the bacterial counts, a greater improvement was observed in the 15 and 30 mg/kg dose groups as compared to the 7.5 mg/kg dose group earlier in the treatment (day 1, 2 to 3). No statistically significant differences in improvement were observed between the 15 and 30 mg/kg groups on day 2 and 3. On day 1, the improvement in the 30 mg/kg group was greater than in the 15 mg/kg group. Because a longer treatment duration period is foreseen (up to 90 days) and a severe infection was induced in this model system, the clinical relevance of this difference on day 1 is probably very limited. Therefore, as basis for the field trial experiments, a clinical dose of 15 mg/kg was selected. In this decision also the aspect of safety, for which a lower dose is always preferred, was taken into consideration.

In conclusion, ibafloxacin was evidently successful, both at a clinical and a bacteriological level, in these experimental studies.

Cystitis model

A cystitis model was developed in Beagle dogs to investigate the efficacy of ibafloxacin and to confirm the dose derived from the wound infection model. In two pilot studies, some initial investigations were performed for the development of the model. These studies showed that the *E.coli* cystitis model could be a valuable tool in the evaluation of the efficacy of ibafloxacin. In this model, cystitis was induced by inoculation of a suspension of a recent canine urinary tract *E. coli* isolate in the bladder after irritation of

the bladder wall with a salicylic acid/ethanol solution. Three days later urine was collected by cystocentesis and the urinary bacterial concentration was determined. Dogs with low and high bacterial counts were equally divided over the ibafloxacin treatment group(s) and the control group. Ibafloxacin treatment was started at day 4 after induction of cystitis. The duration of ibafloxacin treatment was 10 days (directly after treatment food was made available). The dogs were monitored by general examination, body weight, body temperature, frequency of micturitions, thickening of the bladder wall, pain at palpation, urinalysis, haematology and urinary bacterial count.

Three experiments have been performed. In two studies, ibafloxacin tablets were given at a dose of 15 mg/kg/day. In the third study, dosages of 2.5, 5, 10 and 20 mg/kg/day were administered. Untreated controls were included in the experiments.

The clinical signs of cystitis in this model (increased frequency of micturition and thickening of the bladder wall) were not very pronounced. Patterns of urinalysis and haematology were also comparable in treated and control dogs. Therefore, these parameters could not be used to evaluate the efficacy of ibafloxacin. Only the bacteriological cure was proposed to determine efficacy of ibafloxacin. The bacteriological data of the three trials with the cystitis model have been compared. At three to four days after the start of treatment, the number of bacteria in the treated groups was reduced in all dogs and in all groups more than 75% of the urine samples were found to contain little or no bacteria. After seven days of treatment, all urine samples, except from one dog in the 2.5 mg/kg dose group, had log CFU/ml < 2 and the mean log CFU for all groups was < 1. This corresponds with a reduction of 5 log compared to the challenge strain concentration before therapy or a killing of 99.999%. In the untreated control group, the colony counts at those days were unchanged compared to the bacterial concentration before treatment.

At 3 days after cessation of treatment, no re-growth of bacteria was observed in the 20 mg/kg group, while at 5 and 10 mg/kg some re-growth was observed. At 12 days after cessation of treatment, some re-growth was seen in all treated groups. This re-growth was probably caused by the model which induces prostatitis and/or chronic cystitis for which long term ibafloxacin treatment would be required.

In conclusion, the cystitis model experiments confirm that the dose derived from the wound infection model studies of 15 mg/kg, is likely to be also effective in dogs suffering from cystitis. A lower dose is probably also effective for cystitis. However, in order to reduce the potential for re-growth and for the purpose of a uniform dosage for all indications in order to avoid compliance problems, the dose of 15 mg/kg appears appropriate.

In conclusion, it appeared that cystitis could be successfully induced. However whilst cystitis produces classical clinical signs, the diagnosis is largely dependant on abnormal findings on urinalysis (increased WBCs, haematuria, pyuria etc.) and urine culture. Surprisingly, urinalysis was similar between controls and treated animals. The relapse rate after treatment was relatively high, with male animals being especially susceptible to the infection. The animals were only assessed for increased frequency of urination during short specified periods of time. The results of this trial should be compared with the field clinical trial for cystitis, where it is claimed that 10 days of treatment was sufficient for the vast majority of cases.

CLINICAL TRIALS IN THE FIELD

Four field trials, two concerning dermal problems, one concerning urinary tract infections and one concerning respiratory problems were submitted.

A field trial to assess the efficacy of Ibaflin tablets as compared to marbofloxacin tablets for the treatment of pyoderma in dogs

The clinical efficacy and safety of ibafloxacin tablets for the treatment of pyoderma in dogs was investigated in a multicentre, randomised, non-blinded and controlled field trial in The Netherlands, Germany and France. Marbofloxacin tablets were used as positive control product.

Parameters for the clinical response were: proportion of treatment failures, improvement of the general condition scores (rectal temperature, attitude, appetite) and the improvement of the specific disease scores. Bacterial cultures were performed to identify the bacterial species present at admission. The mean duration of treatment was 5-6 weeks. Most frequently, dogs were treated for 3 weeks.

The severity scores in the ibafloxacin group did not differ significantly (P>0.05) when compared with the scores in the marbofloxacin group. In both the ibafloxacin group and the marbofloxacin group all scores were significantly lower (P < 0.0001) at all reported examinations when compared with the scores at the previous examination. The scores for appetite, attitude, papules, pustules, crustae, collarettes, maculae, comedones, fistulae, cellulitis and erythema did not differ significantly (P>0.05) between the treatment groups.

Seven days after last treatment, 74% of the dogs in the ibafloxacin group had responded to treatment. In the marbofloxacin group 81% of the dogs responded to treatment. The overall response to treatment did not differ significantly between the treatment groups (P > 0.05).

The time of administration seemed not to have an influence on the response to treatment. At the day of last treatment + 7, 4 dogs (4%) in the ibafloxacin group and two dogs (2%) in the marbofloxacin group showed a relapse of pyoderma (P>0.05). At the day of last treatment + 28, two dogs (3%) in the ibafloxacin group and ten dogs (11%) in the marbofloxacin group showed a relapse of pyoderma, a significant difference: P=0.03.

Side effects were rare: one case of diarrhoea in the ibafloxacin treated animals and one case of an allergic reaction in the marbofloxacin group.

Conclusions

It is concluded that treatment with ibafloxacin reduced the clinical symptoms of pyoderma as effectively as marbofloxacin. Ibafloxacin used at the recommended dose up to 112 days is tolerated well in dogs kept under field conditions. Antibiotic related side effects occurred at a similar (low) frequency in dogs treated with ibafloxacin or marbofloxacin. However, it should be noted that no relationship with the sensitivity of cultured pathogens has been proven since no sensitivity data have been produced and samples for bacteriological culturing were only taken at Day 0.

A field trial to assess the efficacy of ibafloxacin tablets as compared to enrofloxacin tablets for the treatment of urinary tract infection in dogs

The clinical efficacy and safety of ibafloxacin tablets were investigated in a multicentre, randomised, non-blinded and controlled field trial involving dogs with a urinary tract infection. Enrofloxacin tablets were used as positive control product.

Dogs with bacterial urinary tract infection were treated with ibafloxacin or the control product. Ibafloxacin was dosed at 15.0 mg/kg body weight, preferably at feeding. Enrofloxacin was dosed at 5 mg/kg body weight. Both products were administered orally, once daily. The treatment period was 10 days. The clinical status of each dog was evaluated at admission (Day 0), at Day 5 ± 1, at Day 10 ± 1 and the final examination took place at Day 15 ± 1.

The clinical response of dogs treated with ibafloxacin was compared with that of dogs treated with enrofloxacin. Bacterial cultures were performed at admission and at the final examination to identify the bacterial species present before treatment and to determine the bacteriological cure.

Results

A total of 292 dogs were admitted to the trial. Eleven dogs were withdrawn from the analysis because the protocol was not or could not be correctly implemented. The remaining 281 dogs, were divided to bacteriological result: 204 dogs with a positive bacterial culture at admission and 77 dogs with a negative bacterial culture.

Dogs with a positive bacteriological culture

The bacteria cultured consisted mostly of *E.coli* (52% and 43%) or *Enterobacter spp* (25% and 22%) either as monoculture or mixed culture. In both the ibafloxacin group and the enrofloxacin group the specific condition scores were significantly lower at the examination at day 5, 10 and 15 when compared with the scores at the previous examination. At day 5 the specific condition scores in the Ibaflin group were significantly lower when compared with the enrofloxacin group.

In both the ibafloxacin group and the enrofloxacin group the rectal temperatures at Day 5 and Day 10 were significantly lower ($P < 0.05$) in both treatment groups when compared with the rectal temperatures at the previous examination. No significant differences were found between the treatment groups.

The scores for appetite and attitude did not differ significantly ($P > 0.05$) between both treatment groups.

At day 5, the scores for frequency of urination in the ibafloxacin group were significantly ($P < 0.05$) lower when compared with the scores in the enrofloxacin group. Further, including the scores for volume of urine, no significant differences ($P > 0.05$) were found between the treatment groups.

At Day 15, 79% of the dogs in the ibafloxacin group was considered as cured, in total 93% of the dogs responded to treatment. In the enrofloxacin group 71% were considered as cured, in total also 93% of the dogs responded to treatment. The response to treatment did not differ significantly ($P>0.05$) between the treatment groups. The bacteriological cure could be established in 88 dogs of the ibafloxacin group and 77 dogs of the enrofloxacin group. The bacteriological cure rate did not differ significantly ($P>0.05$) between the treatment groups: 79% in the ibafloxacin group and 87% in the enrofloxacin group. The bacteriological cure of *E.coli* infections was significantly ($P<0.05$) better in the enrofloxacin group when compared with the ibafloxacin group.

Suspected side effects were observed in 3 animals treated with ibafloxacin and 3 animals treated with enrofloxacin. Side effects were vomiting, dullness, pale faeces and diarrhoea. These side effects were of a mild nature, they occurred during treatment and were not a reason to interrupt or stop the treatment.

At Day 15, 93% of the dogs in the ibafloxacin group responded to treatment. In the enrofloxacin group 92% of the dogs responded to treatment. The overall response to treatment did not differ significantly between the treatment groups ($P>0.05$).

Conclusions

It is concluded that:treatment with ibafloxacin reduced the clinical symptoms of urinary tract infections as effectively as enrofloxacin. Ibafloxacin used at the recommended dose during 10 days is tolerated well in dogs kept under field conditions. Antibiotic related side effects occurred at a similar (low) frequency in dogs treated with ibafloxacin or enrofloxacin.

A point of concern out of these studies is that the efficacy of ibafloxacin against *E. coli* was not as high as for enrofloxacin. *E. coli* would be the dominant pathogen in canine urinary tract infections. However, the clinical response was deemed to be adequate. A similar comment as for the first trial is that no sensitivity testing has been performed. The dosage rate may not be as critical for this indication as experience has shown the tremendous concentrating capacity of urine. Side-effects were present at a low frequency and overall tolerance was good.

A field trial to assess the efficacy of Ibaflin tablets as compared to amoxicillin/clavulanic acid tablets for the treatment of soft tissue infection in dogs

The clinical efficacy and safety of ibafloxacin tablets were investigated in a multicentre, randomised, non-blinded and controlled field trial involving dogs with a soft tissue infection. Amoxicillin/clavulanic acid tablets were used as positive control product.

Ibafloxacin was dosed at 15.0 mg/kg body weight, and administered orally once daily, preferably at feeding. Amoxicillin/clavulanic acid was dosed at 12.5 mg/kg body weight, and administered orally twice daily. The treatment period was 10 days. The clinical response of dogs treated with ibafloxacin was compared with that of dogs treated with Amoxicillin/clavulanic acid. Bacterial cultures were performed to identify the bacterial species present before treatment.

Results

The bacterial pathogens found in both treatment groups were mostly *Staphylococci spp*.(55-60%), either as a pure or mixed culture. The rectal temperatures of the dogs in both the ibafloxacin group and amoxicillin/clavulanic acid group were significantly lower at day 5 (P=0.001 and P=0.03 respectively) compared to the rectal temperatures at admission. No significant differences were found between both treatment groups. In both treatment groups the disease-specific clinical parameters (swelling, pain and exudate) were significantly (P<0.001) lower at Day 5 when compared with admission and at Day 10 when compared with day 5.

The mean specific lesion scores decreased significantly in both the ibafloxacin group and the amoxicillin/clavulanic acid group. All were significantly lower (P < 0.0001) at the examination at day 5, 10 and 15 when compared with the scores at the previous examination. No significant differences were found between both treatment groups. At Day 15, 95% of the dogs in the ibafloxacin group had responded to treatment. In the amoxicillin/clavulanic acid group 87% of the dogs responded to treatment. The response to treatment did not differ significantly (P>0.05) between both treatment groups.

In the ibafloxacin group, 3 adverse events were reported: one dog was dull during 4 hours after each treatment, one dog vomited at the second day of treatment and one dog showed watery diarrhoea during six days. Treatment was stopped in the last dog.

In the amoxicillin/clavulanic acid group, 2 adverse events were reported: one dog vomited and had diarrhoea during three days, one dog vomited and had a decreased appetite at day 7 of treatment. Treatment was stopped in both dogs.

Conclusions

Iis concluded that: ibafloxacin is equally effective for the treatment of clinical symptoms of soft tissue infections as amoxicillin/clavulanic acid. Ibafloxacin used at the recommended dose during 10 days is tolerated well in dogs kept under field conditions. Adverse events, probably related to antibiotic administration, occurred at a similar (low) frequency in dogs treated with Ibaflin or amoxicillin/clavulanic acid. This trial was considered to provide sufficient data for the indication of dermal tissue infections.

A field trial to assess the efficacy of ibafloxacin tablets as compared to Amoxicillin/clavulanic acid for the treatment of respiratory tract infection in dogs.

The clinical efficacy and safety of ibafloxacin tablets were investigated in a multicentre, randomised, non-blinded and controlled field trial involving dogs with a respiratory tract infection. Amoxicillin/clavulanic acid tablets were used as positive control product.

Dogs with bacterial respiratory tract infection (both upper and lower tract infections) were treated with ibafloxacin or the control product. Ibafloxacin was dosed at 15.0 mg/kg body weight, and administered orally once daily, preferably at feeding. Amoxicillin/clavulanic acid was dosed at 12.5 mg/kg body weight, and administered orally twice daily. The treatment period was 10 days. The clinical response of dogs treated with ibafloxacin was compared with that of dogs treated with Amoxicillin/clavulanic acid. Bacterial cultures were performed to identify the bacterial species present before treatment.

Results

Groups were comparable regarding age and type of infection. At admission a wide range of bacteria were found, either as a pure or mixed culture. Two dogs (2%) in the ibafloxacin group and six dogs (7%) in the amoxicillin/clavulanic acid group were considered treatment failures by the investigators. In both the ibafloxacin group and the amoxicillin/clavulanic acid group the rectal temperatures at Day 5 and Day 10 were significantly lower in both treatment groups when compared with the rectal temperatures at the previous examination. No significant differences were found between the treatment groups.

The general clinical parameters (appetite and attitude) tended to return to normal earlier (at Day 10) for the Ibaflin treated animals when compared to the amoxicillin/clavulanic acid treated animals. In both treatment groups the scores for sneezing, nasal discharge, respiration rate, respiration effort and auscultation did not differ significantly between the treatment groups.

In both the ibafloxacin group and the amoxicillin/clavulanic acid group the specific condition scores were significantly lower at the examination at day 5, 10 and 15 when compared with the scores at the previous examination. No significant differences were found between the treatment groups. At Day 15, 84% of the dogs in the ibafloxacin group were considered as cured and a total of 95% of the dogs responded to treatment. In the amoxicillin/clavulanic acid group 65% of the dogs were considered as cured and a total of 84% of the dogs responded to treatment. The response to treatment was significantly better in the ibafloxacin group when compared with the amoxicillin/clavulanic acid group.

One adverse event was observed in the ibafloxacin group and 2 in the amoxicillin/clavulanic acid group. The side effects observed were anorexia and diarrhoea with ibafloxacin and epilepsy and diarrhoea with amoxicillin/clavulanic acid. These side effects occurred during treatment, were of a mild nature, and were no reason to discontinue treatment.

Conclusions

It is concluded that ibafloxacin is at least as effective for the treatment of clinical symptoms of respiratory tract infections as amoxicillin/clavulanic acid. Ibafloxacin used at the recommended dose during 10 days is tolerated well in dogs kept under field conditions. Adverse events, probably related to antibiotic administration, occurred at a similar (low) frequency in dogs treated with Ibaflin or amoxicillin/clavulanic acid.

This indication has been adequately addressed by this study, however again it should be noted that it is difficult to find a relationship between pre-clinical and clinical data in view of the poor study design, in view of flaws in bacteriological sampling and dosage of the reference product.

Quinolones are likely to penetrate well into bronchial secretions, with levels equal to or higher than plasma levels. However, there are no data on levels for ibafloxacin and the data on lung tissue levels indicate a moderate penetration. Additionally, protein binding for ibafloxacin is relatively high (~90%), compared to that of other quinolones, with the free fraction of the S-enantiomer being even 3 times lower than that of the R-enantiomer. On the basis of lung tissue levels and MICs of relevant pathogens an effect can be present, but is not likely to persist for a sufficient long period of time (24 hours). Drug concentration data in lung beyond 4 hours is absent. Furthermore, the MIC values for pathogens such as Streptococcus and Pseudomonas species that were isolated in the respiratory trial, were well above the value of 0.5 µg/ml, and cannot be considered susceptible. No Bordetella species organisms were isolated, and so a conclusion on this organism is difficult. Nevertheless, the field trial indicates that ibafloxacin is an effective treatment in case of respiratory tract infections. This signifies probably that in this case lung tissue level, in combination with a MIC, is a poor predictor of efficacy. Probably levels in bronchial secretions persist longer than in lung tissue, with the possibility that the effect is increased by the effect of ibafloxacin against Bordetella as a relevant pathogen.

Oral Gel Formulations

No laboratory trials have been performed with the gel formulation. The applicant refers to the studies performed with tablets. One new field trial was submitted for the dog and three studies were submitted for the cat.

All studies were designed to demonstrate "non-inferiority" between Ibaflin oral gel and a comparator allowing for a 15% difference of an overall response in which the categories "cured" and "improved" were combined to "response" and "unchanged", "worsened" and "treatment failures" to "no response". The studies were non-blinded and the scores were based on the subjective observations of veterinarians which weakens the possible inference from a non-inferiority trial. A 95% confidence interval and a 'delta' of 15% were used. There were no cure-rates provided for the comparators. The relationship between the 15% difference of the overall response and the clinical condition observed in the trials is questionable. Possible bias arising from the combination of the data from the different centres in the multi-centre studies was not considered critical to the outcome of the studies.

Dog Field trials – oral gel formulations

Field trial to assess the efficacy of Ibaflin oral gel as compared to Ibaflin tablets for the treatment of pyoderma in dogs

The objective of the multi-centre, non-blinded, controlled field trial was to demonstrate the clinical equivalence of Ibaflin oral gel with Ibaflin tablets. A difference $\geq$ 15% was considered as clinically relevant.

Pyoderma had been present for less than 5 weeks in 72% of the dogs. Pyoderma was recurrent in 51% of the dogs included in the gel group and in 60% of the dogs included in the tablet group (the medians were 10 and 8 days resp.). Pyoderma was considered to be superficial in 62% (gel), 53% (tablet) of the animals and deep in 38% and 47% of the animals respectively.

The clinical response was assessed on the basis of the change in overall severity scores at D21 and 7 days after the last treatment. Scores were compared by Chi^2- analysis. Ibaflin 5% and 7.5% gel and Ibaflin 150 or 300 mg tablets, both at a dosage of 15 mg ibafloxacin/kg/day, at feeding or with food. The initial treatment period was 21 days. This could be extended with 14 days, depending on the clinical condition of the animal.

The groups were comparable for age, weight, breed and clinical condition. *Staphylococcus intermedius* was the predominant pathogen, isolated from 88% (gel) and 82% (tablet) of cases respectively. Mean duration of treatment was 38.2 $\pm$ 22.5 days for the gel group and 43.7 $\pm$ 26.3 days for the tablet group.

Almost no differences in scores were observed between groups. Only at D21 a statistically significant difference was observed between groups in scores for fistulae. The overall response to treatment at 7 days after the last treatment was 84% for the gel group and 80% for the tablet group.

Conclusion

The reporting of the study was found unsatisfactory. Individual case form records were not submitted. Information on concomitant treatment was absent. Fever is considered to be a less reliable parameter for animals treated with quinolones, as a direct effect of treatment on body temperature through the central nervous system cannot be excluded. The study was not blinded and the overall assessment was based on subjective observations, using a method for which the interpretation on the outcome is not clear. This makes the interpretation of results rather difficult, as bias is likely to be present and treatment effects cannot be differentiated from other effects.

From the experimental infection model study (tablet dossier) it appeared that differences in effects between doses (7.5, 15 and 30 mg/kg respectively) were most obvious in the first days of treatment, with the lower doses being least effective. At D6 no differences were observed anymore. This may indicate that in case of pyoderma, when the primary cause is absent or eliminated, self cure may be

occurring and the ibafloxacin treatment is more supportive in nature. Any difference in improvement between the gel and the tablet may have been present, but was not observed because no observations were made within the first 7 days of treatment.

As no MIC data from the sampled bacteria were submitted, it is difficult to relate the gel study to the tablet studies and to explain the mechanism for the observed effect, taking the pharmacodynamic and pharmacokinetic characteristics of ibafloxacin into account.
In conclusion, the Committee agreed to accept the proposed claim for treatment of pyoderma in dogs as the results from the clinical trial performed with a relatively large number of dogs indicated comparable efficacy of the gel formulation compared to the already approved tablet formulation.

Cat Field trials – oral gel formulations

Clinical trial to assess the efficacy of Ibaflin oral gel as compared to Clavulanic acid/amoxycillin tablets (amoxicillin, clavulanic acid) for the treatment of soft tissue infections in cats

A total of 206 cats, suffering from soft tissue infections such as wounds or abscesses, were included in a multicentre, randomised non-blinded controlled clinical trial, performed in the Netherlands, Germany and Italy. Data form 199 cats were evaluated, 103 being treated with Ibaflin and 96 with clavulanic acid/amoxycillin. Abscesses were present in 64% (Ibaflin) and 68% (clavulanic acid/amoxycillin) of all cases resp.; wounds accounted for 30% and 28% of all cases respectively.

The overall response to treatment was assessed at D14 as "cured", "improved", "not changed", "worsened" or "relapse". Scores were compared by Chi^2 analysis. The Ibaflin group was treated with Ibaflin 3% gel at a dosage of 15 mg/kg/day, once daily for 10 days, preferably at feeding. The clavulanic acid/amoxycillin group was treated with clavulanic acid/amoxycillin tablets at a dosage of 12.5 mg/kg twice daily for 10 days.

Groups were comparable for age, weight and clinical condition. Bacterial culture yielded a wide variety of pathogens, with *Pasteurella* and staphylococci being slightly predominant. At D14, 83% of the animals from the Ibaflin group was considered to be cured and 91% from the clavulanic acid/amoxycillin group. Differences were not statistically different. Only one adverse reaction was observed in the clavulanic acid/amoxycillin group (diarrhoea).

Conclusion

For Ibaflin about 51% of the animals could be considered as cured; for clavulanic acid/amoxycillin this was about 48%. The progression of cure is rather slow, but comparable, for both products. It goes on after the 10 days medication has stopped (D9), but this is likely to be caused by the aspect of the wound (not yet completely healed) rather than the persistence of infection. It is therefore likely that Ibaflin oral gel can be effective in case of dermal infections in the cat when used in a dose of 15 mg/kg.

Field trial to assess the efficacy of Ibaflin oral gel as compared to clavulanic acid/amoxycillin tablets for the treatment of respiratoy tract infections in cats

A total of 204 cats were included in a multi-centre, randomised non-blinded controlled clinical trial, 108 cats being treated with Ibaflin and 96 with clavulanic acid/amoxycillin. Animals were included when coughing or sneezing and/or showing nasal discharge, increased respiratory rate, fever or depression. About 80% of the cats suffered from upper respiratory tract infections.

The overall response to treatment was assessed at D14 as "cured", "improved", "not changed", "worsened" or "relapse". Scores were compared by Chi^2 analysis. The Ibaflin group was treated with Ibaflin 3% gel at a dosage of 15 mg/kg/day, once daily for 10 days, preferably at feeding. The clavulanic acid/amoxycillin group was treated with clavulanic acid/amoxycillin tablets at a dosage of 12.5 mg/kg twice daily for 10 days.

It was furthermore noted that according to the protocol only cases of 'upper respiratory tract infections' (URTD) should have been included according to the protocol. However, the report mentions all respiratory tract infections (incl. lower tract infections), as was claimed by the applicant also. The expected cure rate was set at 85%; however, no definition of cure was given (e.g. "normal" for all parameter categories).

Groups were comparable for age, but not for body weight. Bacterial culture yielded a wide variety of pathogens, with no species being predominant. 30% of the samples were negative. Considering the symptoms recorded in the clinical trial, it is observed that the effect in terms of absence of symptoms after the recommended treatment period is better for ibafloxacin (about 60%) compared to clavulanic acid/amoxycillin (47%). This is mainly caused by the improvement of scores for sneezing and nasal discharge. Differences were not statistically different. Ibafloxacin performs less when breathing frequency is increased and pulmonary sounds at auscultation are present. Very young and very old animals responded less to both treatments. It was also observed that animals falling within the lowest categories for all parameters (and therefore showing no symptoms at all) were yet included. Four cats from the Ibaflin group and 6 from the clavulanic acid/amoxycillin groups were considered as treatment failures.

Conclusion

A beneficial effect of treatment on upper respiratory tract infection in the cat was shown. The treatment is well tolerated.

Clinical trial to assess the efficacy of Ibaflin oral gel compared to clavulanic acid/amoxycillin tablets for the treatment of urinary tract infections in cats

A total of 192 cats with clinical signs of urinary tract infection were included in a multicentre, randomised non-blinded controlled clinical trial, 97 cats being treated with Ibaflin and 84 with clavulanic acid/amoxycillin. The overall response to treatment was assessed at D14 as "cured", "improved", "not changed", "worsened" or "relapse". Scores were compared by Chi^2 - analysis.

The Ibaflin group was treated with Ibaflin 3% gel at a dosage of 15 mg/kg/day, once daily for 10 days, preferably at feeding. The clavulanic acid/amoxycillin group was treated with clavulanic acid/amoxycillin tablets at a dosage of 12.5 mg/kg twice daily for 10 days.

The clinical study was not implemented according to the protocol. It was noted that there was a difference between the exclusion criteria on chronic cases in the protocol compared to the trial report of the results. The protocol furthermore indicates MICs to be established; however, MICs have not been reported. Although urinalysis was to be carried out, no results have been submitted, other than concerning the bacterial culturing. Diagnoses probably have been made, but none were reported. According to the literature, effective treatment of feline bacterial urinary tract infections requires culturing and susceptibility testing.

Groups were comparable for age and body weight. Results for bacterial culturing were dependent on the method of sampling. Sampling via cystocentesis resulted in 32% of the samples being positive; this was 47% for sampling by catheterisation and 81% for sampling at voiding. *E.coli* was the predominant species for cystocentesis (48%). The bacteriological cure rate for *E. coli* (and cystocentesis only) was 88% for Ibaflin oral gel and 80% for clavulanic acid/amoxycillin tablets. At D14 scores for attitude were significantly better for clavulanic acid/amoxycillin. The same holds true for scores on appetite at D0 and D14. However, scores were better for Ibaflin at D4. At D14 55% of the cats in the Ibaflin group were considered to be cured and 63% in the clavulanic acid/amoxycillin group; 85% and 88% respectively were considered as responders. No relationship was found between these results and the outcome of the bacteriological culturing.

Overall cure rates on the basis of absence of symptoms (score "1", including a neg. bacterial culture) are about 52% for Ibaflin and 47% for clavulanic acid/amoxycillin.

Conclusion

It is observed that the applicant differentiates between "urinary tract infections" and "bacterial infection of the lower urinary tract". However, the relevance of this difference is not clear, as the applicant states that the relationship between results of bacteriological culturing and the presence of clinical signs can be weak.
It has to be taken into account that in contrast to the dog, the number of cats suffering from a bacterial urinary tract infection seems to be low. Furthermore, urinary tract infection in the cat is usually secondary to other causes. In cases where antibiotic therapy is used, efforts should be made to eliminate the cause, bacterial infection should be confirmed and susceptibility testing should be performed. Clinical experience would dictate that the majority of cats get better spontaneously over a 5-10 day period, even in the absence of any treatment. It cannot be excluded that many bacterial culture-negative cats that "responded" to ibafloxacin treatment, were not in effect responding to the antimicrobial medication at all.

The proposed urinary claim can is not considered supported by the submitted data.

Overall conclusions on clinical studies

Dog – pyoderma claims The Committee agreed that a comparable beneficial treatment effect was seen in dogs treated with the gel formulation compared to dogs treated with the authorised Ibaflin tablet formulation.

The Committee noted that *Staphylococcus intermedius* is not considered to be the primary cause of pyoderma. As is stated in the SPC of the tablet formulation pyoderma is mostly secondary to an underlying disease. It is advisable to determine the underlying cause and to treat the animal accordingly.

Dog – respiratory and urinary claims Additional clinical trials were requested since there was no bioequivalence between the gel and the tablet.

The applicant did not perform additional clinical trials to prove efficacy of the gel formulation in dogs for the respiratory and the urinary claims.

Dog - Urinary infections claim The applicant considers the gel and the tablet nevertheless therapeutically equivalent. Levels in urine are extrapolated from plasma levels using ratios obtained from tablet studies. According to the applicant levels are well over MICs of relevant pathogens. The AUC is considered to be more relevant and as AUCs for gel and tablet are comparable the applicant concludes that a urinary tract infection claim for the gel is justified.

The Committee considered, however, that adequate scientific conclusions can only be taken from actual urine levels of the active substance following treatment with the gel formulation. Clinical trials are formally required because the gel and the tablet formulations are not bioequivalent The urinary claim could, therefore, not be agreed in the absence of such data.

Dog - Respiratory infections claim For the claim on respiratory tract infections the applicant refers to the qualities of fluoroquinolones in general. As the applicant expects concentrations of ibafloxacin in bronchial secretions to be similar to or higher than in plasma, a claim is considered justified. The applicant also refers to a study performed with the tablet formulation for tissue levels. As lung tissue levels are comparable to those in the skin and on the basis of the clinical trial on pyoderma the gel and the tablet are considered to be equally effective, the applicant concludes that the gel must be effective in case of respiratory tract infections as well.

Although fluoroquinolones are reported to penetrate into tissues well, differences between quinolones in relation to tissue levels exist. So the extrapolation made by the applicant as based on the literature was not considered to be valid. The way in which plasma levels arise may be different for the gel,

compared to the tablet. As the delivery rate is a limiting factor for the gel formulation, the gel in the intestinal tract will be a major source of ibafloxacin. For the tablet tissue and protein binding will be the major source as ibafloxacin is rapidly absorbed. This may imply that, although plasma levels may be comparable, tissue levels may be not and extrapolations/calculations on tissue levels should always be verified. In conclusion, the Committee felt unable to grant the claim of treatment of respiratory infections in the absence of further clinical data performed with the gel formulation in dogs.

Cat - Dose determination For the cat, dose justification was based on pharmacokinetic data and MICs, with clinical trials to confirm efficacy for all indications claimed. The submitted data on MICs and kill curves, in combination with the already submitted pharmacokinetic data for the cat, indicate that ibafloxacin can be effective in the cat against pathogens claimed (*Staphylococcus aureus, Staphylococcus epidermis, E. coli, Proteus spp., Klebsiella spp*. and *Pasteurella spp.*).

As for the dog, bridging studies (dose determination, dose confirmation) are lacking and justification of the dose is based on extrapolation using data for the dog. Since differences in pharmacokinetic properties exist between the cat and the dog, the justification of the dose for the cat on the basis of the dose for the dog is not considered to be justified.

As no dose finding or dose confirmation studies have been performed, justification of dose, treatment scheme and claims must be derived from the clinical trials. In conclusion with regard to the dosage and the treatment scheme the Committee agreed on the dosage of 15 mg ibafloxacin/kg body weight once daily.

Cat - Dermal infections For Ibaflin about 51% of the animals could be considered as cured; for clavulanic acid/amoxycillin this was about 48%. The progression of cure was rather slow, but comparable, for both products. It continued after the 10 days medication has stopped (D9), but this was likely to be caused by the aspect of the wound (not yet completely healed) rather than the persistence of infection. Pathogens that can be considered as relevant fall within the spectrum of activity of ibafloxacin and, taking the lower tissue levels into account, levels are considered to be sufficient for efficacy. It is, therefore, likely that Ibaflin oral gel can be effective in case of dermal infections in the cat when used in a dose of 15 mg/kg.

The Committee accepted the gel formulation be indicated in cats for the treatment of dermal infections (soft tissue infections – wounds, abscesses) caused by susceptible pathogens such as *staphylococci, E. coli, Proteus spp.* and *Pasteurella spp.*

Cat - Urinary tract infections The submitted trial lacks clear differentiation between bacterial urinary tract infections and other urinary tract infections which are far more common in cats. Clinical experience would dictate that the majority of these cats get better spontaneously over a 5-10 day period, even in the absence of any treatment. The Committee did not accept the claim for treating urinary tract infections as further data from bacteriological positive FLUTD (feline lower urinary tract disease) cases would be required.

Cat - Respiratory tract infections Cure rates were 60% for Ibaflin and 47% for clavulanic acid/amoxycillin. It was observed that for Ibaflin cure was mainly achieved in animals indicated as having upper respiratory tract infections. As for the dog and the tablet formulation, also in the cat Ibaflin was more effective than the comparator used. As the plasma level profile of the cat and the gel is quite different from that of the dog and the tablet, the presence of a specific antibacterial effect cannot be excluded. Pathogens that could be considered as relevant fall within the spectrum of activity of ibafloxacin and, taking the lower tissue levels into account, levels are considered to be sufficient for efficacy. It is likely that Ibaflin oral gel can be effective in case of upper respiratory tract infections in the cat when used in a dose of 15 mg/kg. Data indicate that in a number of cases treatment should be longer than the recommended 10 days period.

The Committee accepted the gel formulation be indicated in cats for the treatment of upper respiratory tract infections caused by susceptible pathogens such as *Staphylococci, E. coli, Klebsiella spp*. and *Pasteurella spp.*

Conclusions On Pre-Clinical And Clinical Documentation

The efficacy part of this application is covered from several different approaches. Initial pre-clinical data were presented which concentrated on *in-vitro* efficacy of ibafloxacin against various bacterial strains derived from clinical cases of certain canine diseases. Values for MIC_{50} and MIC_{90} were obtained and the range of sensitive species was relatively wide. As for all flouroquinolones, not all bacterial species tested were sensitive. However, the bacterial species encountered in most cases of canine pyoderma, urinary tract infections and respiratory tract infections were sensitive, with the possible exception of some *Pseudomonas, Bordetella* and *Streptococcal spp*. These studies included sufficient numbers of strains and isolates to allow a positive conclusion on the likely suitability of the test compound for sensitive species involved in the indications sought.

Further pre-clinical studies were conducted *in-vivo* in experimental models of skin wound infections and urinary tract infections. The skin wound study provided evidence for the efficacy of ibafloxacin, and furthermore allowed for the proposal of a recommended treatment dosage. The beneficial antimicrobial effects of the test compound were demonstrated. It should be emphasised that the proposed clinical indications for ibafloxacin are similar to those already in existence in practice for related fluoroquinolones marketed for the dog.

The clinical field trials discussed above were performed in several different centres, with a total of approximately 400 dogs receiving the product. Most of the studies had a very similar trial design, and the treatment period was considered relatively short in some of the studies. Scoring of most of these trials was based on a combination of clinical signs, general condition scores and the results of bacteriology. Those studies in which the underlying pathology could be directly visualised e.g. pyoderma, and those in which pre- and post-treatment bacteriology were performed provided the most valuable information. Problems of diagnosis and heterogeneity of underlying pathology (as well as the bacterial infection) were likely encountered in many of the studies. The scoring systems were based on the visual analogue scale system, which can be problematic with multiple sites and inexperienced personnel. Adverse events and signs of intolerance were occasionally encountered in most of the above studies, but the frequency and severity did not cause alarm. Whilst deficiencies can be identified in study design and occasionally study results, the clinical trial data do provide evidence of efficacy for the proposed indications.

In view of the results from the four submitted field trials ibafloxacin is considered to be effective in cases of acute of infections of the skin (wounds, abcess, pyoderma), in cases of acute and uncomplicated urinary tract infections and in cases of upper tract respiratory infections, however the relationship between pre-clinical and clinical data is not consistent.

RISK-BENEFIT ASSESSMENT

The data submitted confirm the acceptability of the proposed formulations, for both the tablets and oral gels in which the product is presented, the suitability of the specifications for the active substance, the method of manufacture of the products and the validity of the test methods applied to the product.

Adverse effects were only observed at high dosages and therefore a statement was included in the SPC to indicate that diarrhoea, soft faeces, vomiting, dullness and anorexia have been observed with low frequency and that these effects were mild and transient. The oral gel product was well tolerated in cats and dogs when administered at the recommended dosage.

From the toxicity studies it was concluded that ibafloxacin can be administered to the mature dog for up to 90 days at the recommended dose level of 15 mg/kg body weight. Adverse effects were only observed at high dosages.

Signs of arthrogenic potential (induction of cartilage lesions) of ibafloxacin were observed in studies with immature dogs. There were no data available for cats. As a precaution, the use of the product is contra-indicated in dogs and cats less than 8 months of age and in giant dog breeds less than 18 months of age. No potential for maternotoxicity, embryo/foetotoxicity, teratogenicity and genotoxicity was observed in a number of studies submitted. Ibaflin had no effects on pregnancy and lactation at levels up to 45 mg/kg/day.

The use of ibafloxacin may result in an increase in prevalence of resistant strains in the target species although this risk is likely to be less of a concern due to the treatment of individual companion animals with this product. The SPC includes the statement that Ibaflin should only be used based on susceptibility testing due to known concerns with increasing fluoroquinolone resistance.

The pharmacokinetic data presented cover a variety of dose levels, but even at dose levels above the recommended dosage, effective plasma levels seem to be present only for a period of approximately 12 hours. Therefore, in theory, a twice daily dosing should be considered for dermal and respiratory tract infections. However, it became clear from the model studies and field trials that the common scientific approach to evaluate efficacy based on MIC values and plasma concentration was not consistent with the findings of the clinical field trials where a once daily dose proved to be efficacious. This once daily dose has been approved by the Committee.

Bioequivalence studies failed to prove bioequivalence between the tablet and gel formulation as the C_{max} for the gel formulation was considerably lower although the AUCs were comparable. The claims in the dog for treatment of urinary and respiratory infections as from the already authorised tablet formulations were, therefore, not accepted in the absence of further clinical data performed with the gel formulation.

Since it was considered not practical to accurately administer ¼ tablets, the product is contra-indicated for use in dogs of under 3 kg, apart from the 30mg tablet strength. Since test results show that food positively influences the extent of ibafloxacin absorption it is recommended to administer the product simultaneously with food.

The submitted clinical trials were considered to support the following claims:
Tablets 30mg/150mg/300mg/900mg for dogs
Dermal infections (pyoderma – superficial and deep, wounds, abscesses) caused by susceptible strains of *staphylococci, E. coli and Proteus mirabilis.*

Acute, uncomplicated urinary tract infections, caused by susceptible strains of *staphylococci, Proteus spp., Enterobacter spp., E. coli* and *Klebsiella spp.*

Respiratory tract infections (upper tract) caused by susceptible strains of *staphylococci, E. coli,* and *Klebsiella spp.*

From data of two different clinical trials, comparable efficacy was shown between the gel formulation and a positive control to support the following claims in cats for the oral gel formulations

- Dermal infections (soft tissue infections – wounds, abscesses) caused by susceptible pathogens such as *Staphylococcus spp, E. coli, Proteus spp.* and *Pasteurella spp.*
- Upper respiratory tract infections caused by susceptible pathogens such as *Staphylococcus spp, E. coli, Klebsiella spp.* and *Pasteurella spp*.

The indication of treatment of urinary infections in cats was not accepted as the clinical trial lacked differentiation between common idiopathic and less common bacterial urinary infections.

The following claims for the oral gels in dogs are supported:

- Dermal infections (pyoderma – superficial and deep, wounds, abscesses) caused by susceptible pathogens such as *Staphylococcus spp, E. coli and Proteus mirabilis*.

Comparable efficacy of the gel formulation to the tablet formulation was shown for dogs in a clinical trial.

Based on the original and complementary data presented, the Committee for Veterinary Medicinal Products concluded that the quality, safety and efficacy of the product were considered to be in accordance with the requirements of Council Directive 2001/82/EC and supported the claims above.