EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

10 October 2019
EMA/562416/2019
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Mirataz (EMEA/V/C/004733/0000)

INN: mirtazapine

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

Official address Domenico Scarlattilaan 6 ● 1083 HS Amsterdam ● The Netherlands
Address for visits and deliveries Refer to www.ema.europa.eu/how-to-find-us
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Introduction

The applicant Aniserve GmbH submitted on 30 October 2017 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Mirataz, through the centralised procedure under Article 3(2)(a) of Regulation (EC) No 726/2004 (optional scope).

The eligibility to the centralised procedure was agreed upon by the CVMP on 19 January 2017 as Mirataz contains a new active substance (mirtazapine) which is not yet authorised as a veterinary medicinal product in the Union.

The applicant applied for the following indication: For the management of weight loss in cats.

The active substance of Mirataz is mirtazapine, an α2-adrenergic receptor antagonist, which is known to be a potent antagonist of 5-hydroxytryptamine $(HT)_2$ and 5-HT_3 receptors in the central nervous system (CNS), and a potent inhibitor of histamine H_1 receptors. Inhibition of 5-HT_2 receptors may account for the orexigenic effects of the molecule. Mirtazapine-induced weight gain may also be secondary to changes in leptin and tumour necrosis factor (TNF). The target species is cats.

Mirataz transdermal ointment contains 20 mg/ml mirtazapine and is presented in a clear plastic bottle containing 1 tube with 5 g of ointment.

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

The rapporteur appointed is Sylvie Louet and the co-rapporteur is Anna Wachnik-Święcicka.

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

On 10 October 2019, the CVMP adopted an opinion and CVMP assessment report.

On 10 December 2019, the European Commission adopted a Commission Decision granting the marketing authorisation for Mirataz.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (dated 20 August 2014) which fulfils the requirements of Directive 2001/82/EC. Based on the information provided the applicant has the services of a qualified person responsible for pharmacovigilance and the necessary means for the notification of any adverse reaction occurring either in the Community or in a third country.

Manufacturing authorisations and inspection status

Manufacture of the dosage form, primary, secondary packaging and batch control takes place outside the EEA. The site has a manufacturing authorisation and compliance with EU GMP has been confirmed by the Competent Authority in the Netherlands.

Batch release takes place at Klifovet AG, Munich, Germany which holds a manufacturing authorisation and GMP certificate issued by the Competent Authority in Germany issued on 21 June 2017.

A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site.

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 finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

Part 2 - Quality

Composition

The drug product is a transdermal ointment containing 2% w/w mirtazapine (as hemihydrate). The active substance is described in the European Pharmacopoeia (Ph. Eur.). The excipients are commonly used in the manufacture of this pharmaceutical form. The list of excipients is as described in section 6.1 of the SPC.

Containers

The ointment is packaged in a multidose, blind end aluminium tube with a white low density polyethylene (LDPE) cap and a crimp sealant. Each tube contains 5 grams of ointment. The tube is stored in a child resistant clear plastic bottle.

The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Development pharmaceutics

A polyethyleneglycol-based formulation was selected as the final prototype gave satisfactory results for mirtazapine assay and achieved the target product profile (transdermal, non-greasy, washable, non-irritating, non-allergenic, good stability).

A study demonstrated that a length of 1.5 inch (3.8 cm) of a 2% mirtazapine ointment allows the delivery of an amount corresponding to 0.10 mL of product or 2 mg mirtazapine/cat. While it is difficult to achieve a precise dose with this kind of pharmaceutical form, the product information of Mirataz displays a line with the recommended length of the strip of ointment to be applied, which was accepted by the CVMP.

Pharmaceutical development is generally satisfactorily detailed.

Method of manufacture

The manufacturing process is considered a non-standard manufacturing process as it is a specialised dosage form according to the annex II of the Guideline on process validation (EMEA/CHMP/CVMP/QWP/BWP/70278/2012-Rev 1). Satisfactory process validation results have been provided in accordance with the aforementioned guideline. Critical steps have been correctly identified.

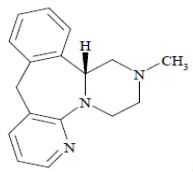
The filling process is standard for this pharmaceutical form. The filling process has also been satisfactorily validated.

It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner. The in-process controls are adequate for this type of manufacturing process and pharmaceutical form.

Control of starting materials

Active substance

The chemical name of mirtazapine is (14b*RS*)-2-methyl-1,2,3,4,10,14b-hexahydropyrazino[2,1-a]pyrido[2,3-c]benzazepine and it has the following structure:



and enantiomer

The active substance is a white to creamy white crystalline powder, non-hygroscopic, practically insoluble in water and freely soluble in methanol.

Mirtazapine exhibits stereoisomerism due to the presence of one chiral centre.

Polymorphism has been observed for this active substance and the hemihydrate form is the polymorphic form always obtained by this manufacturer.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

There is a monograph of mirtazapine in the Ph. Eur. The control tests were carried out to comply with the specifications and test methods of this monograph. Additional specifications have been set for residual solvents.

The characterisation of the active substance and its impurities are in accordance with the CVMP guideline on chemistry of new active substances. Potential and actual impurities were well discussed with regards to their origin and characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented and are acceptable.

Detailed information on the manufacturing of the active substance has been provided in the

restricted part of the ASMF and is considered satisfactory.

The active substance specification includes tests for appearance, solubility, identity optical rotation, assay, impurities residual solvents, water content and residue on ignition (Ph. Eur.).

The analytical methods used have been adequately described and non-compendial methods appropriately validated in accordance with the VICH GL2. Satisfactory information regarding the reference standards used for assay testing has been presented.

Batch analysis data from 3 consecutive batches of the active substance have been provided. The results are within the specifications and consistent from batch to batch.

Stability data of active substance from the proposed manufacturer, for 60 and 24 months under long term conditions at 25 ± 2 °C/60 ± 5% RH and for up to 6 months under accelerated conditions at 40 ± 2 °C /75±5% RH according to the VICH guidelines were provided. The active substance is found to be very stable at long term and accelerated conditions. All tested parameters were within the specification. A re-test period of 5 years may be granted.

Photostability testing according to VICH GL5 was performed. Results from stability testing performed under stress conditions (aqueous reflux, acid, basic, oxidant, heat and light) were also provided.

Reference to the ASMF dossier is made in the medicinal product dossier. The specifications at the dosage form site are consistent with specifications of active substance manufacturer and include specifications for residual solvents and particle size.

Excipients

The finished product contains the following excipients: macrogol 400, macrogol 3350, BHT, diethylene glycol monoethyl ether, caprylocaproyl macrogol-8 glycerides, oleyl alcohol, dimethicone and tapioca starch polymethylsilsesquioxane.

There are no novel excipients used in the finished product formulation. All excipients are analysed according to current Ph. Eur. except for BHT, tapioca starch polymethylsilsesquioxane and oleyl alcohol. The applicant indicates that the future quality standards of BHT and oleyl alcohol will comply with Ph. Eur. for the manufacturing process of commercial batches, which is acceptable. BHT and oleyl alcohol are analysed according to USP/NF criteria. Non-compendial methods are correctly described.

Specifications for tapioca starch polymethylsilsesquioxane are provided, and the methods are described. Data on this excipient are considered satisfactory.

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

The product does not contain any materials derived from human or animal origin.

None of the starting materials used for the active substance or the finished product are risk materials as defined in the current version of the 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.

Control tests on the finished product

The specifications proposed at release are appropriate to control the quality of the finished product. The tests proposed are description, viscosity, identification, mirtazapine assay, mirtazapine related substances, uniformity in container, BHT assay, water determination and microbial limits (Ph. Eur.).

The analytical methods for assay of mirtazapine and impurities and BHT assay have been adequately described and appropriately validated in accordance with VICH guidelines. Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Validation of analytical methods are provided and correctly validated.

Batch analysis results are provided which comply with current product specifications.

Stability

Stability data of three batches of finished product stored under long term conditions for 36 months at 30 ± 2 °C/65 ± 5% RH, at 25 ± 2 °C/65 ± 5% RH and for up to 6 months under accelerated conditions at 40 ± 2 °C/75 ± 5% RH according to the VICH guidelines were provided. These product batches are different from those proposed for marketing and were packed in the primary packaging proposed for marketing.

The specification at the end of shelf life is the same as that proposed at release, except for mirtazapine assay, BHT and related substances assay for which limits have been widened. Package integrity and weight loss are added.

The analytical procedures used are stability indicating.

Stability results are compliant with the proposed limits. The viscosity remains stable and the microbial limits test is compliant with Ph. Eur. limits.

Observed physical and chemical changes were small, and not likely to have a significant effect on efficacy and safety of the product when used according to the directions in the SPC.

In addition, one batch was exposed to light as defined in the VICH GL5 on photostability testing of new veterinary drug substances and medicinal products. The packaging is protective against light. Freeze/thaw testing has been performed on one batch and the product remains stable.

An in-use stability study on a 1-year-old batch shows that the finished product is stable 30 days after first opening.

Based on the available stability data, the proposed shelf-life of 36 months is accepted without any special storage conditions.

Overall conclusions on quality

Information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The quality of this product is considered acceptable when used in accordance with the conditions defined in the SPC. Physicochemical aspects relevant to the performance of the product have been

investigated and are controlled in a satisfactory way. Data has been presented to give reassurance on TSE safety.

Part 3 – Safety

The active substance of Mirataz is mirtazapine, an α2-adrenergic, H1-histaminergic and serotonergic receptor antagonist used as an antidepressant in human medicine.

Mirtazapine is a new active substance not authorised in a veterinary medicinal product in the EU before.

Pharmacodynamics

See part 4.

Pharmacokinetics

See part 4.

Toxicological studies

No toxicity studies have been conducted by the applicant in rodent laboratory animals. The applicant has provided literature data including summaries of toxicology studies reported in the monograph for an existing product as well as public FDA and EMA documents relating to already approved medicinal products for human use containing mirtazapine as active substance. With the exception of data on genotoxicity and carcinogenicity the information on laboratory species can only be considered as supporting data, due to the low level of detail in the published literature. These are briefly reported below.

An acute oral toxicity study was carried out in cats.

One pilot and one pivotal tolerance study in cats were conducted after transdermal application of a 2% w/w mirtazapine ointment to document the repeat dose toxicity of mirtazapine.

Single dose toxicity

Data on acute toxicity is derived from published literature, which includes only very short summaries of results of studies performed in laboratory animals.

See also 'Part 4: Tolerance'.

Repeat dose toxicity

No repeat dose toxicity studies have been carried out by the applicant in rodent laboratory species. However, reference is made to target animal studies, which included repeated administrations of mirtazapine to cats. This approach is accepted as the use of results of a TAS study addresses the data required with respect to the repeat dose endpoint (in compliance with Annex I of Directive 2001/82/EC) since Mirataz is intended solely for use in non-food producing species. Nevertheless, no definite 'no adverse effect level' (NOAEL) can be drawn from the TAS study as adverse events were observed in all groups, including the control group. See 'Part 4: Tolerance' for further detail.

Other data on repeat dose toxicity came from published literature, which included only very short

summaries of results of studies performed in laboratory animals. In these documents, a 13-week study in rats with an oral NOEL of 10 mg/kg/day and a 12 month study in rats with a LOEL (slight effect on bodyweight) of 2.5 mg/kg were reported. However, these summaries can only be considered to provide supporting information as they do not provide the data required to allow the establishment of a NOAEL. This information therefore has limited value for the purpose of the risk assessment, especially regarding user risk assessment.

Tolerance in the target species of animal

See Part 4.

Reproductive toxicity

Study of the effect on reproduction

No studies of the effect of mirtazapine on reproduction have been carried out by the applicant. The absence of these studies can be accepted as, for companion animal products, they are not specifically required by Annex I of Directive 2001/82/EC.

Study of developmental toxicity

No developmental toxicity studies with mirtazapine have been carried out by the applicant.

According to the published literature, reproductive toxicity studies in rats and rabbits did not show any teratogenic effects. At two-fold systemic exposure compared to maximum human therapeutic exposure, there was an increase in post-implantation loss, decrease in the pup birth weights, and reduction in pup survival during the first three days of lactation in rats.

Although the use of the product is contraindicated in breeding, pregnant or lactating cats, there is also a need to consider user safety, as significant exposure to the product is expected, considering the route of administration.

Mirtazapine has a long history of use in human medicine. Several bibliographic references were provided, a number of which reported retrospective studies on the possible reprotoxic effects of antidepressants, including serotoninergic antidepressants such as mirtazapine when administered to pregnant women.

These articles showed that mirtazapine does not appear to be associated with an increased risk for major malformations in newborns above the baseline rate of 1% to 3% (Einarson *et al*, 2005; Djulus *et al*, 2006). However, in one of these articles (Djulus *et al*, 2006), the potential role of mirtazapine in two unexplained preterm births cannot be excluded and in two others (Yaris *et al*, 2014; Kjaersgaard *et al*, 2013) its involvement in spontaneous abortions is not clearly ruled out. In addition, the studies reported by Djulus *et al* (2006) did not assess possible long-term neurobehavioral effects in babies and other variables such as birth weight, head circumference and prematurity, which have not been investigated.

Furthermore, at present, it is recommended that human medicines containing mirtazapine are prescribed with caution to pregnant women and that a post-natal survey be performed to explore possible reactions from mirtazapine treatment discontinuation.

It should also be noted that the possibility of an increased risk of persistent pulmonary hypertension in the newborn (PPHN) cannot be ruled out as mirtazapine acts on the same systems as

selective-serotonin reuptake inhibitors.

There is global acknowledgement that available data on the reprotoxicity of mirtazapine in pregnant women are too scarce to definitively conclude on the risk to such a sub-population. As a consequence, the therapeutic dose in humans (15 to 45 mg per person i.e. 0.25 to 0.75 mg/kg bw) should be considered as a dose with potential effects in pregnant women.

Genotoxicity

No genotoxicity studies with mirtazapine have been carried out by the applicant.

The data provided are reported in the published literature including robust bibliographic references.

The documents report that mirtazapine is not mutagenic or clastogenic and does not induce DNA damage as determined in several genotoxicity tests, namely the Ames test, the *in vitro* gene mutation assay in Chinese hamster V79 cells, the *in vitro* sister chromatid exchange assay in cultured rabbit lymphocytes, the *in vivo* bone marrow micronucleus test in rats and the unscheduled DNA synthesis assay in HeLa cells. The absence of mutagenic potential of mirtazapine is confirmed in an *in vitro* chromosomal aberration test, an *in vitro* sister chromatid exchange test*,* an *in vitro* micronucleus assay on peripheral human lymphocytes with Remeron, a human medicinal product containing mirtazapine as active substance. All tests gave negative results.

The absence of mutagenic/genotoxic potential is further confirmed by Snyder *et al* (2001) and Brambilla *et al* (2009) who published reviews on the genotoxicity of marketed pharmaceuticals, including mirtazapine.

In conclusion, in a suitable battery of tests, mirtazapine was neither genotoxic, nor mutagenic or clastogenic.

Carcinogenicity

No carcinogenicity studies with mirtazapine have been carried out by the applicant.

While carcinogenicity potential was identified in the public literature in mice and rats, this process was shown to be irrelevant for humans because of fundamental qualitative differences between the species.

Overall, it can be concluded that there is no evidence of carcinogenicity of mirtazapine in humans.

Studies of other effects

The acute dermal irritation potential of the final formulation was evaluated *in vivo* in New Zealand White rabbits according to OECD guideline 404. The substance was found to be irritating for intact skin.

No data are provided on the impact of applying the product on broken skin. A warning is included in the SPC (section 4.5.i).

In a local lymph node assay in mice, which was conducted in accordance with OECD guideline 442B (although only one concentration was tested while three are recommended in the guideline), the final formulation was a dermal sensitizer.

Acute eye irritation/corrosion of the final formulation was assayed *in vivo* in New Zealand White rabbits according to OECD guideline 405. The final formulation was irritating for the eyes.

No specific studies on the neurotoxicity of mirtazapine were provided. This is acceptable because effects on the nervous system are assessed through tolerance and efficacy assays.

Mirtazapine is used in human medicine for the symptomatic relief of depressive illness. The usual recommended dose is 15 to 45 mg/day (or 0.25 to 0.75 mg/kg for a 60 kg adult). The use of this substance is not recommended in patients of less than 18 years of age.

The product information for the human medicinal product indicates that, as the safe use of mirtazapine has not been assessed during pregnancy, the medicine should not be administered to women of childbearing potential or nursing mothers, or only according to a benefit/risk assessment undertaken by the physician.

In humans, common observed adverse effects are sedation, increased appetite, swollen ankles or feet, nausea and headache.

Excipients

The safety of the excipients of the final formulation of Mirataz is sufficiently documented.

All excipients of the formulation are well known with regard to their use as excipients in veterinary medicinal products. No specific risk is expected to arise from their use in the veterinary medicinal product.

User safety

The applicant has presented a user safety assessment which has been conducted in accordance with the Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1) and the Guideline on user safety of topically administered veterinary medicinal products (EMA/CVMP/SWP/721059/2014).

The product will be administered by pet owners or professionals (including veterinarians). The main potential routes of accidental contact with the product are considered to be dermal and oral.

The product is provided in child resistant packaging, limiting the risk of direct dermal contact and accidental ingestion by a child. Furthermore, warnings in the product information highlight the need to avoid leaving the opened product unattended and are considered to adequately mitigate against the possibility of children coming into direct contact with the product during its application.

Dermal contact and oral ingestion via hand-to-mouth contact following interaction with treated animals is considered to be the most relevant exposure route for adults and children. In addition, adults may become dermally exposed every time they apply the ointment, i.e. daily for 14 days according to the claimed treatment schedule. Eye contact (due to hand-to-eye contact) and oral contact (due to hand-to-mouth contact) may also occur if personal hygiene measures (i.e. washing of hands after application) are not maintained.

Hazard

A LOAEL of 2.5 mg/kg bw was derived from the 12 month rat study. However, as only a summary of the relevant study is available, the data are not considered to be robust and consequently can only be considered supportive. It is noteworthy that if this LOAEL could be used in the user safety evaluation, the acceptable MOE would not be less than 1000 (based on factors of 10 for interspecies differences, 10 for intraspecies differences and further 10 for the fact that the value is not a NOAEL, and that only a summary of the study is available). The resulting acceptable human oral exposure

level would therefore be 0.0025 mg/kg bw.

Mirtazapine has a long history of use in human medicine where the recommended treatment dose is typically in the range of 15 to 45 mg/day, but the use of lower doses has been reported. The applicant proposed, therefore, that the toxicological reference value (TRV) should be based on a dose of 3.75 mg/person (0.0625 mg/kg bw assuming a bodyweight of 60kg), which is reported by Shuman *et al*. (2019) to be a low dose sometimes used in human medicine (that is, considerably lower than the lowest authorised dose of 15 mg/person). If the value of 0.0625 mg/kg bw were used in the user safety evaluation, the resulting acceptable human oral exposure level would therefore be 0.0021 mg/kg bw.

Finally, the lowest authorised human therapeutic dose is 15 mg/person (0.25 mg/kg bw assuming a bodyweight of 60kg). However, as indicated in the guideline on user safety of topically administered veterinary medicinal products, human therapeutic doses are not generally accepted for use in user risk assessments. If this value could be used in the user safety evaluation, the resulting acceptable human oral exposure level would be 0.0025 mg/kg bw.

While none of the data sources referenced above provide data which, on their own, could be considered sufficiently robust to allow determination of an acceptable human exposure level, it is noteworthy that the three approaches detailed above lead to very similar conclusions. Therefore, based on the totality of available data, 0.0025 mg/kg bw can be confidently considered to be an oral dose that would not be associated with any effect in exposed users. This value is therefore considered to be the threshold below which oral exposure must remain.

Data on the dermal absorption of mirtazapine in humans are not available. However, as transdermal absorption in cats is known to be significantly lower than oral absorption (approximately 50%) it is considered that a dose of 0.0025 mg/kg bw (i.e. the oral dose considered to be free of effects in exposed users) can safely be considered to also be a dermal dose that would not be associated with any effects in exposed users. This value is therefore also considered to be the threshold below which dermal exposure must remain.

Local effects

Skin and eye toxicity studies using a 2% w/w mirtazapine ointment (final formulation) were provided. Based on these studies, it is concluded that the tested product may be irritating to the skin and to the eye.

A 2% w/w mirtazapine ointment (final formulation) was considered to be a skin sensitizer in a local lymph node assay in the mouse.

The risk of skin/eye irritation and sensitisation are considered to be adequately mitigated against by warnings in the product literature and by the fact that users should use gloves when applying the product.

Exposure calculations and comparisons with the acceptable human exposure levels

Accidental exposure by children during pre-application phase

With regards to accidental oral exposure by children, the ingestion of 10% of the total content of the product (100 mg mirtazapine/tube) was considered. Thus, by applying the recommended equation, the CVMP calculated an exposure of 0.8 mg/kg bw assuming a 12.5 kg child.

The value is substantially greater than the acceptable oral exposure level of 0.0025 mg/kg bw. However, the product is presented in a child resistant container, which prevents the child having

access to the tube. The risk is therefore considered to be adequately mitigated.

Accidental dermal contact of children may also occur in the case of access to a stored tube. This risk is also adequately mitigated by the fact that the product is presented in child resistant packaging.

Possible dermal exposure of an adult during the application phase

Assuming the possibility of exposure during the application phase, when an adult user accidentally covers a finger with ointment without putting gloves on, the CVMP calculated a dermal exposure of 0.0033 mg/kg (in line with the CVMP guideline on user safety of topically administered veterinary medicinal products direct dermal exposure during application is considered to be 10% of the administered dose).

Accidental oral exposure of an adult during application phase

The CVMP calculated an accidental oral exposure of 0.00033 mg/kg (1% of the administered dose).

The oral and dermal exposure values of 0.00033 mg/kg and of 0.0033 mg/kg are compared to the acceptable (oral and dermal) exposure level of 0.0025 mg/kg bw resulting in a margin of exposure of 7.5 (oral exposure) and 0.75 (dermal exposure), respectively. A risk is thus identified for the dermal exposure. This risk is mitigated by the recommendation to wear gloves for each application.

Child exposure in the post application phase

With regards to exposure resulting from stroking treated animals, children are considered to represent the worst case exposure scenario.

A wipe test was provided to determine the dislodgeable fraction from treated animals. The test was performed as described in the 'Guideline on user safety of topically administered veterinary medicinal products' (EMA/CVMP/SWP/721059/2014). The highest dislodgeable fractions were found 0.5 hours after the last administration. After 96 hours post-treatment, residues at both the application site and body residues were below the limit of quantification (250 ng/glove).

The dermal exposure from contact with a treated cat was calculated by using the method as described in the Guideline on user safety of topically administered veterinary medicinal products.

The estimated dermal exposure (DE) is only lower than the acceptable dermal exposure level of 0.0025 mg/kg bw from 12 hours post administration (DE= 0.0013 mg/kg). An unacceptable risk is identified at 4 hours (DE= 0.0086 mg/kg) and 8 hours (DE = 0.0053 mg/kg) after application. The risk becomes acceptable from 12 hours after the daily application.

The estimated oral exposure is below the acceptable oral exposure level of 0.0025 mg/kg bw from 1 hour post administration.

Based on the unacceptable risk resulting from dermal exposure of children to mirtazapine as a result of contact with a treated cat, contact with treated animals should be avoided during 12 hours after each daily application (warning sentences are included in the SPC, section 4.5.ii).

As data on the reproductive toxicity of mirtazapine are limited, particular consideration was given to the risk for pregnant women. Given the limited data available on the reproductive toxicity of mirtazapine, pregnant women or women trying to conceive should avoid handling the product and contact with treated animals throughout the treatment period.

Environmental risk assessment

An ERA was provided according to CVMP/VICH guidelines. Based on the data provided, the ERA can stop at Phase I, as the product is intended to be administered to cats, a non-food producing animal. Mirataz is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

Data for acute and chronic toxicity, reproductive toxicity and the mutagenic/carcinogenic potential of mirtazapine are derived from literature including summaries of toxicology studies reported in the monograph for an existing product as well as public FDA and EMA documents relating to already approved medicinal products for human use containing mirtazapine as active substance. With the exception of data on genotoxicity and carcinogenicity the information on laboratory animal toxicity can only be regarded as supportive, as it does not contain the detail needed to draw assessment conclusions.

Tolerance studies performed in the target species are used for documenting repeat dose toxicity of mirtazapine. No NOEL can be retained from these studies.

Mirtazapine is neither genotoxic, nor mutagenic or clastogenic.

Carcinogenic potential has been identified in the published literature in that mirtazapine is a non-genotoxic carcinogen in mice and rats. The underlying molecular mechanisms of this finding have been shown not to be relevant for humans.

The safety of the excipients of Mirataz is sufficiently documented. The excipients are currently used in human and veterinary medicinal products and do not raise toxicological concerns.

Mirtazapine as a 2% (w/w) ointment was shown to be irritating to intact skin, to eyes and to be a skin sensitizer.

No data on effects on broken skin have been provided. The product should only be used on intact skin. This is specified in the product literature.

The literature provided is not sufficient to exclude a risk of the product to pregnant women.

A user safety assessment in line with the Guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1) and the Guideline on user safety of topically administered veterinary medicinal products (EMA/CVMP/SWP/721059/2014) has been presented.

Numerous warnings are included in the SPC notably regarding the use of gloves when applying the product, the need to avoid contact with the treated animals for 12 hours following application of the product and the fact that pregnant women should avoid contact with the product. The packaging is childproof to avoid accidental ingestion by children. A pictogram of gloves is present on the outer package and the following wording is stated: "read carefully the user safety warnings before use".

An appropriate environmental risk assessment was provided. The product is not expected to pose a risk for the environment when used according to the SPC.

Part 4 – Efficacy

Pharmacodynamics

The active substance in Miratаz, mirtazapine, is novel in veterinary medicines, but is authorised for human use mainly as an antidepressant, but also in other indications such as appetite stimulant. Mirtazapine is a tetracyclic noradrenergic and specific serotonergic antidepressant. It is a potent antagonist of central auto and hetero α_2-adrenoreceptors, histamine H_1 as well as 5-HT_2 and 5-HT_3 serotonin receptors.

The applicant provided reports demonstrating the effect of mirtazapine as an appetite stimulant in humans. The underlying mechanism of action for appetite stimulation is not well known and may involve antagonism of the 5-HT_{2c} receptor in the central nervous system, which is known for its appetite-inhibiting activity, as well as antagonism of the histamine H_1 receptor, which also plays a role in appetite regulation. Mirtazapine-induced weight gain may also be secondary to changes in leptin and tumour necrosis factor (TNF) expression.

According to the review of Agnew (2014), administration of mirtazapine in cats for appetite stimulation was first reported in 2006. The dosage of mirtazapine ranged from 1.88 mg/cat per os (PO) every 12-24 h to 3.5 mg/cat PO every 72 h. Quimby (2010 and 2011) reported a significant increase in food consumed after oral administration of mirtazapine at 1.88 mg/cat every 24 h to healthy young cats, with an extended dosing regimen (every 48 h) in cats with chronic kidney disease, whereas Benson (2016, see below under dose justification) showed increased appetite and rate of food ingestion after mirtazapine transdermal application at 7.5 mg/cat/day for 6 consecutive days in healthy cats.

The 5-HT_2 blocking effects contribute to the anxiolytic effects of mirtazapine and enhance sleep. In cats (see 'Part 4: Tolerance'), this effect was expressed by a dose-dependent lethargy/weakness.

In humans, the 5-HT_3 receptor blockade by mirtazapine may help to prevent nausea and vomiting and the applicant provided several reports describing the effect of mirtazapine in human medicines on the treatment of nausea or vomiting from secondary causes. Paradoxically, in the pivotal target animal safety study (see 'Part 4: Tolerance'), vomiting was an adverse event commonly reported in cats. However, as this was observed in all groups, including the control group, the effect is assumed to be related to an excipient of Miratаz.

Pharmacokinetics

Absorption, distribution, metabolism and excretion studies were not performed in the cat.

Five plasma pharmacokinetic mirtazapine studies in healthy adult cats are provided. Three studies were conducted with the final formulation of which only the pivotal tolerance study was conducted under GLP conditions.

Results from two pilot studies, using a non-final formulation, show that mirtazapine is absorbed transdermally after application to the internal pinna of the ear. There are large inter-individual pharmacokinetic variations, larger than after oral administration of tablets. The absorption is slow with sustained plasma concentrations of mirtazapine and a prolonged half-life. Plasma mirtazapine concentrations peak between 1 and 4 hours after dosing. In one study, steady state after a topical dose of 0.5 mg/kg bw is reached after 48 to 72 hours with a factor of accumulation of 3–5 after 13 days of treatment.

A non-GLP study, using the final formulation, was conducted comparing the pharmacokinetic profiles of a single dose of 0.5 mg/kg bw of mirtazapine when administered by two routes of administration (oral versus topical) in a cross-over design with two groups of 4 cats and with a short washout period of 5 days. All cats were individually housed and wore Elizabethan collars throughout the entire study, to prevent unintended oral uptake. Bioavailability following topical administration was 34% compared to oral administration during the first 24 hours (range: 6.5 to 89% based on 8 animals) and 65% based on $AUC_{0-\infty}$ (range: 40.1 to 128.0% based on 6 animals). After a single topical administration, the mean peak plasma concentration of 21.5 ng/ml (± 43.5) is reached with a mean T_{max} of 15.9 hours (1–48 hours). The harmonic mean terminal half-life of mirtazapine was 25.6 h (± 5.5) and the mean AUC_{0-24} was 100 ng*h/ml (± 51.7).

Another non-GLP study using the final formulation was conducted to determine the effects of mirtazapine on body weight and food consumption when topically administered for 14 days at doses of 0.5 and 2 mg/kg bw once daily and to evaluate the pharmacokinetics at steady state, in a parallel design. There were 20 cats (6.2 to 13.0 years old): 8 cats (3.77–7.45 kg) per treated group and 4 cats (4.74–7.15 kg) in the untreated control group. Elizabethan collars were placed on all the cats for the duration of the study. Blood mirtazapine concentrations were measured on day 13. The average plasma concentration over the dosing interval (24 h) was 16.4 ± 4.01 ng/ml for the low dose and 47.4 ± 11.8 ng/ml for the high dose. The mean steady state C_{min} was 7.64 ± 4.66 ng/ml in the low dosage group and 25.9 ± 6.27 ng/ml in the high dosage group. The extent of absorption ($AUC_{0-\infty}$) after 14 days is comparable to that after single oral administration (additional study) at the same dose (0.5 mg/kg bw). Nearly linear plasma pharmacokinetics of mirtazapine is demonstrated between 0.5 and 2 mg/kg bw based on AUC_{0-24h} and C_{max}, whereas the elimination half-lives tended to be roughly in the same order (20.7 versus 28.4 hours). The mean peak plasma concentration of 39.6 ng/ml (± 9.72) is reached with a mean T_{max} of 2.13 hours (1–4 hours). The harmonic mean terminal half-life of mirtazapine was 19.9 h (± 3.7) and the mean AUC_{0-24} was 400 ng*h/ml (± 100).

Compared to the pre-treatment period, mean daily food consumption during the treatment phase increased in the 2 mg/kg bw group and decreased in the placebo control group. Mean food consumption during the treatment phase in the 0.5 mg/kg bw group was slightly lower than before treatment. The mean bodyweight increased in both treated groups during the 14 days of treatment but was not statistically different to cats in the placebo group. No conclusion could be drawn due to the small size of the treatment groups.

The only GLP-compliant study is the pivotal tolerance study, where mirtazapine was administered topically once daily for 42 consecutive days at 1, 3 and 5 mg/kg bw (16 cats in the 0 and 5x groups and 8 cats in 1x and 3x groups). In this study, dose linearity was determined over the dose range at day 0 and at steady state. The plasma pharmacokinetics of mirtazapine was linear between 1 and 5 mg/kg bw in this study at day 0 (based on AUC_{0-24} and C_{max}) and at day 35 (based on AUC_{0-24}).

Dose justification

Initially, a dose of 0.5 mg mirtazapine/kg bw to be applied once daily for 14 days for transdermal use was selected based on the different pharmacokinetic (PK) data available in healthy adult cats (see pharmacokinetics, above) for the parameters "food consumption" and "bodyweight". Although differences with the placebo group for those parameters were statistically not significant, the CVMP agreed that the lower dose tested in these pre-clinical studies (0.5 mg/kg bw) may be considered as the minimal effective dose, as the application of this dose resulted in a similar effect as that of the

higher doses, and the effect was numerically higher than the effect of a placebo, although not statistically significant. Based on PK data available, the absorption extent ($AUC_{0-\infty}$) following daily transdermal administrations of 0.5 mg mirtazapine/kg bw for 14 days was similar to that following a single oral administration of 0.5 mg/kg bw. Although the oral dose is not authorised, considering that the dose was confirmed in later studies, the proposed dose is considered justified.

To justify the recommendation of a fixed dose for all cats (2 mg mirtazapine/cat) instead of a dose depending on the bodyweight (0.5 mg/kg bw), the applicant argued that a fixed dose provides ease of dosing. This argument was accepted. The fixed dose of 2 mg mirtazapine/cat was based on a mean cat weight of 4 kg that generally corresponds to the target population, i.e. old cats.

Finally, the use of the proposed fixed dose as recommended in the product literature (3.8 cm ointment per day, using a measured line displayed on the carton and in the package leaflet with the correct length of the string of ointment) was confirmed in the clinical trials (see below).

Other studies

A published non-GCP, non-GLP pilot study (Benson, 2016) investigating pharmacokinetics (PK) and pharmacodynamics (PD) was provided in support of dose finding.

Seven healthy research cats (1–2 years) were included in the PK phase and 20 healthy client-owned cats (1–7 years) in the PD phase. The active substance mirtazapine was not administered using the final formulation product. The doses administered by transdermal route via the ear's pinna were higher than the one recommended (i.e. 3.75 and 7.5 mg of mirtazapine per cat instead of 2 mg per cat).

Results indicate that topical administration of a single dose (3.75 mg or 7.5 mg per cat) of mirtazapine achieved serum concentrations similar to administration of 1.88 mg oral mirtazapine, while repeated daily dosing of 7.5 mg of topical mirtazapine resulted in significantly higher drug exposure after 6 days. In this study the efficacy of transdermal mirtazapine as an appetite stimulant was also tested and a statistically significant increase in food consumption in comparison with placebo was demonstrated. At a dose of 7.5 mg per cat given daily for six consecutive days, a significant number of the cats showed an increase in their appetite scores ($p = 0.003$) and rate of food ingestion scores ($p = 0.002$) (as observed by their owners). However, cats also showed a significant increase in undesirable effects such as increased vocalisation, begging behaviour and increased activity, with two cats subjectively showing a marked increase in food-seeking behaviour, indicating that a lower dose would be more appropriate.

This pilot study did not allow conclusions on the efficacy of Miratax at the proposed dose as a different product formulation was used, and mirtazapine was administered using a different dose and duration than proposed by the applicant. The study could therefore only be considered supportive in regard to the selected route of administration, that is, by transdermal route via the ear's pinna instead of the oral route.

Target animal tolerance

One pivotal GLP-compliant study, one pilot non-GLP compliant laboratory study and two supportive publications were provided to investigate target animal safety of the product, in addition to the safety data obtained from pre-clinical and clinical efficacy trials.

Pilot non-GLP compliant laboratory study (KB108T, Ref 3a3-13-kb108t)

This study was conducted with the final formulation in 7 adult cats. It was not carried out in accordance with requirements of VICH GL43 (low number of cats, only one dose was tested, no control group). Consequently, results of this study are only considered informative.

The product was administered topically (transdermal use) once daily for 28 days (twice the claimed duration) to 7 adult cats at a dose of 5 mg/kg bw, i.e. 5 x the maximum recommended treatment dose. The product was applied into the inner (anterior) surface of both *pinnae* followed by rubbing and spreading the ointment onto the surface area of the *pinnae*. Approximately half of the total volume was applied to each ear.

All cats showed mild erythema and flaking skin on the inner surface of the *pinna*. These lesions occurred from day 2 and persisted up to day 28 and progressed to moderate erythema in 3 cats, which returned to mild erythema within 4–10 days of the initial finding. A small lesion of the inner *pinna* (crust/scab) was observed in 2 out of 7 cats which healed within 4 days of the initial finding. Histopathological examinations showed that lesions consisted in hyperplastic dermatitis.

Three cats showed behavioural changes: increased vocalisations (1 cat), increased activity scores (1 cat) and increased interaction score and spasms/ataxia (1 cat).

Pivotal target animal safety study (KLI-076-SF-3315, 2015; Ref 4a3-18-kb115tas)

This 6-week masked, non-randomised, controlled and parallel design GLP-compliant study was conducted with the final formulation in adult cats in accordance with requirements of VICH GL43. Animals were aged from 230 days (7.5 months) to 315 days (10.5 months) and weighed 2.6 to 5.7 kg. Since studies were only conducted in cats aged 7 months or older, a contraindication not to use Mirataz in cats younger than 7.5 months has been included in the SPC.

The test product was applied once daily over 42 days topically into the *pinna* of the ear at the dose of 1 mg/kg bw, at 3 mg/kg bw and 5 mg/kg bw. A control group (T0) received only the excipients of the final formulation. Eight cats per sex were included in the control group and in the group receiving 5 mg/kg bw, and 4 animals per sex were included in the groups receiving 1 mg/kg bw and 3 mg/kg bw. The 42-day dosing period was followed by a 4-week recovery period for the control group and the highest dose group only.

The most commonly reported clinical signs were head shaking, ear flicking post dosing and local reactions on the ears, i.e. ear erythema and flaking (in 62.5% to 100% of cats in all groups, including the control group). Gross pathology and histology findings confirmed local effects at the application sites. Alopecia, hyperkeratosis, thickening and ceruminous gland secretion were frequently documented at all doses, including the control group. The lesions persisted up to the end of the recovery period, except for the tissue thickening, which disappeared before the start of the recovery period. A dose-related effect was not obvious and at the end of the treatment period, severity of lesions was similar across all the dose groups including the control group, suggesting that the effect was related to the vehicle of the product rather than mirtazapine and/or to the application procedure (rubbing into the ear). These local reactions are mentioned in the SPC, section 4.6, as very common adverse effects.

A number of very commonly observed behavioural changes were also noted at all dose levels, including reduced activity scores, increased vocalisation and reduced interaction scores; these are included in the SPC, section 4.6, as very common adverse effects:
Average activity scores declined in all groups, including the control group, throughout the study due to lethargy and/or weakness but significantly improved during the recovery period. The reduced activity scores might be related to the excipients of the final formulation.

Vocalisation was described in all groups, although the only statistically significant difference in this study was seen between the control group and treated cats in the group at 5 mg/kg bw during the first 2 weeks. However, vocalisation is a common effect after oral administration of mirtazapine to cats and was also very commonly observed in other preclinical and clinical studies following topical use. While increased interaction is a known effect after oral administration of mirtazapine in cats (Agnew *et al*, 2014), it was not observed in this study; indeed, average interaction scores declined in all groups including the control during the 1st week dosing. However, an outbreak of gastroenteritis may have influenced these results, and an increase in interaction ("attention seeking") was reported in other preclinical and clinical studies following topical administration of mirtazapine at the recommended (and higher) doses.

The following effects reported in this study are included in the SPC as common adverse reactions:

Vomiting was observed in all groups (25% of cats in the control group and groups tested with 1 and 5 mg/kg bw, and 50% of cats tested with 3 mg/kg bw). A clear dose-related effect was not shown and the number of cats affected suggests a relationship with the product's excipients rather than the active substance.

Polyuria was noted in all groups in a dose-dependent manner (incidence of 18.75%, 25%, 50% and of 50% in the control group, in groups tested with 1 mg/kg, 3 mg/kg and 5 mg/kg bw, respectively) which is considered toxicologically/clinically significant. This finding was associated with reduced urine specific gravity.

Except for sustained increased ALT activity observed in the control group and in both overdosed groups, there were no biochemical changes. The increase of ALT was not associated with gross or histopathological findings and reversible at the end of the treatment course. Although the association between these ALT elevations and the product administration is unclear, ALT increases have also been reported in humans after mirtazapine administration.

Other clinical/physical findings were observed with a low frequency in all groups and were not considered test article related. There were no clinically or toxicologically relevant findings in haematology, coagulation, ophthalmic or ECG evaluations.

Although this study met the requirements of the VICH GL43, the general health status of the animals used in the trial is questionable (numerous cats with cystitis, outbreak of an infectious gastro-enteritis during the recovery period, manifestation of a feline eosinophilic granuloma complex). These signs were unlikely related to the product as they did not appear in other clinical studies nor in field trials.

Pivotal field efficacy trial (KB105)

Cats with a history of ≥5% weight loss of at least 2 weeks duration and suffering from a wide variety of underlying conditions including renal insufficiency and history of vomiting, received Mirataz (2 mg mirtazapine/cat equivalent to 0.1 g ointment/cat) or a control product (excipients only) once daily for 14 days. Adverse events were recorded for 75 out of 115 (65.2%) placebo treated cats and 70 out of 115 (60.9%) cats treated with mirtazapine. Most common adverse events were reactions at the application sites (erythema, redness, crust, dermatitis and irritation), which resolved spontaneously without treatment, vomiting and behavioural changes (vocalisation, hyperactivity or lethargy). Dehydration was also noted. Elevated blood urea nitrogen (BUN) was reported in the treated group only (7.0%).

As these systemic reactions sometimes necessitated the discontinuation of the treatment in the studies, discontinuation of the administration of the product may also be considered under the responsibility of the veterinarian, depending on the severity of vomiting, dehydration or behavioural changes. This precaution is stated in section 4.6. of the SPC.

The results from the pivotal target animal safety study and pivotal clinical studies were also confirmed by other preclinical studies and published reports. Two publications were provided. Observations from them can only be considered as informative.

Benson *et al.* (2016) assessed clinical effects after daily transdermal application of 3.75 mg and 7.5 mg mirtazapine to cats (median weight 4.65 kg) for 6 days. At 7.5 mg mirtazapine/cat (1.6 mg mirtazapine/kg bw), the authors observed an increase in appetite, increase in rate of food ingestion, activity, begging and vocalisation. These signs are suggestive of serotonin syndrome.

Ferguson *et al.* (2015) published a retrospective study (January 2006 to December 2011) to highlight the most common adverse effects following oral administration of mirtazapine to cats. Cats received less than 0.75 mg mirtazapine/kg bw, 0.75–1.5 mg mirtazapine /kg bw or more than 15 mg mirtazapine /kg bw. The most reported adverse effects were suggestive of a serotonin syndrome with vocalisation, agitation, vomiting, ataxia/abnormal gait, tremors/trembling, hypersalivation, tachypnoea, tachycardia and lethargy. A dose-dependent relationship was noted.

Other effects (oral)

An increase in tremors is a known effect of mirtazapine when orally administered to cats; however, this was neither observed in preclinical studies nor in field trials following topical administration. It seems therefore that this effect might only appear after oral administration of mirtazapine and therefore mentioned in the SPC specifying that it might occur after oral administration.

An acute toxicity study in five cats (KB110) showed increased salivation within 15 min after administration of 10 mg mirtazapine. Although the relevance of the study is low and results should only be considered as informative, the occurrence of salivation has been included in the section of the SPC, as an effect, which may occur in the case of accidental ingestion by the cat.

Overall, the CVMP considered that although some deficiencies were identified in the pivotal tolerance study, when considering the results from the field trials and the preclinical studies, the tolerance of the product is considered to be sufficiently documented.

Clinical field trials

Two clinical studies were performed under field conditions using the recommended daily dose of 2 mg mirtazapine/cat. One is a pilot study over 28 days (KB104P) and the second one a pivotal study (KB105) which was performed over 14 days. Both field trials were conducted according to VICH GL9 on 'Good Clinical Practice' as multicenter, randomised (1:1), blinded, placebo-controlled field trial.

Both clinical field trials were performed outside Europe, in the USA. However, the pathophysiology and response to treatment of weight loss secondary to chronic, underlying disease such as chronic kidney disease and heart disease are not dependent on the geographical location of the cat. Thus, cats used in those trials are considered to be representative of a similar cat population in Europe.

Pilot field study over 28 days (KB104P)

In the pilot study, cats were enrolled with decreased food intake and at least 5% weight loss of at least 2 weeks duration caused by various conditions such as chronic renal failure and

hyperthyroidism. The animals were either treated with Miratаz at the recommended daily dose of 2 mg mirtazapine/cat or a placebo with the same excipients, administered aurally by transdermal route every day for 28 days.

The desired quantity of ointment was placed onto the pinna of the cat's ear and spread over the inner (anterior) surface of the pinna using a gloved finger. Dosing cards were given to owners to assist with measuring out the desired dose. To demonstrate administration to the owner, the product dispenser(s) administered the first dose on Day 1 in the clinic. If possible, the same owner provided all further doses to the cat.

The final formulation of Miratаz was used; however, the device (packaging) was different to the proposed final packaging (3.5 g tube instead of 5 g tube).

Thirty two cats were enrolled at 5 study sites, 24 were available for analysis at week 2 and 22 for analysis at week 4. The age of cats ranged from 4 to 20 years. The mean (± SD) bodyweight at the start of treatment (day 1) was 4.01 kg (± 0.93) and 4 kg (± 0.91), in the mirtazapine group and placebo group, respectively.

The primary efficacy parameter was the percentage change in bodyweight from day 1 to week 4. Secondary efficacy parameters were the proportion of cats which experienced improvement from day 1 to week 4 in the Body Condition Score (BCS) and Muscle Condition Score (MCS), as well as scoring of appetite by the owner.

In comparison with the placebo group, a significant weight gain from day 1 (Wilcoxon rank-sum test, $p = 0.0027$) was observed 2 weeks after daily treatment, as well as a significant appetite increase at week 2 (90% of cats treated with Miratаz compared to 30% of cats treated with placebo). From day 1 to week 2, the mean bodyweight increased by 3.25% (from -2.0 to 8.0%) for the mirtazapine group and decreased by -1.65% for the placebo group. No significant additional weight gain was observed by week 4 in the mirtazapine group. The percentage change in bodyweight from day 1 to week 4 was 3.39% (from -2.1 to 6.6%) in the treated group.

Compared to baseline, 8 out of 11 cats (72.7%) treated with Miratаz gained weight in a 2-week period versus 4 out of 13 (30.8%) cats in the placebo group. Three out of these 11 cats (27.3%) treated with Miratаz gained more than 5% of their bodyweight. In contrast, 0% of cats treated with a placebo gained more than 5% of their bodyweight. A single cat in the mirtazapine group lost weight compared to 5 in the placebo group. Considering the 11 cats for which data were collected after day 1 in the mirtazapine group, the mean weight gain over 2 weeks was approximatively 140 g (median weight gain: approximately 150 g), which appears similar to published results with oral mirtazapine administered every other day for 3 weeks.

No significant changes were reported in the secondary variables BCS and MCS.

Adverse events were identified in 3 cats out of 16 in the mirtazapine group (19%) and 2 out of 16 cats in the placebo group (13%), which developed local irritation at the site of application. Vomiting was also noted in 31% of cats on mirtazapine and 13% of cats on placebo. Both adverse events are mentioned in the product literature as very commonly or commonly observed. Two serious adverse events were reported; however, both were in the placebo group and both were attributed to underlying disease.

Pivotal field study over 14 days (KB105)

In the pivotal field study, cats from 20 study sites were enrolled that suffered from at least 5% weight loss deemed clinically significant by the investigator and not readily curable. The weight loss

lasted more than 2 weeks for most of the cats (92.6%) suggesting an unintended weight loss secondary to a chronic condition. The cats were either treated with Mirataz or a negative control (placebo with the same excipients), administered aurally by transdermal route every day for approximately 14 days at the recommended daily dose of 2 mg mirtazapine/cat. Cats presented with a bodyweight of less than 2.0 kg or diagnosed with neoplasia or severe renal failure (IRIS grade >3 or serum creatinine >5.0 mg/dl) were not eligible for the study. Bias was minimised by means of double-masking and advance randomisation.

The product was administered by the cat owners who were instructed to treat the cat once daily by spreading 1.5 inches (i.e. 3.8 cm) of ointment, equivalent to approximately 0.1 g of Mirataz, onto the inner (anterior) surface of the cat's ear using a gloved finger. A dosing card was provided to the owner to assist in estimating the appropriate ribbon length. The owners could either administer the product on the same single ear or alternate between ears. They were also instructed to separate the treated cat from people and other household pets for approximately 2 hours following administration. These recommendations correspond to the ones specified in the SPC.

Two hundred and thirty-one cats were enrolled and treated with either Mirataz (n = 115) or the placebo (n = 115). A total of 16 cats had no data available at week 2, whereas 37 cats were excluded due to severe protocol deviations and as such 177 cats were eligible for the efficacy analysis (Per Protocol population): 83 cats in the mirtazapine group and 94 in the placebo group.

At enrolment, the age of cats ranged from 2.8 to 24.6 years and the bodyweight from 2.1 to 9.2 kg. By considering the per protocol (PP) population the bodyweight at treatment initiation ranged from 2.1 to 7.05 kg in the mirtazapine group. This consists in the target population of cats specified in the product literature of Mirataz.

Bodyweight was the single efficacy parameter measured in this pivotal field trial. Cats were weighed by the investigator at the screening visit (within 14 days before treatment initiation), at day 1 (first day of treatment), at week 2 visit (14 ± 3 days after day 1) and if necessary at unscheduled visit(s). Appetite and activity of the cat were not assessed. The primary efficacy endpoint was the percentage change in bodyweight from day 1 to the week 2 visit. Weight measurements were not taken within two hours of feeding and were taken prior to a subcutaneous fluid administration. Although measurement accuracy might be criticised based on the overall fairly low mean weight gain in the mirtazapine-treated group (approximately 0.15 kg), overall it is considered that measurement of the primary variable was adequate.

The cats enrolled in the trial were diagnosed with a wide variety of underlying conditions: renal insufficiency (36.5%), vomiting (26.1%), hyperthyroidism (15.7%), dental disease and periodontal disorder (13.0% and 11.7%), heart murmur (12.2%), arthritis (11.3%) and elevated Blood Urea Nitrogen (10.9%). Treatment with Mirataz was effective in inducing weight gain in cats when compared to the placebo-treated group, regardless of the pre-existing medical conditions. As such, it is considered acceptable to recommend the product in cats suffering from bodyweight loss due to any pre-existing medical condition.

A number of cats also received other medications concomitantly, including some medications that may impact the cat's bodyweight (e.g. lactated ringer's solution, vitamin B-12 and prednisolone). The possible impact of the concomitant medications on the study findings was adequately discussed by the applicant and it was concluded that this impact was limited.

A mean weight gain of approximately 150 g was observed in the mirtazapine group (median weight gain = 200 g) compared to approximately 10 g in the placebo group (median = 0 g) 2 weeks after

the start of treatment in the PP population. The mean percentage bodyweight change at week 2 from day 1 was 3.94% in the group treated with mirtazapine and 0.41% in the placebo group, demonstrating a statistically significant superiority of mirtazapine over placebo treatment. The mean difference in weight change was 3.53%, with a 95% confidence interval of 2.22–4.84%. Those results were confirmed for the ITT population (3.39% weight gain or average of 130 grams in the mirtazapine group versus 0.09% weight gain or average of 10 grams in the placebo group). These latter figures are the ones reflected in section 5.1 of the SPC.

Compared to baseline, 63 out of 83 cats (75.9%) treated with Mirataz gained weight in a 2-week period versus 38 out of 94 (40.4%) cats in the placebo group (PP population). The incidence of cats treated with Mirataz that gained more than 5% of their bodyweight within 2 weeks was 37 out of 83 (44.6%) in the PP population whereas only 6 out of 94 (6.4%) cats treated with the placebo gained more than 5% of their bodyweight in the PP population. Similar figures were observed in the ITT population.

Ten cats in the mirtazapine group lost weight despite the treatment (compared to 21 cats in the placebo group) and 10 cats did not present any bodyweight change (compared to 35 in the placebo group) (PP population). These observations may be explained by the multiple pre-existing medical conditions in those cats that could not be resolved during the short-time period of the study.

Overall, according to the study results and considering also the expected positive effect on feed intake described for mirtazapine, the following claim was agreed for the product:

"For bodyweight gain in cats experiencing poor appetite and weight loss resulting from chronic medical conditions."

All treated cats were included in the evaluation of safety. Adverse events were recorded in 70 out of 115 (60.9%) cats treated with mirtazapine and in 75 out of 115 (65.2%) placebo-treated cats. The following adverse events were observed in cats treated with Mirataz or the placebo, respectively: application site reactions, including pinna erythema (14.8%, 31.3%), vomiting (11.3%, 13.0%), elevated blood urea nitrogen (7.0%, 0.0%), abnormal behaviour such as restlessness (11.3%, 7.8%) and vocalisation including meowing and crying (11.3%, 1.7%). The majority of serious adverse events noted during the study were related to the underlying diseases in the cats present at enrolment. Serious adverse events (SAEs) were noted in 9 cats (3 treated with mirtazapine and 6 treated with placebo), but not considered related to treatment.

As no data to support repetition of treatment and adequate interval between two administrations were provided, a warning is included in section 4.4 to avoid repetition of treatment without a thorough benefit-risk balance assessment performed by the veterinarian.

Cats with neoplasia or severe renal disease were excluded from the study, thus a warning is added in section 4.4 that the efficacy and safety of Mirataz has not been established in cats with severe renal disease and/or neoplasia.

Other studies

The applicant also provided public literature to support the use of mirtazapine in situations where weight gain is wanted. According to the different authors, mirtazapine is recommended for appetite stimulation in cats with the following affections: cachexia caused by congestive heart failure, chronic kidney disease or cancer, sarcopenia due to aging. The loss of weight in cats is principally observed in the case of congestive heart failure (CHF), cancer and chronic kidney disease (CKD), as well as during aging (sarcopenia syndrome). Quimby (2017) recommends the use of mirtazapine in thin cats

with chronic renal disease (CKD) by either the oral route or the transdermal route as an appetite stimulant.

Kidney disease may cause reduced clearance of mirtazapine, which may result in higher drug exposure. For cats with CKD, some reports recommend using an alternate-day administration pattern in order to delay renal clearance of mirtazapine (Quimby, 2017; Quimby and Lunn, 2013). However, the CVMP considered that the risk for cats with CKD following mirtazapine administration by transdermal route is expected to be lower than after oral administration, given the PK differences observed between both routes (see pharmacokinetics, above). In addition, Miratаz was safely used following daily administrations for 14 days at the recommended dose in cats with suspected kidney disease in the pivotal field study (approx. 50% of the cats included) or with confirmed kidney disease (42.6%), without increased toxicity compared to other cats. An alternate-day administration pattern is therefore not recommended for those cats; however, a special precaution is nevertheless added in the SPC (section 4.5) to use the product with caution in cats with kidney disease.

It should also be noted that, the key for the management of weight loss in cats seems to be appropriate nutrition and a diet might need to be adapted to an individual cat. Importance is also given to the monitoring of the bodyweight, body condition score and appetite by both the veterinarian and the owner. Concomitant factors that might be involved in anorexia/decreased food intake should also be investigated and, if possible, resolved (dental and oral problems, e.g. palatability problems or incidence of periodontitis, gastric alterations in the case of CKD, depression). Appropriate information regarding the use of mirtazapine in cats that well reflects these literature findings has been added in the SPC.

Overall conclusion on efficacy

Pharmacodynamics:

Mirtazapine is a tetracyclic noradrenergic and specific serotonergic antidepressant. It is a potent antagonist of central auto and hetero α_2-adrenoreceptors and H_1 histamine receptors as well as an antagonist of 5-HT_2 and 5-HT_3 receptors. While the effect of mirtazapine as appetite stimulant has been demonstrated in humans and animals, its underlying mode of action is not well known. It is thought that it may involve antagonism of the $5HT_{2c}$ receptor, which is known for its appetite inhibition activity, as well as antagonism of the H_1 histamine receptor, which also plays a role in appetite regulation.

Pharmacokinetics:

Mirtazapine is absorbed transdermally after application to the internal *pinna* of the ear. There are large inter-individual pharmacokinetic variations, larger than after oral administration. The absorption is slow with sustained plasma concentrations of mirtazapine and a prolonged half-life. Plasma mirtazapine concentrations peak between 1 and 4 hours after dosing.

Compared to oral administration (tablet), bioavailability following single topical administration of 0.5 mg/kg bw is estimated to be 65% and the extent of absorption ($AUC_{0-\infty}$) after 14 days is comparable to that after single oral administration at the same dose. With a formulation different to the final product formulation, at 0.5 mg/kg bw, the steady state is reached after 48 to 72 hours with a factor of accumulation of 3–5 after 13 days of treatment. The linear plasma pharmacokinetics of mirtazapine is roughly demonstrated between 0.5 and 2 mg/kg bw in one study and between 1 and 5 mg/kg bw in the pivotal tolerance study.

Ear swab samples show that 2 hours after topical application of 0.5 mg mirtazapine/kg bw of a non-

final formulation, a mean of 7% of the dose remained on the ear.

Dose justification:

Initially, a dose of 0.5 mg mirtazapine/kg bw was selected to be applied topically once daily for 14 days based on different PK studies available in healthy adult cats. The CVMP agreed that the effects of this dose on the parameters "food consumption" and "bodyweight" were numerically higher than the effect of placebo (although not statistically significant) and similar to the same dose administered orally. Considering that the dose was confirmed in later studies, the CVMP accepted the proposed dose justification.

The final dose, though, is a fixed dose of 2 mg mirtazapine per cat (considering a mean adult cat weight of 4 kg) instead of a dose depending on the individual bodyweight (0.5 mg/kg). The applicant argued that this would provide an ease of dosing by the animal owner. This argument was accepted.

Finally, the use of the proposed fixed dose as recommended in the product literature (3.8 cm ointment per day, using the provided measured line) was confirmed in the clinical trials.

Tolerance:

In the pivotal target animal safety (TAS) study, adverse events were noted at all tested doses (control group administered with excipients and groups tested with 1, 3 or 5 mg/kg/day, i.e. approximately 1x, 3x and 5x the maximum recommended treatment dose). Most common adverse effects were reactions at the application site (such as erythema, signs of dermatitis) and behavioural changes (such as vocalisations, hyperactivity or lethargy, attention seeking). Vomiting was also commonly observed. These signs were also reported in pre-clinical and clinical studies and in field trials at the recommended treatment dose.

Polyuria was observed in the pivotal TAS only, with a dose-dependent incidence. This effect is stated in the SPC (section 4.6).

After overdose, the same signs as those observed at the recommended dose were observed with a higher incidence. In the case of overdose, the setting up of a symptomatic supportive treatment is recommended in the SPC.

In the pivotal field efficacy trial, elevated blood urea nitrogen (BUN) was reported in the treated group only (7.0%). This adverse event is stated in the SPC.

The tolerance of the product is sufficiently documented.

Efficacy:

The results from two clinical field trials performed with the final formulation show that the active substance mirtazapine applied by the transdermal route at the proposed dose of 2 mg of mirtazapine per cat is effective for bodyweight gain in cats suffering from weight loss resulting from any underlying medical condition, following 2 weeks of daily administration. The average weight gain after 14 days of product administration (PP population) was approximately 150 grams per cat and significantly higher than in the placebo group (approximately 10 g/cat).

Both clinical field trials, a pilot (KB104P) study and the pivotal (KB105) study, were performed outside Europe, in the USA. However, the pathophysiology and response to treatment of weight loss secondary to a chronic underlying disease are not dependent on the geographical location of the cat. Thus, cats used in those trials are considered to be representative for a similar cat population in

Europe.

Appropriate warnings and precautions for use have been added in the SPC to guarantee a safe and effective use of the product.

Part 5 – Benefit-risk assessment

Introduction

Mirataz is a transdermal ointment containing mirtazapine. The active substance is used in human medicinal products but has not been authorised in a veterinary medicinal product previously.

The active substance, mirtazapine, is an α_2-adrenergic, histamine and serotonin receptor antagonist. The product is intended as an appetite stimulant, for the management of weight loss in cats. The proposed dose is 0.1 g ointment/cat (2 mg mirtazapine/cat) applied to the inner *pinna* once daily for 14 days.

The application has been submitted in accordance with Article 12(3) of Directive 2001/82/EC (full application).

Benefit assessment

Direct therapeutic benefit

The results from the pivotal field study and one pilot field trial show that the active substance mirtazapine applied by the transdermal route at the proposed dose of 2 mg of mirtazapine per cat per day for 14 days is effective in producing a gain in bodyweight in cats with underlying conditions known to be associated with weight loss. The average weight gain noted in the pivotal field study was approximately 150 grams after 14 days of product administration (per protocol population). It is acknowledged that the product has an expected positive effect on feed intake by stimulating the appetite; this effect was measured in the pre-clinical trials but not in the clinical trials. The product is therefore approved with the following indications for use: "For bodyweight gain in cats experiencing poor appetite and weight loss resulting from chronic medical conditions."

Additional benefits

The product increases the range of available treatment possibilities for cats experiencing poor appetite and weight loss resulting from an underlying condition.

Risk assessment

Quality:

Information on the development, manufacture and control of the active substance and the finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC. Physicochemical aspects relevant to the performance of the product have been investigated and are controlled in a satisfactory way. Data has been presented to give

reassurance on TSE safety.

Safety:

Risks for the target animal:

In the target animal safety study, adverse effects were noted at all tested doses. Very common adverse effects were reactions at the application site (erythema, signs of dermatitis) and behavioural changes (vocalisations, hyperactivity or lethargy, attention seeking). Vomiting and polyuria associated with reduced urine specific gravity, elevated blood urea nitrogen (BUN) and dehydration were also commonly observed.

These signs were also reported in pre-clinical and clinical studies and in field trials at the recommended treatment dose. The expected adverse effects are generally transient and have been reported in the SPC.

Risk for the user:

A user safety assessment in line with the Guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1) and the Guideline on user safety of topically administered veterinary medicinal products (EMA/CVMP/SWP/721059/2014) has been presented.

If proposed mitigation measures are followed (see SPC, section 4.5.ii), the user safety will be ensured.

Risk for the environment:

Mirataz is not expected to pose a risk for the environment when used according to the SPC recommendations. Standard advice on waste disposal is included in the SPC.

Risk management or mitigation measures

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

User safety:

A number of warnings are included in the SPC notably regarding the use of gloves when applying the product, the need to avoid contact with the treated animals for 12 hours following administration of each dose and the fact that pregnant women should avoid contact with the product. The packaging is childproof and so mitigates against accidental ingestion of the product by a child. A pictogram of gloves is present on the outer package and the following wording is stated: "read carefully the user safety warnings before use".

Evaluation of the benefit-risk balance

Based on the data presented, the overall benefit-risk is considered positive.

The product has been shown to be efficacious for bodyweight gain in cats experiencing poor appetite and weight loss resulting from chronic medical conditions.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

It is well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended. Appropriate precautionary measures have been included in the SPC and other product information.

Conclusion

Based on the original and complementary data presented on quality, safety and efficacy the Committee for Medicinal Products for Veterinary Use (CVMP) concluded that the application for Mirataz is approvable since these data satisfy the requirements for an authorisation set out in the legislation (Regulation (EC) No 726/2004 in conjunction with Directive 2001/82/EC).

The CVMP considers that the benefit-risk balance is positive and, therefore, recommends the granting of the marketing authorisation for the above mentioned medicinal product.