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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Fungitraxx (EMEA/V/C/002722/0000)

International non-proprietary name: itraconazole

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

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Introduction

On 22 October 2012 the applicant Avimedical B.V. submitted an application for marketing authorisation to the European Medicines Agency (the Agency) for Fungitraxx 10 mg/ml oral solution for ornamental birds, through the centralised procedure under Article 3(2)(b) of Regulation (EC) No 726/2004.

The eligibility to the centralised procedure was agreed upon by the CVMP on 13 April 2012 as the applicant showed that the product would be in the interests of animal health at Community level (Article 3(2)(b) of Regulation (EC) No 726/2004) as no antifungal was authorised at that time for the treatment of aspergillosis and candidiasis in the target species, that is, ornamental birds (non-food producing). The rapporteur appointed was M. Holzhauser-Alberti and co-rapporteur B. Kolar.

The dossier has been submitted in line with the requirements for submissions under Article 12(3) of Directive 2001/82/EC.

The applicant is registered as an SME pursuant to the definition set out in Commission Recommendation 2003/361/EC.

Fungitraxx oral solution contains 10 mg/ml itraconazole and is presented in packs containing 1 bottle of either 10 ml or 50 ml. The route of administration is oral use.

The product is indicated for the treatment of aspergillosis in Psittaciformes, Falconiformes, Accipitriformes, Strigiformes, and Anseriformes and for the treatment of candidiasis in Psittaciformes.

On 15 January 2014 the CVMP adopted a positive opinion, recommending the granting of a marketing authorisation for the veterinary medicinal product Fungitraxx 10 mg/ml oral solution for ornamental birds.

On 12 March 2014, the European Commission adopted a Commission Decision for this application.

Scientific advice

The applicant received scientific advice from the CVMP on 9 March 2011. The scientific advice pertained to advice on the safety requirements for the development of the veterinary medicinal product.

The CVMP considered that for the target species swans, diurnal raptors, canaries, finches, song birds, parrots, cockatiels, parakeets and budgerigars, the establishment of maximum residue limits (MRLs) was not required as the product is not for use in for food-producing species. However, for the use of the product in ducks, geese, pigeons, turkeys, grouse, quails, and pheasants, the establishment of MRLs in relation to those species would be required.

The applicant followed the scientific advice as the list of target species was limited to non-food producing species for which the establishment of MRLs is not required.

MUMS status

The applicant requested classification for minor use minor species (MUMS)/limited market status for this product by the CVMP. The CVMP confirmed at their June 2010 meeting the MUMS classification on the basis of the species being minor, but in addition minor use (the low prevalence of aspergillosis and candidiasis in the target species) and therefore, where appropriate, the data requirements in the relevant CVMP guidelines on MUMS were applied when assessing the application.

The applicant has shown the well-established use of the product in avian medicine.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant stated that all pharmacovigilance activities have been subcontracted by Avimedical BV to Farma Research Animal Health BV. A description of the Farma Research Animal Health BV pharmacovigilance system was provided.

A statement signed by the applicant (Avimedical BV) and the qualified person for pharmacovigilance (in Farma Research Animal Health BV) has been provided stating that the applicant has the services of a qualified person responsible for pharmacovigilance. The pharmacovigilance system described fulfils the requirements and shows the applicant has the necessary means for the notification of any adverse reaction suspected of occurring either in the European Union (EU) or in a third country.

Manufacturing authorisations and inspection status

The applicant has adequately addressed this section both for the manufacturing authorisation and the inspection status. Fungitraxx oral solution is manufactured packaged and batches are released by Floris Veterinaire Produkten B.V., Kempenlandstraat 33, 5262 GK Vught, The Netherlands. A valid manufacturing authorisation and a GMP certificate were provided. This certificate (dated 2 December 2010) confirms the date of the last inspection and that the site is authorised for the manufacture and batch release of non-sterile veterinary products, including liquids for internal use.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system was considered in line with legal requirements.

The GMP status of both the active substance and dosage form manufacturing sites has been satisfactorily established and are in line with legal requirements.

Part 2 - Quality

Composition

The finished product Fungitraxx is an oral solution containing 10 mg/ml itraconazole as the active ingredient.

The product also contains as excipients: hydroxypropylbetadex, caramel flavour, propylene glycol, hydrochloric acid, purified water and, if required, sodium hydroxide.

No preservative is present in the formulation of this multidose product.

Development pharmaceutics

This oral solution has been formulated to be similar to the product Sporanox (called Trisporal in some EU member states), an oral solution authorised as a human medicinal product and which contains itraconazole at the same concentration.

Itraconazole has a low solubility in water. A solvent system based on water and propylene glycol only was not suitable, and although no data were provided to support this information it was considered acceptable in the light of the following information. Hydroxypropylbetadex was included in the formulation to enhance the solubility of the active substance. The solvent system finally chosen, based on the two excipients hydroxypropylbetadex and propylene glycol, demonstrates good solubilisation of the active substance at the desired concentration.

The inclusion of a flavour (caramel) in the formulation was justified.

No preservative is included since the pH of the formulation is low (1.6–1.9) and it has been demonstrated to be self-preserving in accordance with the European Pharmacopoeia (Ph. Eur.) chapter 5.1.3. More than one batch was tested, and this justified the absence of inclusion of a preservative.

The impurity profiles of the finished product and Sporanox/Trisporal were investigated and compared; graphical data show a clear decrease in assay value and an increase of two degradation products under accelerated conditions. The degradation is time-dependant, but not packaging-dependant. Results remain compliant with the set limits. Dosing accuracy data of 0.15 ml for the 1 ml syringe and 1.0, 1.2 and 5 ml for the 5 ml syringe obtained with the candidate formulation have been provided as recommended by the Ph. Eur. chapter 2.9.27.

Method of manufacture

The manufacturing process is a standard method involving the preparation of two separate solutions which are then mixed, prior to filling into the final primary containers (glass bottles). If necessary, sodium hydroxide solution can be used to adjust the pH of the final solution. No overages are used. Adequate details have generally been provided for the manufacturing process.

In-process controls (IPC) are defined.

No process validation studies have yet been undertaken at the commercial scale as the manufacturing process is accepted to be a standard one. The applicant is recommended to perform process validation studies further to the granting of a marketing authorisation of the product and a validation protocol has been provided to support the proposed batch size.

Control of starting materials

Active substance

For the control and manufacture of the active substance, itraconazole, the proposed supplier has a Ph. Eur. certificate of suitability (CEP) which includes a 2 year retest period. Corresponding certificates of analysis have been provided.

In addition to the Ph. Eur. monograph requirements, the itraconazole specification includes tests and limits for residual solvents which are in compliance with VICH (International Cooperation on Harmonisation of Technical Requirements for Registration of Veterinary Medicinal Products) GL18 'Impurities: Residual solvents in new veterinary medicinal products, active substances and excipients'.

Excipients

The excipients, hydroxypropylbetadex, propylene glycol, hydrochloric acid (concentrated), sodium hydroxide and purified water, are each stated to be controlled according to the requirements of the respective Ph. Eur. monograph. The specifications and certificates of analysis provided comply with the relevant requirements. All excipients have previously been used before in veterinary medicinal products authorised within the EU.

An in-house monograph has been provided for the control of the flavouring ingredient, caramel flavour. Full details of its composition have been provided by the flavour manufacturer. Compliance with Regulation (EC) No 1334/2008 was demonstrated.

Container-closure system

The product is presented in 10 ml or 50 ml brown type III glass bottles closed with an HDPE (high-density polyethylene)/LDPE (low-density polyethylene) tamper-evident closure. Each bottle has an LDPE adapter insert in its neck, which, when the oral syringe is inserted, prevents any spillage when the product is drawn up into the syringe. A 1 ml (appropriately graduated in 0.01 ml increments) and a 5 ml syringe (with a dosing accuracy of 0.2 ml) polypropylene oral syringe is also included in each pack in order to facilitate accurate administration of the product.

All the materials in contact with the product comply with Directive 2002/72/EC and/or the relevant Ph. Eur. requirements and sufficient details have been provided.

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

A transmissible spongiform encephalopathies (TSE) statement has been presented stating that the active ingredient and the excipients used for the manufacture of Fungitraxx 10 mg/ml oral solution are not derived from any starting materials that fall within the scope of the current Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev.3). The product is therefore out of the scope of the relevant Ph. Eur. monograph and the Note for Guidance.

TSE certificates for all the Fungitraxx components have also been provided.

Control tests on the finished product

The proposed release specifications are acceptable for this type of dosage form and are in accordance with VICH GL39 on test procedures and acceptance criteria for new veterinary drug substances and new medicinal products: chemical substances, and limits for density have been tightened.

The analytical methods are sufficiently well described and appropriately validated. The same test method is used for the determination of the active substance and related substances.

Stability

In the shelf life specification, the total impurity limit and the limit for unknown impurities have been widened, based on the stability data obtained from 3 pilot batches and this has been justified.

During the stability studies, one impurity has been observed above the qualification threshold (1.0%). The identification studies undertaken by the applicant demonstrate that the impurity and the active substance are structurally related; however no safety concern has been identified and in the finished product specifications this impurity is limited to ≤ 1.0% as a specified degradation product, which is considered acceptable.

Based on the stability data provided, from 3 pilot scale batches stored under VICH conditions in the proposed commercial packaging, a shelf life of 18 months, with a precaution for a maximum storage temperature of 25 °C is justified. Further confirmatory stability studies are in progress. As the samples were not exposed to light during the stability study, a recommendation is included in the summary of product characteristics (SPC) and the rest of product information to keep the bottle in the original carton in order to protect from light.

The claimed in-use shelf life of 28 days has been sufficiently justified given that the applicant has committed to perform a further in-use stability study on batches approaching the end of their shelf life.

As the product can also be administered with the birds' food if necessary, an appropriate instruction is included in section 4.9 of the SPC and equivalent section of the package leaflet to indicate that if the product has to be administered with the bird's food, it should then be offered immediately to the bird(s), and discarded within 1 hour if it has not been consumed by then. A specific instruction is included for raptors as an example.

Overall conclusions on quality

The data provided in part 2 of the dossier are adequately detailed in line with the relevant current quality guidelines.

The product is an oral solution of itraconazole at a concentration of 10 mg/ml, which utilises standard pharmaceutical excipients and a caramel flavour. It is presented in 10 ml or 50 ml brown glass bottles sealed with a plastic closure, and is measured and administered with a 1 ml or 5 ml plastic oral syringe. Compliance of the formulation with the Ph. Eur. chapter 5.1.3 (efficacy of antimicrobial preservation) for oral preparations has been demonstrated.

The product has been developed to be essentially similar to a medicinal product authorised for human use containing the same active substance at the same concentration. A comparison of the impurity profiles of both products has been provided.

Although no preservative is included in the formulation, due to its low pH the product has been shown to be self-preserving in accordance with the Ph. Eur.

All the excipients present in the finished product, except the flavour, are described in the Ph. Eur. and are routinely controlled to the required standard. Information on the composition, specification and control tests for the flavouring has been provided and is considered satisfactory.

A copy of the current CEP for the active substance has been provided, and this includes the retest period.

The manufacturing process is a standard one and therefore no validation data on industrial scale batches is required. However, a validation protocol has been submitted and validation of two pilot scale batches has been performed showing that the manufacturing process is satisfactorily controlled and capable of producing consistent batches of the appropriate quality.

The finished product release specifications are acceptable and the test methods have been described and appropriately validated.

The impurity levels in the shelf life specification have been tightened to be in compliance with current EU guideline requirements. Based on the stability data provided, a shelf life of 18 months, with a precaution for a maximum storage temperature (of not above 25 °C) is justified.

An in-use shelf life of 28 days is considered acceptable and the applicant is recommended to perform a further in-use stability study on batches approaching the end of their shelf life.

Part 3 – Safety

Safety documentation

Pharmacodynamics

See part 4.

Pharmacokinetics

See part 4.

Toxicological studies

Itraconazole has been used for several decades as an antifungal substance in human medicine, and for several years as a veterinary medicinal product (ITRAFUNGOL 10 mg/ml oral solution for cats). The toxicological profile of itraconazole is therefore considered to be well known. Its acute oral toxicity is low, with an oral LD_{50} in the range of 160 to 320 mg/kg bodyweight (bw) (in guinea pigs, dogs, rats and mice).

From oral repeated dose toxicity studies, no-observed-effect levels (NOELs) of 10 mg/kg bw and 2.5 mg/kg bw were established for rats and dogs, respectively. In these studies, the main target organs were the mononuclear phagocyte system and the adrenal glands.

Reproductive toxicity studies were conducted in rats and rabbits. For rats, a NOEL for maternotoxicity and embryotoxicity of 10 mg/kg bw was retained; at higher dosages, maternotoxicity and embryotoxicity were noted. In rabbits, the NOEL for maternotoxicity and embryotoxicity was higher than 80 mg/kg.

No teratogenicity was reported.

Itraconazole was not mutagenic or genotoxic in a suitable battery of mutagenicity tests.

No carcinogenicity data were provided. However, as itraconazole was shown to be devoid of mutagenic/genotoxic potential in a suitable battery of tests, the absence of such data/studies is acceptable. In addition the molecule does not possess any structural alerts related to a potential carcinogenic risk. Itraconazole should be considered as devoid of carcinogenic potential.

The toxicological data provided are considered as sufficient.

Tolerance in the target species of animal

See part 4.

Studies of other effects

Observations in humans

Itraconazole has been used in human medicinal products for many years, where it is authorised for the treatment and/or the prophylaxis of fungal infections in both adults and children.

Formulations are oral solution, capsule and intravenous formulation.

Therapeutic doses in humans range from 100 to 200 mg, with up to twice daily administration. The highest doses are recommended for immuno-compromised individuals.

Oral formulations can be administered for up to 3 months (depending on the type of fungal infection being treated).

The main adverse events reported in humans for all formulations are similar: gastrointestinal disturbances, headache, rash and hepatic impairment.

User safety

A user risk assessment is provided. It was conducted in accordance with the current CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1).

Regarding the risk after oral ingestion by the user, it is noted that Fungitraxx has the same formulation as the human medicine Sporanox/Trisporal (except for the flavour). The applicant therefore used human therapeutic doses for the quantitative risk characterisation, which appears to be a pertinent approach for this kind of product. The toxicological profile of the human product is well known, including when used in children.

The risk for a child is particularly well identified and assessed. The caramel flavour may make this medicine more palatable to children and thereby increase the chance of its accidental ingestion by children, however for stability (to light) reasons there is warning on the outer carton that the bottle should be stored in the outer carton and this will help limit exposure to the product by children. The narrow neck of the LDPE adapter insert (onto which the oral syringe fits for withdrawing the dose) also further limits exposure. Acute adverse effects, after oral ingestion, are similar in adults and children and mainly consist of gastro-intestinal disturbances (vomiting, diarrhoea or abdominal pain). The bottle is sealed with a tamper-evident closure, there are appropriate warnings on the carton, label and package leaflet, and the toxicity profiles of the active ingredient and the major excipients are satisfactory.

The CVMP considered that it was necessary to take the zoonotic nature of aspergillosis into consideration. Infected birds should be handled by the owner in a restricted manner as part of good handling practice. In the case of zoonosis it is prudent to include explicit warnings in the SPC addressing the need for heightened awareness in handling treated birds. Therefore the warning sentences in section 4.5 of the SPC include a recommendation to wear gloves, not because of the possibility of contact with the product, but in order to avoid contact with treated birds, as some fungal infestations may be zoonotic. As aspergillosis is transmitted via aerosol infection, the wearing of a mask is also recommended.

Environmental risk assessment

A Phase I environmental risk assessment (ERA) was provided according to the VICH guidelines. The product is for individual use in ornamental birds only and the quantity to be used is small.

Based on the data provided the ERA can stop at Phase I. The product is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

In oral repeated dose toxicity studies, the main target organs were the mononuclear phagocyte system and the adrenal glands.

The lowest NOEL was determined in dogs (2.5 mg/kg bw).

Reproductive toxicity studies were conducted in rats and rabbits. For rats, a NOEL for maternotoxicity and embryotoxicity were established of 10 mg/kg bw was retained; at higher dosages, maternotoxicity and embryotoxicity were noted. In rabbits, the NOEL for maternotoxicity and embryotoxicity was higher than 80 mg/kg.

No teratogenicity was reported.

Although the submitted data about the oral single, repeated dose and reproductive toxicity of itraconazole were sourced from an old publication, the toxicological profile of itraconazole can be considered as well characterised. As itraconazole was shown to be devoid of mutagenic/genotoxic potential in a suitable battery of tests, the absence of any further carcinogenicity data/studies is acceptable. In addition the molecule has no structural alerts related to any potential carcinogenic risk. Itraconazole should therefore be considered as devoid of mutagenic/genotoxic and carcinogenic potential.

The provided data on the toxicological profile of itraconazole can be considered as acceptable and sufficient.

A well conducted user risk assessment is provided in accordance with applicable guidelines. Acute adverse effects, after oral ingestion, are similar in adults and children and mainly consist of gastro-intestinal disturbances (vomiting, diarrhoea or abdominal pain). The risk for a child is particularly well identified and has been satisfactorily addressed. The risk is mitigated by the use of a tamper-evident closure on the primary container (bottle).

The product is not expected to pose a risk for the environment when used according to the SPC.

Residues documentation

Not applicable as the product is not for use in food-producing species.

Part 4 – Efficacy

To support efficacy, the applicant submitted bibliographical references, data from one clinical trial and also additional information regarding several clinical cases between October 2011 and August 2013 (referred to as "retrospective data").

Only relevant pharmacological data consistent with the proposed indications for use and the target species, as presented in the clinical data, were assessed. The data obtained from food-producing species and/or human beings were noted by the CVMP however were not considered relevant and therefore not taken into account for the assessment of efficacy of the product.

In terms of preclinical requirements, no pharmacokinetic studies were provided with the final formulation in the target species. This was considered acceptable because this would not be considered critical for the choice of a proposed recommended dose.

In terms of clinical efficacy, no original separate studies for dose determination and dose confirmation were provided by the applicant. The CVMP considered that the dose used in the field trial provided had been adequately justified by reference to the literature.

Pharmacodynamics

The mechanism of action of itraconazole is well known and well described in the published literature. Itraconazole acts selectively on fungal membranes, leading to fungal cell death. There were sufficient data provided to give a range of minimum inhibitory concentrations (MICs) for itraconazole for different *Aspergillus* isolates in birds in Europe, but the data provided were more limited for different *Candida* species.

Section 5.1 of the SPC sufficiently summarises the data provided in the dossier.

Development of resistance

Theoretical mechanisms of resistance were described by the applicant, but neither susceptibility data nor epidemiological survey data were provided. The lack of epidemiological data on target pathogens in the target species was considered and the CVMP considered this was acceptable, taking into account the difficulties in collecting data from these target species and that these are minor species. Therefore, at present, the uncertainty of the epidemiological situation was not considered a concern.

Resistance to itraconazole in *Candida* and *Aspergillus* species is known in human medicine.

Data from *Aspergillus fumigatus* isolated from humans were provided. Resistance against the class of azole compounds, to which imidazole belongs, has been observed in human patients receiving long-term azole therapy, and also in treatment-naïve patients, according to provided literature. Data on acquisition of resistance in the environment were provided. Such resistance might be induced by the extensive use of azoles for plant protection purposes. Resistance might also arise in the environment from avian isolates of *Aspergillus fumigatus*. As evident from the provided literature, cross-resistance against azole compounds: to voriconazole, posaconazole, itraconazole and to 6 triazole fungicides used extensively in agriculture, has also been observed in *Aspergillus fumigatus*.

The risk of increased resistance to itraconazole against pathogens following use of this product is plausible.

Taking into account the above data, the CVMP agreed the risk of increased resistance needs to be acknowledged however that the proposed warnings in section 4.5 of the SPC were considered appropriate for addressing this potential risk.

Pharmacokinetics

A published scientific review article was provided on the administration of itraconazole in a variety of bird species, showing that itraconazole plasma concentrations vary with the type of bird. No pharmacokinetic data were provided following the administration of this particular product. Therefore, no relevant kinetic parameters are available after exposure to the product to include in the section on pharmacokinetics (5.2) in the SPC.

The effect of food on the bioavailability of itraconazole in the target species has not been documented. However, it is evident from published literature that food decreases the bioavailability of itraconazole and that the magnitude of this depends on the formulation used.

The anatomical and physiological differences in the avian gastrointestinal tract suggest that drug absorption may also differ between types of birds, therefore it would be difficult to extrapolate any kinetic data, even if such were available, between the different types of birds for which this product is indicated.

The CVMP agreed that detailed pharmacokinetic information were not necessary in order to conclude on the efficacy of this product.

Dose determination/justification

Data demonstrating the relationship between the dose and the effect of the product, in order to justify the proposed dosage regimen, was provided, but the data were from studies in rabbits and humans only. The CVMP agreed that these results could not be extrapolated to the target species not only because of the anticipated differences in metabolism between humans and rabbits and birds, but also because of the different metabolic profiles in the different types of birds.

However, the proposed dose and duration of treatment of itraconazole are commonly used in avian medicine in practice. These were documented in the literature provided in the application.

From this literature, the applicant defined a baseline dose and treatment regimen that were subsequently used in a clinical study intended for dose confirmation and for the demonstration of the efficacy of itraconazole in birds by the oral route against aspergillosis and candidiasis.

The CVMP agreed with the approach and the data provided for the identification of a dose and duration of treatment. The dose and duration are detailed under "Field trials".

Target animal tolerance

No target animal safety studies in accordance with VICH GL43 'Target animal safety for veterinary pharmaceutical products' have been provided in this application.

The tolerance of an itraconazole solution for oral administration was supported by an uncontrolled, unblinded, single-arm GCP-compliant efficacy/tolerance study in several bird species belonging to different bird families. In addition, two literature references were provided.

In this efficacy/tolerance study, 62 ornamental birds diagnosed with aspergillosis and 18 ornamental birds diagnosed with candidiasis were included.

The test product was administered orally, at a dosage of 5 mg or (maximum) 10 mg itraconazole per kg bw (depending on the bird species) at intervals of approximately 24 hours for at least 8 weeks (for aspergillosis), or for at least 2 weeks (for candidiasis). This is the recommended dosage for Fungitraxx.

The test product had the same composition as the final product (Fungitraxx).

The parameters used to evaluate the product's target animal tolerance were clinical findings and chemical blood examination in the case of birds with aspergillosis, and only clinical findings for the birds with candidiasis.

Only some of the proposed target species were tested in this study. The birds tested belong to the following orders: Psittaciformes, Falconiformes (diurnal and nocturnal raptors) and Anseriformes. The tolerance of birds belonging to the family Passeriformes has not been assessed in this study.

Across the range of birds tested, the applicant noted somnolence, decreased appetite and weight loss as possible adverse effects following administration of the test product. However, all of these possible adverse effects are also the clinical signs of aspergillosis, therefore, in the absence of a control group in the study it is not possible to distinguish whether or not these effects resulted from administration of the product, or if they were due to the disease being treated.

In addition to the safety results from the pivotal clinical study, a retrospective study was provided.

Data from a total of 1,257 birds were received from a veterinary clinic specialised in birds. These data covered all the birds treated for "fungal infections" with an itraconazole-containing test product of identical formulation to Fungitraxx over the period from October 2011 to March 2013. These retrospective data evaluated consisted of birds from 10 orders, 18 families and 75 species. It should be noted that the totality of birds in this retrospective data set provided data for tolerance purposes; however, in terms of efficacy, not all treated birds were considered relevant by the CVMP (see also below).

The doses administered varied from 2 to 40 mg itraconazole/kg bw.

All African Grey Parrots received the lowest dose (2 to 6 mg/kg bw).

The treatment durations varied from 5 days to 8 months.

The product was either administered directly orally (n = 106), in chicks or in meat fed to the birds (n = 68), in the birds' drinking water (n= 222) or mixed with the birds' food (n = 861). All birds of prey received their medication with their food (chicks or meat).

A total of 814 Passeriformes were included in this study. Only one bird showed an adverse effect (inability to fly). This suspected adverse effect was however completely transient and disappeared after cessation of administration of the product.

In other birds, side effects were reported in 18 cases. Breeding results were recorded in a group of 25 African Grey Parrots and in a group of 4 Eclectus Parrots. In this group of birds, the breeding performance was unusual (breeding was delayed). It is not clear if this was due to the product administration, or the disease itself, including the birds' breeding environment.

In a group of 16 Vosmaer's Eclectus, a subspecies of the Eclectus parrot, unfertilized eggs and thin egg shells were observed.

Diminished appetite was recorded in Gyrfalcons, Northern Goshawks, African Grey Parrots and in one Senegal Parrot.

Rough feathers were noted in Brant Geese and African Grey Parrots.

Vomiting was noted in two African Grey Parrots (one bird vomited once, no such detail was provided regarding the vomiting frequency for the other bird), one Senegal Parrot (no further information) and Northern Goshawks (incidental vomiting for both birds).

It should be highlighted that adverse effects were more often observed in Psittaciformes, and more specifically in African Grey Parrots. This observation confirms the higher sensitivity in general of Psittaciformes, and more specifically in African Grey Parrots, to itraconazole than other bird classes.

Other data on tolerance was provided in literature references as follows:

- Blue-Fronted Amazon Parrots (Psittaciformes). Birds were orally administered (by gavage) with 5 or 10 mg/kg bw itraconazole per day for 14 days, in 2 studies, that were separated by a period of 3 months. No signs of toxicosis were observed.
- *Ad libitum* administration of itraconazole-medicated seeds (20 or 100 mg itraconazole/100 g seed) to Gouldian Finches (Passeriformes), for an extended time period. Histopathological examinations of the finches showed no evidence of findings attributable to itraconazole toxicity.
- In a 3rd publication, 11 Red-tailed Hawks received an itraconazole solution by gavage at a dosage of 5 mg/kg bw (n = 4) and 10 mg/kg bw (n = 10), once daily for 15 days. No medicine induced toxicosis was observed.

It was noted that all 3 published studies referred to above were conducted specifically to further study safety aspects of itraconazole in different species of birds after different types of administration, rather than to study the tolerance of itraconazole. Therefore the tolerance data from these publications are relatively poor and do not allow a clear conclusion about the safety of the product to be drawn. For example, there is no information on overdose. However, these studies were particularly interesting as they showed that the anatomical and physiological characteristics of the birds' gastrointestinal tracts are very different which suggests that drug absorption may also differ between different types of birds. Therefore this supports that extrapolation of the kinetic and tolerance data between different families of birds does not appear feasible.

African Grey Parrots appear to be very sensitive to itraconazole and may exhibit adverse reactions at normal dosage levels. Therefore in addition to advice in the dosage section (4.9) of the SPC and similarly in the package leaflet not to use a dose of itraconazole above 5 mg/kg bw in African Grey Parrots ("For the treatment of African Grey Parrots (see section 4.5) use no more than 5 mg (0.5 ml) itraconazole per kg bodyweight per day. If clinical signs show that the product is not well tolerated, then the treatment should be stopped."), the following advice for the safe use of the product in African Grey Parrots and other Psittaciformes is given in the SPC (section 4.5):

"Itraconazole is generally not well tolerated by African Grey Parrots and therefore the product should only be used with care in this species and if no alternative treatment is available, and with the lowest recommended dose for the whole of the recommended treatment period.

Other Psittaciformes also appear less tolerant to itraconazole than other birds. Therefore if suspected medicinal product related adverse events such as emesis, anorexia or weight loss occur, the dose should be lowered, or treatment with the medicinal product should be discontinued."

In addition to other tolerance studies, results of a retrospective study including supplementary numbers of Passeriformes, Psittaciformes, birds of prey, Cuculiformes, Anseriformes, Piciformes, Coraciformes and Columbiformes are also provided. Although neither individual case report forms nor the identification of the study sites were provided, the CVMP considered that the recorded data did provide confirmatory evidence of the product's tolerance in the majority of the proposed target species. However, some bird orders, in particular the Passeriformes were not considered to have sufficient demonstration of efficacy and tolerance from the pivotal clinical trial, so these orders could not be included in the final agreed list of target species.

In the retrospective study, eight of the 1,257 treated birds died, for unknown reasons but including 6 cases of concomitant aspergillosis.

In conclusion, regarding the low incidence of mortality and the low incidence of reported adverse events (18 cases of reported adverse events amongst 1,257 treated birds) when the product is used as recommended, the CVMP considered that the product can be considered as well tolerated in treated birds.

Field trials

In order to support the efficacy and safety of Fungitraxx in the treatment of aspergillosis and candidiasis in a range of different types of ornamental birds, the applicant submitted a series of bibliographic references, summarising data from several studies in different bird species (as well as some laboratory animals), in which the active substance itraconazole was tested in different treatment regimens and under different experimental conditions. From these references, the applicant retained a base-line dose and treatment regimen that were subsequently used in a clinical study, including two distinct trials intended for dose confirmation and for demonstration of the efficacy of itraconazole by the oral route against aspergillosis and candidiasis in birds.

A field study was provided, encompassing two distinct trials, for the aspergillosis and candidiasis indications. This study was GCP-compliant. It was performed in the Netherlands, in both laboratory conditions (institute for research) and field situations, and this was deemed acceptable for this type of application for use in birds. Though the study was limited to one country, the conditions are considered representative of various regions within the EU and were therefore considered acceptable.

The objective of this clinical study was to confirm the proposed dosage and treatment regimen of the product and also to demonstrate the efficacy of such a posology for this product in the treatment of aspergillosis and candidiasis in the field situation.

Considering the circumstances, i.e. that this application holds MUMS status and that there is high lethality of these fungal infections in untreated birds, a non-controlled single arm study design was considered acceptable.

The MUMS classification of this application also made it justifiable for a field trial to also include the objectives of dose confirmation and tolerance, and so the need to perform separate studies for the latter purposes was not considered essential.

For the aspergillosis part of the trial, endoscopy was performed and birds were included in the study only if the presence of *Aspergillus* fungi in air sacs was confirmed by the cultured biopsies and/or microscopic examination.

For the candidiasis trial, birds were included if clinical signs of candidiasis were present and the infection could be confirmed by crop and/or cloacal swab examinations. These inclusion criteria are considered satisfactory and ensure that the birds studied had clinical forms of aspergillosis or candidiasis.

In the aspergillosis trial, 62 birds were treated with itraconazole (using an identical formulation oral solution for birds), at a dose of 5–10 mg/kg bodyweight depending on bird species, at intervals of approximately 24 hours for at least 8 weeks.

In the candidiasis trial, 18 birds were treated with itraconazole (using an identical formulation oral solution for birds), at an average daily dose of 10 mg/kg bw for 13–14 consecutive days.

The treatment was classified as successful if there was:

- Disappearance of clinical findings: the main signs that were monitored were somnolence, decreased appetite and bodyweight loss
- Disappearance of growth of aspergillosis, as observed during endoscopy
- Disappearance of candidiasis in crop swab.

The clinical study protocol was acceptable overall, and the results tend to support a therapeutic effect of the tested treatment regimens of the product, as 56 birds out of the 62 treated against aspergillosis

did recover (the remaining 6 died), as well as all 18 animals treated against candidiasis. However, not all the proposed target species were represented in this field trial (in particular Passeriformes), and the number of birds included remained limited.

Thus, additional retrospective data were provided by the applicant, with the aim to further support the determination of target species. These data were gathered from a veterinary clinic specialized in birds and cover 1,257 birds treated for "fungal infections" with a formulation identical to that of Fungitraxx over the period from October 2011 to March 2013.

However, insufficient details were provided as regards the circumstances and experimental conditions in which those results were obtained (e.g. clinical and analytical criteria for positive diagnosis and confirmation of treatment success). As a consequence, the CVMP concluded that these data could not be regarded as fully valid and could serve only to support the conclusions obtained from the field trials.

The retrospective data include a number of documented treatments in several bird species. However, with regard to efficacy claims, only the cases in which birds were treated according to the exact indication and posology recommended in the present application were taken into account. As a consequence, all treatments with doses superior to 10 mg/kg and/or duration longer than 16 weeks for aspergillosis (considering the recommendation to repeat the whole course if need be) and 14 days for candidiasis were excluded from the analysis. Cases where the indication was not clearly identified as aspergillosis or candidiasis in the table were also excluded.

Following the identified exclusions, relevant information from these retrospective data and the field trial were available as follows:

- Psittaciformes:
    - 99 birds were treated for aspergillosis in the retrospective data, with additional data for 39 more birds from the field trial. Among those 138 treatments, 127 were successful (the remaining 11 birds died before the end of the protocol). Considering the experience with the product, and taking into account the MUMS status, the totality of available data was deemed sufficient to support efficacy claims against aspergillosis in Psittaciformes.
    - 37 birds were treated for candidiasis in the retrospective data, with additional data for 18 more birds from the field trial. Among those 55 treatments, 54 were successful (the remaining one was interrupted). Considering the experience with the product, and taking into account the context of a MUMS authorisation procedure, the totality of available data was deemed sufficient to support efficacy claims against candidiasis in Psittaciformes.
- Anseriformes:
    - 26 birds were treated for aspergillosis in the retrospective data, with additional data for 6 more birds from the field trial. Among those 32 treatments, 30 were successful (the remaining 2 birds died before the end of the protocol). Considering the cumulative experience with the product, and taking into account the MUMS status, the available data was deemed sufficient to support efficacy claims against aspergillosis in Anseriformes.
    - No information is available from either retrospective data or a field trial with regard to the product's efficacy against candidiasis in Anseriformes. Therefore the proposed claim for the treatment of candidiasis in this order was not accepted by the CVMP.
- Passeriformes:
    - 17 birds were treated for aspergillosis in the retrospective data, but none in the field trial.
    - 40 birds were treated for candidiasis in the retrospective data, but none in the field trial.

- The retrospective data were not considered sufficient to demonstrate efficacy and tolerance in this order. Therefore the proposed claims for the treatment of candidiasis in this order were not accepted by the CVMP.

- Falconiformes:
  - 32 birds were treated for aspergillosis in the retrospective data, with additional data for 7 more birds from the field trial. All 39 treatments were successful. Considering the experience with the product, and taking into account the MUMS status, the available data was deemed sufficient to support the efficacy claims against aspergillosis in Falconiformes.
  - No information is available from either retrospective data or from a field trial with regard to the product's efficacy against candidiasis in Falconiformes. Therefore the proposed claim for the treatment of candidiasis in this order was not accepted by the CVMP.
- Accipitriformes:
  - 18 birds were treated for aspergillosis in the retrospective data, with additional data for 3 more birds from the field trial. All 21 treatments were successful. Considering the cumulative experience with the product, and taking into account the MUMS status, the available data was deemed sufficient to support the proposed efficacy claim against aspergillosis in Accipitriformes.
  - No information is available from either retrospective data or a field trial with regard to the product's efficacy against candidiasis in Accipitriformes. Therefore the proposed claim for the treatment of candidiasis in this order was not accepted by the CVMP.
- Strigiformes:
  - 19 birds were treated for aspergillosis in the retrospective data, with additional data for 2 more birds from the field trial. All 21 treatments were successful. Considering the experience with the product, and taking into account the MUMS status, the available data was deemed sufficient to support the proposed efficacy claims against aspergillosis in Strigiformes.
  - 1 animal was treated for candidiasis in the retrospective data, but none in the field trial. Therefore the proposed claim for the treatment of candidiasis in this order was not accepted by the CVMP.

The totality of data support efficacy in the following target species.

The data is not sufficiently established to fully support indications in other species, in particular Passeriformes, specifically in the absence of any clinical data present in the initial field trial for Passeriformes.

Overall conclusion on efficacy

On the basis of the published literature, the field trial data and the retrospective data provided, the CVMP concluded that sufficient information is available to support the indications for the treatment of aspergillosis and candidiasis in the following target species, at the following doses:

- Aspergillosis: 5 to 10 mg (0.5 ml to 1 ml) itraconazole per kg bodyweight per day for 8 weeks.

  For the treatment of aspergillosis the accepted list of target species, as included in section 4.1 of the SPC, is:

  Ornamental birds, particularly:

Psittaciformes (specifically cockatoos and true parrots: parakeets; budgerigars)

Falconiformes (falcons)

Accipitriformes (hawks)

Strigiformes (owls)

Anseriformes (specifically swans)

- Candidiasis (Psittaciformes only): 10 mg (1 ml) itraconazole per kg bodyweight per day for 14 days.

With regard to efficacy claims against *Candida*, no clinical data were provided in Anseriformes, and therefore this proposed indication could not be supported in these birds and was removed.

Special precautions should be exercised when treating Psittaciformes, and in particular African Grey Parrots, because of their recognised sensitivity to itraconazole. Advice to this effect is included in the SPC and package leaflet.

Part 5 – Benefit-risk assessment

Introduction

Fungitraxx is an orally administered veterinary medicinal product for use in a number of different species of ornamental birds. Such birds are by definition not intended for human consumption. Fungitraxx contains itraconazole as the active substance. The active substance is a well-known active substance for the treatment of fungal diseases in humans and it is also available in an EU authorised veterinary medicinal product for use in cats. The submitted dossier for marketing authorisation includes extensive reference to the published literature, indicating the well-established use of the active substance in the indications for use in birds at the recommended dose. In birds, Fungitraxx is intended to be used at the dose of 5 to 10 mg itraconazole per kg bodyweight, for 8 weeks in the case of aspergillosis, and 10 mg/kg bw for 14 days in the case of candidiasis.

Fungitraxx is classified as MUMS/limited market for the proposed indication and target species.

Benefit assessment

Direct therapeutic benefit

Fungitraxx contains itraconazole, and its mode of action is by a selective action on the fungal cell structure, causing death of the fungus.

Fungitraxx has been demonstrated to be efficacious in the treatment of fungal diseases due to *Candida* in Psittaciformes and *Aspergillus* species in Psittaciformes (specifically cockatoos and true parrots: parakeets; budgerigars), Falconiformes (falcons), Accipitriformes (hawks), Strigiformes (owls) and Anseriformes (specifically swans). These fungi can cause diseases in a variety of anatomical sites in birds, mainly leading to respiratory disease. Such diseases can be fatal in birds. These diseases can also be chronic, necessitating long-term treatment.

A non-controlled, unblinded clinical trial provided relevant information for the efficacy of the product in the treatment of fungal disease in the above bird species at the proposed dose and duration of

treatment. In addition, retrospective data was sufficient to confirm the conclusions from the initial clinical study on efficacy and tolerance in each of the proposed bird orders.

Additional benefits

Fungitraxx solution is given by the oral route (via an oral syringe) which helps ensure infected ornamental birds receive the correct dose. The formulation contains a flavour. Although there are no data on palatability of the product in birds, experience from the field study and retrospective data allow concluding that the product is well accepted by different types of birds, especially when administered mixed in food. Fungitraxx provides a new authorised treatment option for the specified minor species.

Risk assessment

The main potential risks are the following:

For the target species:

Vomiting is the most commonly reported adverse event from the data provided. No traditional tolerance study is available in the target species with the final formulation and repeat toxicity data are also very scarce for this product. Safety data were obtained in the clinical trial, from published literature and from a retrospective data obtained from a veterinary clinic specialized in birds. In the retrospective study, the incidence of adverse effects was low (18 reported cases which may include several birds/1,257 treated birds). This allowed concluding that the product is generally well tolerated when used as recommended.

For the user:

A well conducted user risk assessment is provided. The risk for a child is particularly well identified and has been satisfactorily addressed. The risk is further mitigated by the use of a tamper-evident closure on the primary container (bottle).

For the environment:

The product is not expected to pose any risk to the environment when used as recommended.

Consumer safety:

Consumer safety is not applicable, as the product is intended for use in ornamental birds. A specific warning has been included not to use the product in in birds intended for human consumption.

Specific potential risks:

Concerning emergence of resistance, it is acknowledged that a risk of increased resistance to itraconazole against pathogens following use of this product is plausible.

The likelihood for the development and spread of resistance to itraconazole in *Aspergillus* and *Candida*, both in the target species and in humans coming into contact with treated animals, such as the user, have been addressed through the addition of appropriate warnings in the SPC and other product literature.

Concerning risk for zoonosis, *Aspergillus* and *Candida* are potentially zoonotic agents. The zoonotic nature of aspergillosis needs to be taken into consideration. Explicit warnings were therefore included in the SPC and package leaflet addressing the need for heightened awareness in handling treated birds to prevent exposure to aspergillosis. Warning sentences in section 4.5 of the SPC (and section 12 of

the package leaflet) include a recommendation to wear gloves, not because of the possibility of contact with the product, but in order to avoid exposure to the disease. As aspergillosis is transmitted via aerosol infection, the wearing of a mask is also recommended.

Consumer safety is not applicable, as the product is not intended for use in non-food producing animals.

Risk management or mitigation measures

Appropriate information has been included in the SPC to inform on the potential risks relevant to the target animals, the user and the environment and to provide advice on how to prevent or reduce these risks.

Because of the special sensitivity of Psittaciformes, if product related adverse events occur, the dose should be lowered or the treatment discontinued.

As the product is generally not well tolerated by African Grey Parrots, the product should only be used in this species if no alternative treatment is available, and then with care and with the lowest recommended dose for the whole of the recommended treatment period.

The product information contains a contraindication to prevent use of the product in birds intended for human consumption.

Warning sentences for the user in the product information include a recommendation to wear gloves, not because of the possibility of contact with the product, but in order to avoid exposure to aspergillosis. As aspergillosis is transmitted via aerosol infection, the wearing of a mask is also recommended.

Evaluation of the benefit-risk balance

The product has been shown to have a positive benefit-risk balance overall.

The formulation and manufacture of Fungitraxx is well described and the specifications set will ensure that product of consistent quality will be produced.

Tolerance in the target species has been appropriately investigated for this product, the active substance in which has well-established use for a variety of birds. The potential adverse reactions are clearly described in the SPC and package leaflet.

Fungitraxx presents a low risk for users and the environment and appropriate warnings have been included in the SPC and package leaflet.

The product has been shown to be efficacious for the treatment of aspergillosis in Psittaciformes, Falconiformes, Accipitriformes, Strigiformes and Anseriformes, and also for the treatment of candidiasis in Psittaciformes, as further specified in the SPC.

Conclusion on the overall benefit-risk balance

The overall benefit-risk evaluation for the product is deemed positive with a sufficiently clear and complete SPC and other product literature.

Conclusion

Based on the original and complementary data presented the CVMP concluded that the quality, safety and efficacy of Fungitraxx were considered to be in accordance with the requirements of Directive 2001/82/EC and that the benefit–risk balance was favourable.

Based on the CVMP review of the data on quality, safety and efficacy, the CVMP recommends the granting of the marketing authorisation for Fungitraxx.