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Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Bonqat (EMA/V/C/005489/0000)

INN: pregabalin

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



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Introduction

The applicant Orion Corporation submitted on 14 May 2020 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Bonqat, 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 8 November 2019 as Bonqat contains a new active substance (pregabalin), which is not yet authorised as a veterinary medicinal product in the Union.

At the time of submission, the applicant applied for the following indication: "Alleviation of acute anxiety and fear associated with transportation and veterinary visits".

The active substance of Bonqat is pregabalin, a new active substance, which acts in the central nervous system by reducing the release of various neurotransmitters (glutamate and monoaminergic neurotransmitters), resulting in an anxiolytic effect. The target species is the cat.

Bonqat is an oral solution containing 50 mg/ml pregabalin. It is available in a box containing one 5 ml bottle with 2 ml of oral solution and a graduated syringe.

The rapporteur appointed is Mary O'Grady 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 12 May 2021, the CVMP adopted an opinion and CVMP assessment report.

On 13 July 2021, the European Commission adopted a Commission Decision granting the marketing authorisation for Bonqat.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided documents that set out a detailed description of the system of pharmacovigilance (Version 11, dated 29 October 2019), 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

Batch release takes place at Orion Oyj/Orion Corporation/Orion Pharma, Turku, Finland. The site has GMP certification, which confirms the date of the last inspection and shows that the site is authorised for the batch release of such veterinary dosage forms.

GMP certification for the chemical, physical and microbiological testing sites has been provided, which confirms the date of the last inspection and shows that the sites are authorised for the activities indicated above.

A GMP declaration for the active substance manufacturing sites was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on on-site audits of the active substance and active substance intermediate manufacturing sites.

Overall conclusions on administrative particulars

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

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and is in line with legal requirements.

Part 2 - Quality

Composition

The finished product is presented as a clear colourless oral solution containing 50 mg/ml pregabalin as the active substance. Pregabalin is licensed in human medicines for the treatment of generalised anxiety disorder, neuropathic pain and epilepsy. Pregabalin is not previously registered as a veterinary medicine in the European Union. Therefore, it is considered as a New Active Substance (NAS).

Other ingredients in the formulation are: sodium benzoate, ethyl maltol, hydrochloric acid, sodium hydroxide and purified water.

The product is available in a 5 ml Type III glass bottle with a 2 ml filling volume. The bottle has an adapter and a child-proof closure/cap and is supplied with a 1 ml syringe for dosing and administration of the product. The bottle and measuring device are packaged in a cardboard carton.

Containers

The primary packaging is a multidose type III glass bottle of 5 ml with a polypropylene (PP) child-resistant closure and a high density polyethylene (HDPE) liner integrated with a low-density polyethylene (LDPE) adapter. A child-resistant closure is required for user safety. A syringe composed of low density polyethylene (LDPE) is supplied with the product, the syringe is graduated in 0.1 ml increments. The packaging materials comply with the relevant European Pharmacopoeia (Ph. Eur.) requirements and EU Regulation 10/2011 on plastic materials and articles intended to come into contact with food. The choice of the container closure system has been validated by stability data and is suitable for the intended use of the product.

Development pharmaceuticals

The primary aim of the product development studies was to develop a water-based solution with acceptable stability which is capable of being delivered orally via a syringe in variable dose volumes so that the dose could be accurately delivered to cats of various bodyweights. The starting point for development was the commercially available human product, Lyrica 20 mg/ml which was used in the early clinical studies. A concentration of 50 mg/ml was chosen since the lower concentration in the human product would have required the administration of too large volumes for administration to a cat.

A series of excipient compatibility studies were conducted with commonly used excipients at concentrations typically used in pharmaceutical products. Short term stress studies were conducted using a range of excipients including investigation of the formation of the primary degradation product of the active substance. Three preservatives were evaluated in these studies based on their antimicrobial activity at low pH, with sodium benzoate selected and its concentration confirmed as appropriate based on preservative efficacy studies. Three flavouring agents were investigated with respect to uptake of the formulation by cats and ethyl maltol was selected for use in the product. Significant conclusions with respect to various aspects of the product formulation were based largely on the results of the ASAP stability studies. Another important conclusion from the ASAP study is the need to store the product under refrigerated conditions which was based on predicted median shelf life of the various formulations used in the studies, all of which indicated that stability at 25 °C was insufficient to allow for a meaningful shelf life at that temperature. Therefore, the recommended storage condition for the product is 2-8 °C. In terms of the manufacturing process development, limited information relating to manufacturing development is provided given the simple standard nature of the manufacturing process. Process development work was conducted with placebo solutions and on scale up with batches including pregabalin. This work was at laboratory scale and at production scale (no pilot scale batches were produced) and focused on the order of addition, proportion of excipients added at a time and the timing of mixing steps. In each case, production of a clear colourless solution with no undissolved particles was the relevant endpoint.

As part of pharmaceutical development, studies were also carried out to establish the suitability of the dosing device provided with the product. Dose accuracy studies have been conducted in accordance with Ph. Eur. 2.9.27 *Uniformity of mass of delivered dose from multidose containers* for the dosing syringe provided with the product and the test is included on the specification for the syringe. Dose volumes of 0.1 ml, 0.5 ml and 1.0 ml were tested and compliant results are presented.

Method of manufacture

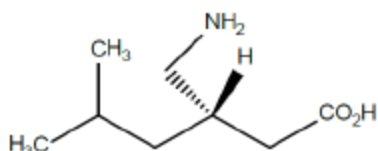
The finished product is an oral solution which is manufactured in a process involving sequential addition and dissolution of the product ingredients with mixing between each addition. No adjustment for active substance potency is carried out during manufacture. No overages are included in the formulation. The manufacturing process is a simple standard process. In-process controls involve pH, visual confirmation of the dissolution of excipients and fill weight. The bulk solution is filtered into an intermediate container, in which it can be held before filling into the immediate container. Supporting data to justify this hold period is to be provided post-authorisation and implemented after approval of a variation.

No process validation data is provided in the dossier. The absence of process validation data in the dossier can be accepted based on the standard nature of the manufacturing process. In accordance with the Guideline EMA/CHMP/CVMP/QWP/BWP/70278/2012 *Process validation for finished products – information and data to be provided in regulatory submissions*, a process validation protocol is provided for full-scale batches. Given the simple manufacturing process involved, the validation scheme can be accepted.

Control of starting materials

Active substance

The active substance is pregabalin, a new active substance, which acts in the central nervous system by reducing the release of various neurotransmitters (glutamate and monoaminergic neurotransmitters), resulting in an anxiolytic effect. Pregabalin has the following structure:



Pregabalin is a pure (S)-enantiomer of a chiral compound. No racemization or interconversion to the (R) enantiomer has been observed and enantiomeric purity is controlled on the active substance specification in accordance with the Ph. Eur. monograph with a limit of 0.15%.

The active substance is a white or almost white powder which is sparingly soluble in water, very slightly soluble in methanol, practically insoluble in heptane.

As the active substance is in solution in the dosage form, physico-chemical characteristics such as particle size and polymorphism are not relevant for this product.

There is a monograph of pregabalin in the Ph. Eur., and the manufacturer of the active substance has been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for pregabalin, a copy of which has been provided within the application. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability. The following additional details are included on the CEP:

- Test for the residual solvents 2-propanol (NMT 5000 ppm) and chloroform (NMT 60 ppm).
- Water is used in the last steps of the synthesis.
- No elemental impurity classified in ICH Q3D is intentionally added.
- A re-test period of 36 months is applied when stored in double polyethylene bags placed in a fibre drum.
- The holder of the CEP has declared the absence of use of material of human or animal origin in the manufacture of the substance.

The applicant's specification for pregabalin is provided in the dossier and includes all tests listed in its Ph. Eur. monograph and those tests for residual solvents detailed on the CEP and limits for microbiological purity. Batch data for the active substance has been provided in the dossier and demonstrates full compliance with the Ph. Eur. specification and CEP for the active substance. Impurity levels are noted to be very low with individual impurities below or just above the reporting value.

A re-test period of 36 months when stored in double polyethylene bags placed in a fibre drum is detailed on the CEP and provision of stability data is therefore not necessary.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. (sodium benzoate, hydrochloric acid, dilute, purified water, 2M sodium hydroxide (prepared with sodium hydroxide Ph. Eur.) or USP/NF (ethyl maltol). Reference to USP/NF for the excipient ethyl maltol is

acceptable in the absence of a Ph. Eur. monograph. The dossier includes a specification for ethyl maltol and the analytical methods used. Microbiological limits for both total aerobic microbial count (TAMC) and total yeasts and moulds count (TYMC) according to Ph. Eur. 2.6.12. are detailed in the dossier for ethyl maltol.

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. A declaration confirming compliance is provided.

Control tests on the finished product

Specifications are provided for release and shelf life in a single document. As such, all tests listed are common to both specifications and include the same acceptance criteria at release and shelf life. The test for identification of the active substance and the preservative are designated to only be performed at release. The specifications include tests for colour and clarity, pH, deliverable volume, identification and assay of pregabalin, identification and assay of sodium benzoate, related substances and microbiological requirements. The test for microbiological quality is proposed to be tested on a skip-test basis which is considered to be acceptable based on data presented for three production scale batches. The finished product specifications are generally acceptable and include relevant test parameters for the dosage form. Dose accuracy has been demonstrated for the dosing syringe in accordance with Ph. Eur. 2.9.27 test for Uniformity of mass of delivered doses from multi-dose containers at the maximum, minimum and an intermediate dose volume. This test is included as a routine test on the specification for the dosing syringe.

The applicant has confirmed that a risk assessment for the potential for elemental impurities has been conducted and PDE values detailed in ICH Q3D are not exceeded. Conduct of the risk assessment, as summarised by the applicant, is in accordance with *EMA/CVMP/QWP/153641/2018 Reflection paper on risk management requirements for elemental impurities in veterinary medicinal products* and the summary report of the risk management has been provided.

Analytical methods are well described and have been validated in accordance with VICH GL2: *Validation of analytical procedures: methodology*. The test methods and validation for the tests for total aerobic microbial count, total combined yeasts/moulds count, and *Escherichia coli* are included in the dossier and suitably validated.

Pregabalin Ph. Eur. CRS or pregabalin working standard, which has been tested against the pregabalin Ph. Eur. CRS, are used as reference standards in the test for identification, assay and related substances. Sodium benzoate working standard used for identification and assay of sodium benzoate is purchased from a reliable vendor and analysed according to Ph. Eur. monograph before use as a standard.

Batch analysis results are provided for three production scale batches and results demonstrate full compliance with the finished product specification.

Stability

Stability data is presented for studies carried out on three production scale batches, manufactured at the proposed dosage form manufacturing site. The stability batches are manufactured using different batches of active substance and are packaged in the intended commercial packaging.

In accordance with the conclusions of the pharmaceutical product development, real time studies are conducted at 2-8 °C and accelerated studies at 25 °C/60% RH. Samples were stored in upright and inverted positions at both temperatures. The applicant has presented 18 months data for product stored at long-term (2-8 °C) and for 6 months at accelerated (+25 °C/60% RH) conditions.

The results of the stability studies to date do not show any adverse trends. Under real time storage at 2-8 °C colour and clarity remain unchanged, very minor fluctuations are seen in sodium benzoate and pregabalin assay values, but no trends are observed. pH, remains unchanged at the target pH throughout the studies. Impurity levels are very low with specified, unspecified and total impurities all below the reporting threshold. There are no differences between samples stored in upright and inverted positions.

Samples stored at accelerated conditions of 25 °C/60% RH show similar stability results to those at 2-8 °C for all parameters except impurities. Increases in Impurity A are observed from 2 months onwards and results for this impurity are 0.9% after 6 months. There is a corresponding increase in total impurities.

Photostability studies were conducted in accordance with VICH GL5 *Stability Testing: Photostability Testing of New Veterinary Drug Substances and Medicinal Products*. The product is not sensitive to light and no associated storage precautions are therefore required. Freeze-thaw studies were conducted over 14 days at -20 °C for at least two days, 25 °C /60% RH for at least two days, three cycles. No differences were observed between initial and final time points, indicating no impact of freezing and thawing on the product.

In-use stability studies were conducted at 2-8 °C over 6 months and in a second study at 2-8 °C over 6 months which included a 1 month 'excursion' at 25 °C/60% RH. No adverse trends are observed and only very minor fluctuations are seen in sodium benzoate and pregabalin assay values, but no trends are observed. pH remains unchanged throughout the study. Colour and clarity remain unchanged.

The proposed shelf-life of the product as packaged for sale is 24 months when stored at 2-8 °C. The proposed shelf-life after first opening is 6 months at 2-8 °C of which up to one month can be stored at or below 25 °C. In accordance with VICH GL51 extrapolation of the real time data from the long term storage condition beyond the observed range to extend the shelf life can be undertaken, up to a maximum of 6 months. The proposed shelf life is therefore acceptable based on extrapolation of real time data. The proposed in-use shelf life is adequately supported by the data provided.

With respect to the in-use stability study, satisfactory data is presented to support the proposed in-use shelf life of 6 months at 2-8 °C, including the possibility to store the product at or below 25 °C/60% RH for a maximum of 1 month within this 6 month in-use period.

Overall conclusions on quality

The finished product is presented as a clear colourless oral solution containing 50 mg/ml pregabalin as the active substance. The formulation is an aqueous oral solution containing sodium benzoate as an antimicrobial preservative and ethyl maltol as a flavouring agent. Hydrochloric acid and sodium hydroxide are used for pH adjustment and purified water as the solvent.

The product is available in a multidose 5 ml Type III glass bottle with a 2 ml filling volume. The bottle has an adapter and a child-proof closure/cap and is supplied with a 1 ml syringe.

In the development pharmaceuticals section, the applicant provides a summary of the development of the formulation and the development of the manufacturing process. Development of the formulation is described in a stepwise and logical manner. Dose accuracy studies have been conducted in accordance with Ph. Eur. 2.9.27 Uniformity of mass of delivered dose from multidose containers for the dosing syringe provided with the product and the test is included on the specification for the syringe. Dose volumes of 0.1 ml, 0.5 ml and 1.0 ml were tested.

The oral solution is manufactured in a process involving sequential mixing and dissolution of the product constituents in purified water. The manufacturing process is a simple standard process and is adequately described in the dossier. The absence of process validation data in the dossier can be accepted based on the standard nature of the manufacturing process and the process validation protocol provided.

Information on the control of starting materials has been provided. The active substance pregabalin is monographed in the Ph. Eur. and a CEP issued by EDQM is provided in the dossier. Satisfactory active substance batch data has been provided. A re-test period of 36 months when stored in double polyethylene bags placed in a fibre drum is detailed on the CEP and provision of stability data is therefore not necessary.

All of the product excipients are supplied to either Ph. Eur. or USP/NF grade. A specification for the flavour ethyl maltol, which is USP compliant material is included in the dossier. The finished product container closure system is considered to be appropriate and the required supporting information is included in the dossier.

The finished product specification at time of release controls those parameters appropriate for the dosage form. Analytical methods for determination of the active substance assay and related substances and the preservative assay have been provided. The methods are well described, and validation has been provided. The test for microbiological quality and its validation are provided in the dossier. Satisfactory batch data for three production scale batches has been provided.

A finished product shelf-life specification has been provided. In terms of dosage form stability, satisfactory data is provided for three production scale batches stored under real time conditions of 2-8 °C and accelerated conditions of 25 °C/60% RH. The results of the stability studies to date do not show any adverse trends. pH is very stable and no trends in active substance content or significant levels of impurities are observed. All finished product batches analysed comply with the finished product specifications at shelf-life under long term storage conditions and accelerated storage conditions in upright and inverted positions for the duration of the studies to-date (18 months and 6 months respectively). Based on extrapolation of 18 month real time data, the proposed shelf life of 24 months is acceptable. With respect to the in-use stability study, satisfactory data is presented to support the proposed in-use shelf life of 6 months at 2-8°C, including the possibility to store the product at or below 25°C/60% RH for a maximum of 1 month within this 6 month in-use period. The efficacy of preservative system will be repeated in-use studies towards the end of the shelf life.

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SPC.

Part 3 – Safety

The active substance of Bonqat 50 mg/ml oral solution is pregabalin, a compound that selectively binds to two auxiliary subunits of voltage-gated calcium channels, alpha2-delta-1 and alpha2-delta-2,

thereby reducing the release of various neurotransmitters in the central nervous system and leading to anxiolytic, anti-nociceptive and anti-seizure effects.

Pregabalin is a new active substance that has not been authorised in a veterinary medicinal product in the EU before.

Pharmacodynamics

See part 4.

Pharmacokinetics

See part 4.

Toxicological studies

Single dose toxicity

No single dose toxicity studies were conducted by the applicant. Instead, the applicant has provided results from a small-scale dose range-finding study in dogs, in addition to literature data published by Moshiri et al. (2017) and summaries of toxicology studies reported for a human medicinal product, Lyrica.

No mortality was observed after single oral administration of 5,000 mg/kg bodyweight (bw) and single intravenous administration of 300 mg/kg bw to mice and rats. Observed effects were hypoactivity in mice and rats as well as diarrhoea, ataxia and urine staining in rats.

To evaluate the general tolerance of pregabalin, ascending doses of the compound (5, 10 and 22.5 mg/kg) were administered to 2 adult beagle dogs daily for 3 days with a washout period of 11 days between doses. Red-coloured skin in the ears and red ocular and buccal mucous membranes were noted after the first administration of 10 mg/kg bw, and red-coloured skin in the ears and red buccal mucous membranes were noted after the first and third administrations of 22.5 mg/kg bw. This study is considered of limited value in assessing acute toxicity on account of the low number of study animals, low doses of test item administered and the absence of a control group.

According to Moshiri et al. (2017), an LD₅₀ > 5 g/kg bw was established following a single intraperitoneal administration in mice.

Notwithstanding the fact that conventional acute dose studies were not conducted by the applicant and that references to the findings of acute dose studies as presented in the Lyrica product monograph are not considered to satisfy regulatory requirements on their own, it is accepted, based on the totality of information presented, that the acute toxic potential of pregabalin in laboratory animal species appears to be low. Further, it is noted that pregabalin has a long history of safe use in human medicine. As a consequence, no further information is requested.

Repeat dose toxicity

A target animal safety (TAS) study in dogs was provided by the applicant in place of repeat dose toxicity studies. According to Annex I to Directive 2001/82/EC, 'in the case of pharmacologically active substances or veterinary medicinal products intended solely for use in non-food producing animals, a repeat-dose toxicity study in one species of experimental animal shall normally be sufficient. This study

may be replaced by a study conducted in the target animal. The frequency and route of administration, and the duration of the study shall be chosen having regard to the proposed conditions of clinical use'. Therefore, use of this study, in principle, is accepted as fulfilling the repeat toxicity requirements for the active substance as detailed in Annex I to Directive 2001/82/EC. The study demonstrates that, following treatment at dose rates of 0, 5, 10 and 22.5 mg/kg bw/day for a 4-week period, there are no adverse toxicological effects in dogs, although a higher mean bodyweight gain was noted in treated males at all dose levels and in females at 10 or 22.5 mg/kg bw/day. The applicant proposes a NOAEL of 22.5 mg/kg bw/day, i.e. 4.5x the recommended treatment dose (RTD) based on this 4-week safety study in dogs.

Taking into account the fact that no NOAEL can be determined from the pivotal TAS study in cats (see part 4), in which clinical signs including sedative effects were noted in all pregabalin-treated groups (i.e. 5 mg/kg bw, 15 mg/kg bw and 25 mg/kg bw), the proposed NOAEL determined from this pilot study in dogs is considered to be of limited value for the assessment of user safety. Furthermore, according to the CHMP EPAR for the human medicinal product Lyrica, in dogs, approximately 45% of the pregabalin dose is excreted in urine as the *N*-methyl metabolite, which stands in contrast to other animal species and humans (species in which pregabalin undergoes minimal metabolism with unchanged parent representing at least 90% of drug-derived material in urine), confirming the selection of the rat and monkey as more appropriate species for toxicology studies in humans and so emphasising the limited value of data determined in the dog.

Toxicity data for the human medicinal product Lyrica were provided. These summary data can only be considered supportive and, in the absence of full study reports, they cannot be used to derive a toxicological reference value (TRV). It is reported that studies were conducted at dose levels of up to 5,000 mg/kg bw/day for 4 weeks, 1,250 mg/kg bw/day for 13 weeks and 500 mg/kg bw/day for 52 weeks in rats, and dose levels of up to 1,000 mg/kg bw/day for 4 weeks and 500 mg/kg bw/day for 69 weeks in monkeys. The principal toxicological target organs include the haematological system, bone marrow, skin (dermatopathy), kidneys, urinary bladder and the reproductive system. In rats, no adverse effects were noted at dose levels of up to 50 mg/kg bw/day for 13 weeks and tail dermatopathy was observed in monkeys at ≥ 25 mg/kg bw with no other significant effects at dose levels of up to 100 mg/kg/day for up to 65 weeks. Central nervous system effects were observed in both species, including hypoactivity and ataxia at ≥ 500 mg/kg bw/day. The applicant proposes a NOAEL of 50 mg/kg bw/day based on the 4 and 13 weeks study in rats and a NOAEL of 10 mg/kg bw/day based on the 65 weeks study in monkeys and a reference value of 0.5 mg/kg bw (derived from applying a safety factor of 100 to the NOAEL of 50 mg/kg bw) to be the most relevant endpoint for the assessment of user safety. However, as stated above, in the absence of full study reports, they cannot be used to derive a TRV.

According to Moshiri et al. (2017), intra-peritoneal injections of 20, 40 and 80 mg/kg bw pregabalin to mice for 21 days demonstrated elevated troponin-I levels at 80 mg/kg bw and increased creatine kinase MM isoenzyme (CK-MM) activity at ≥ 40 mg/kg bw, with corresponding pathological findings in the skeletal muscle. While the information in this publication suggests that a dose of 20 mg/kg bw administered daily for 21 days was well tolerated by mice and was not associated with muscle injury, the study was not conducted in accordance with relevant OECD guidance and there is insufficient detail in the report to determine a NOAEL that could be used as a TRV for the assessment of user safety.

Whilst the data provided fulfil the repeat dose toxicity requirements for the active substance, the information is generally of limited value to derive a TRV for the purpose of user risk assessment (see user safety below).

Tolerance in the target species of animal

See part 4.

Reproductive toxicity

Study of the effect on reproduction

The applicant has cited summaries of toxicological studies reported in a publicly available documents to describe the reproductive toxicity of pregabalin. Doses $\geq 1,250$ mg/kg bw administered to male rats caused marked reproductive toxicity and adverse effects on embryonic development. The NOAEL for male reproductive toxicity was established at 250 mg/kg bw/day. The administration of 500, 1,250 or 2,500 mg/kg bw/day to female rats resulted in reproductive toxicity and lethality in embryos. A NOAEL for female reproductive toxicity in rats was not established.

While fertility studies in rats have shown adverse reproductive and developmental effects, it is acknowledged that the doses at which reproductive and developmental effects were observed were significantly higher than the proposed treatment dose of 5 mg/kg bw for Bonqat 50 mg/ml oral solution for cats. Therefore, the effects observed may be of limited clinical relevance in the target animal species. That said, it is noted that the product information for the human medicinal product product Lyrica authorised in the EU (containing pregabalin) includes warnings relating to use in women of child-bearing age or pregnant women.

It is noted that studies on the effects of reproduction in non-food animal species are not a legal requirement of Annex I to Directive 2001/82/EC. Further, according to VICH GL 43, reproductive safety studies are only required for systemically absorbed APIs intended for use in breeding animals and if reproductive safety studies have not been conducted in the target species. Thus, the product information should reflect this and state that safety has not been determined in breeding, pregnant or lactating animals or their offspring.

Section 4.7 of the SPC includes text advising that the product should only be used in breeding cats or during pregnancy and lactation (see study of developmental toxicity below) following a benefit-risk assessment by the responsible veterinarian, noting that safety in such animals has not been investigated.

Given that only summary data relating to reproductive toxicity are available (absence of full study reports), these data cannot be used to derive a TRV for the purposes of user safety assessment (see the section user safety below).

Study of developmental toxicity

The applicant presented peer-reviewed publications which investigated maternal and embryo-foetal development in rats, mice and rabbits. In a series of four studies conducted in rats (Morse, 2016; Morse et al., 2016), maternal toxicity was observed at doses ≥ 500 mg/kg bw and signs of developmental toxicity including reduced foetal bodyweight was seen at 2,500 mg/kg bw. Advanced ossification including early closure of bones and reduced ossification were observed at doses $\geq 1,250$ mg/kg bw. The advanced skull bone fusions were classified as anatomic variations and were not considered clinically relevant. No maternal or developmental toxicity effects were observed in mice administered pregabalin at oral doses up to 2,500 mg/kg bw during the period of organogenesis. In rabbits (Morse, 2016), maternal toxicity characterised by ataxia and hypoactivity were observed at all doses (250, 500

and 1,250 mg/kg bw) and signs of developmental toxicity including abortion, decreased foetal and placental weights and decreased ossification were observed at 1,250 mg/kg bw.

The developmental toxicity has been well documented through published scientific studies in three different species (rats, rabbits and mice) and signs of developmental toxicity in rats and rabbits were generally associated with maternal toxicity. The doses at which reproductive and developmental effects were observed were thereby significantly higher than the proposed treatment dose of 5 mg/kg bw of Bonqat 50 mg/ml oral solution for cats.

In light of the observations reported in publicly available scientific literature, the SPC reflects the fact that laboratory studies in rats and rabbits have shown evidence of embryofoetotoxic and maternotoxic effects at high doses.

It is noted that, based on the totality of data presented, there is no evidence that pregabalin has teratogenic potential. Further, the data published by Morse (2016) can be used to derive a TRV for developmental toxicity for the purposes of user risk assessment. Based on these data, the proposed NOAEL of 500 mg/kg bw for developmental (embryo-foetal) toxicity can be accepted.

Genotoxicity

The genotoxic potential of pregabalin was investigated by means of a bacterial reverse mutation assay (Ames test) and a human lymphocyte micronucleus assay. Both studies were GLP-compliant. Although no statement of compliance relating to OECD technical guidelines was included in the study reports, the studies were considered to be generally conducted in accordance with the relevant OECD technical guidelines (OECD GL 471 and 487, respectively). Pregabalin showed no mutagenic activity in the Ames test and did not induce biologically relevant increases in micronuclei in the human lymphocyte micronucleus assay.

Data from public literature documenting the genotoxic and carcinogenic potential of pregabalin in rodents are also provided. According to Pegg et al. (2012), pregabalin was not genotoxic based on an extensive battery of in vivo and in vitro tests in bacterial and mammalian systems (bacterial mutagenicity, structural chromosomal aberrations [SCA], in vitro mammalian cell mutagenicity, in vivo micronucleus [MN] in rats and unscheduled DNA synthesis [UDS] in mice).

It is noted that, according to the CHMP EPAR for Lyrica, pregabalin was not genotoxic based on results of a battery of in vitro and in vivo tests:

- In vitro: Ames test performed in the presence and absence of various metabolic activation systems and point mutation and structural chromosome aberration assays in Chinese hamster ovary cells.
- In vivo: micronucleus test in mouse and rat bone marrow and unscheduled DNA synthesis test in rat and mouse hepatocytes.

Indeed, it appears that the series of in vitro and in vivo tests reported in the EPAR for Lyrica are the same series of tests reported in the publication by Pegg et al. (2012).

Considering all of the above, the available data can be accepted as convincing evidence that pregabalin lacks genotoxic potential.

Carcinogenicity

Based on the data provided by Pegg et al. (2012) and Criswell et al. (2012), it is accepted that pregabalin can be considered a single-species, single-tumour type, non-genotoxic mouse carcinogen.

The non-genotoxic mechanism of pregabalin-induced tumour formation involves platelet changes and associated endothelial cell proliferation that occurs in mice but not in rats. Given that platelet changes also do not occur in humans, there is no evidence to suggest a carcinogenic risk to humans.

Studies of other effects

Local effect studies

A series of studies were conducted for the purpose of investigating potential local effects of the final product formulation. All studies were conducted according to GLP specifications and in accordance with the relevant OECD guidelines (GL 428 for percutaneous absorption, GL 439 for skin irritation, GL 492 for ocular irritation and GL 429 for skin sensitisation). These studies show that pregabalin, when formulated as Bonqat 50 mg/ml oral solution, has low percutaneous absorption (mean total absorption of 0.12% in 24 hours), is not irritant to the skin or eyes and has no potential to induce skin sensitisation.

Neurotoxicity

Neurological effects were studied in rats, mice and squirrel monkeys (FDA, 2004; Vartanian et al., 2006). Pregabalin was found to reduce spontaneous locomotor activity and/or cause ataxia in rats at ≥ 30 mg/kg bw administered orally, in mice at ≥ 300 mg/kg bw administered intravenously or 1,000 mg/kg bw administered orally, and in squirrel monkeys at 30 and 100 mg/kg bw administered orally.

Given that neurological effects in rats, mice and squirrel monkeys were observed at doses significantly higher than the proposed treatment dose of Bonqat 50 mg/ml oral solution for cats, no further information relating to neurotoxicity will be requested.

Observations in humans

Pregabalin use in humans is associated with benign central nervous system and systemic adverse effects. Most of the adverse effects tend to be mild to moderate in severity and are often transient. Frequently, these adverse effects are self-limited and may dissipate over the first 2–4 weeks of use. Sedation, dizziness, peripheral oedema and dry mouth are the most prevalent adverse events experienced in all clinical populations. The dose range in adults is 150 to 600 mg per day given in either two or three divided doses. In one study on the effects of pregabalin in adults, no significant adverse effects were seen at doses of 75 or 150 mg. At a dose of 300 mg, the sedation scores were significantly higher compared to the control group and significant increases were seen in dizziness, blurred vision and headache.

Observations in humans following the use of pregabalin have been adequately characterised by the applicant given the widespread use of pregabalin in humans over a significant period of time.

Excipients

All excipients are either approved food additives or approved for use in pharmaceutical formulations. It is accepted that the excipients are not likely to pose any risk to the user.

User safety

The user risk assessment provided is broadly in accordance with the CVMP 'Guideline on user safety for pharmaceutical medicinal products' (EMA/CVMP/543/03-Rev.1). Any substantive deviations from the approach outlined in the guideline are highlighted in the summary below.

Bonqat 50 mg/ml oral solution is presented in a 5 ml clear glass bottle closed with a child-resistant polypropylene closure and a high-density polyethylene liner integrated with a low-density polyethylene adapter. A 1 ml measuring syringe which fits directly onto the bottle is provided. The filling volume is 2 ml.

Based on the information presented in respect to the excipients, it is accepted that the substance of most interest for the user safety assessment is the active substance pregabalin.

The toxicological properties of pregabalin are described in the sections above. The use of pregabalin in humans is widely documented. The majority of the information on the safety of pregabalin in humans referred to by the applicant has been previously reviewed by the CHMP and FDA within the context of the application for the authorisation of the human product Lyrica. Given that full study reports for the majority of the acute dose toxicity studies, repeat dose toxicity studies and studies investigating fertility effects have not been provided, this information can only be considered supportive. However, when these data are considered together with data from other sources (proprietary data and information from publicly available scientific literature), it is accepted that the substance has a low toxic potential, is not teratogenic, is not genotoxic and is neither a skin/ocular irritant or skin sensitiser.

Exposure assessment:

The product will be administered to cats by their owners at home following veterinary prescription. This exposure will be sporadic given the recommended use of the product on a single occasion.

The most relevant exposure route of the adult pet owner is dermal exposure during administration of the product to the cat. The adult pet owner could also potentially be exposed to trace amounts of the active substance through oral (hand-to-mouth) and ocular exposure (hand-to-eye transfer).

Risk characterisation:

In view of the presentation (bottles with syringe plug-in adapter), the risk of user exposure to the active substance is low and exposure will most likely arise from contact with the surface of the syringe or product rejected by the cat at the time of product administration. In this situation, the volume to which the user will be exposed is likely to be low.

The applicant has not conducted a quantitative risk assessment for dermal or ocular exposure. That said, in view of the low percutaneous absorption characteristics of pregabalin (mean total absorption of 0.12% in 24 hours) and the sporadic use of the product, there appears to be a very low probability of the material affecting or penetrating the skin and thus the user. Further, the final product formulation was shown to be non-irritating to the skin and non-sensitising. Similarly, the final formulation was shown to be non-irritating to the eyes and there is a very low probability of the product entering the eye, which, e.g., could occur by transfer from contaminated fingers or spilling. Accordingly, the risk to adult pet owners from dermal or ocular contact at the time of administration is low.

Regarding exposure in children, accidental access to the product (from a syringe prepared for treatment and left unattended by the animal owner) may result in oral or dermal exposure.

In terms of quantitative risk characterisation, the applicant has determined a toxicological reference value of 0.5 mg/kg bw (derived by applying a safety factor of 100 to a NOAEL of 50 mg/kg bw based on the repeat dose toxicity study summary in rats) to be the most relevant value for the assessment of

user safety. As discussed in the 'repeat dose toxicity' section above, given that the raw data of the relevant repeat dose toxicity study was not provided in the dossier, the use of the NOAEL proposed by the applicant is not considered an acceptable TRV for the determination of a margin of exposure (MOE). Furthermore, the applicant has not presented actual MOE calculations by comparing the estimated exposure to the relevant TRV as outlined in the guideline.

The applicant has compared the estimated exposure values for a 60 kg adult ingesting 0.25, 0.5 or 1 ml of product (equivalent to 0.21, 0.42 and 0.83 mg/kg bw) to the human therapeutic doses at which adverse effects in adults were reported in published literature: according to Hetta et al. (2016), no significant adverse effects were observed after single doses of 75 mg (1.25 mg/kg bw) or 150 mg (2.5 mg/kg bw), but higher levels of sedation, dizziness, blurred vision and headache were reported at 300 mg (5 mg/kg bw). Although the applicant concludes that accidental ingestion by an adult user is unlikely to cause any clinical adverse effects, a number of user safety statements are proposed.

It is considered that there are a number of deficiencies pertaining to the applicant's approach to quantifying the risk to user safety. It is agreed that the dose of 0.1 ml/kg bw for a 10 kg cat approximates to 1 ml (50 mg) of product. If a 60 kg user were to be exposed to this entire therapeutic dose, the dermal exposure would be equivalent to 0.83 mg/kg bw.

However, it is highly unlikely that the entire therapeutic dose intended for the cat will be deposited on the hands. A more realistic dermal exposure scenario might be considered to be a fraction, such as one-tenth of the entire therapeutic dose or 0.1 ml (this is in line with the CVMP 'Guideline on user safety of topically administered VMPs', which suggests that, for topically administered products, direct dermal exposure to the final product formulation during application shall be considered as a default to be 10% of the administered dose). This would result in a dermal exposure of adult users to 5 mg pregabalin or 0.083 mg/kg bw. Taking into account the very limited percutaneous absorption (mean total absorption of 0.12% in 24 hours), this would result in systemic absorption of 0.006 mg pregabalin or 0.0001 mg/kg bw in 60 kg adult users.

Concerning accidental oral (hand-to-mouth) ingestion, it is also considered highly unlikely that the entire therapeutic dose intended for the cat will be deposited on the hands and in turn transferred in its entirety to the user's mouth. A more realistic oral exposure scenario might be considered to be a fraction such as one-tenth of the dermal exposure or 0.01 ml. This would result in a maximum oral exposure of adult users to 0.5 mg pregabalin or approximately 0.01 mg/kg bw.

Human therapeutic doses are not generally accepted to assess a human user risk. However, no NOAEL for general systemic toxicity is considered appropriate based on the current data provided by the applicant to calculate the MOE. Therefore, given that the use of pregabalin in humans is widely documented in scientific literature and that such use is generally well tolerated, with most of the adverse effects noted to be mild to moderate in severity and often transient (Toth, 2012), it is considered acceptable to use the lowest human therapeutic dose and applying a sufficient safety factor for estimating the margin of exposure in this instance.

According to the publicly available SPC for Lyrica authorised in the EU, the dose range is 150 to 600 mg per day given in either two or three divided doses (2.5 to 10 mg/kg bw/day assuming a 60 kg adult). When a safety factor of 10 is added to the lowest human therapeutic dose, a TRV of 0.25 mg/kg bw is considered to be an appropriately conservative value for estimating the MOE (a safety factor of 10 is considered appropriate to convert the human therapeutic dose to a NOEL in this case). Furthermore, given that human data is being used, an MOE of 10 (rather than 100) is considered to be acceptable.

The calculated MOE following dermal and oral exposure based on the revised endpoints is greater than 10 (0.25/0.0001 and 0.25/0.01, respectively). Given the limited potential for exposure and noting that a

number of prudent risk mitigation measures have been proposed by the applicant to minimise dermal/ocular exposure, it can be concluded that there is an absence of risk for adult users.

In terms of handling of pregabalin by pregnant women, the proposed NOAEL of 500 mg/kg bw for developmental (embryo-foetal) toxicity can be accepted. When a safety factor of 100 is added to the NOAEL, a TRV of 5 mg/kg bw is considered to be an appropriately conservative value in estimating the MOE for this potential subset of users. Given that the calculated MOE following dermal and oral exposure is greater than 100 (5/0.0001 and 5/0.01), an absence of risk for pregnant women handling the product can be concluded. As a consequence, the omission of specific risk mitigation measures for this subset of potential users is considered acceptable.

Concerning children, the applicant has used a similar quantitative risk assessment approach to that described above for adult users. The applicant compared the estimated exposure values for a 10 kg child ingesting a single dose of 0.25, 0.5 or 1 ml of product (equivalent to 1.25, 2.5 or 5 mg/kg) to the doses at which adverse effects in children were reported in published literature: according to Eskandarian et al. (2015), somnolence, nausea and vomiting was reported in 5-year-old children weighing approximately 15 kg and administered doses of 75 mg (equivalent to 5 mg/kg bw). The applicant concludes that a child accidentally ingesting 0.25 or 0.5 ml of product will not suffer any clinical adverse effects. However, a child accidentally ingesting 1 ml of the product may show signs of sedation, dizziness, blurred vision and headache.

It is acknowledged that the approach used by the applicant to quantify the risk associated with a child accidentally ingesting the product (use of human therapeutic doses for MOE calculation) is also not in line with the approach outlined in the CVMP user safety guideline (EMA/CVMP/543/03-Rev.1). Furthermore, the study by Eskandarian et al. (2015) does not allow a 'real' no adverse effect level (lowest tested dose in children was 5 mg/kg bw) to be determined given that adverse effects were reported at this dose.

That said, based on the approach used, a risk for this exposure scenario cannot be excluded and measures have been introduced to mitigate the identified risk. The product is to be supplied in containers with child-resistant packaging in accordance with ISO 8317. In addition, bottles which are in use will have the plug-in inserted, making removal of the product without the special syringe even more difficult. Therefore, given the design of the packaging materials, it is unlikely that children will have access to the product or will be able to open the product if they gain access. As a consequence, a revised user risk assessment including a more precise quantification of the risk associated with a child accidentally ingesting the product, is not considered necessary in this instance.

Risk management:

The applicant has proposed a number of risk mitigation measures as follows:

- The product will be subject to prescription. It is expected that cat owners will be shown how to administer the product by their veterinarian.
- The product is supplied in containers with child-resistant packaging to prevent or limit access to the product. In addition, the product information will carry the standard statements: 'For animal treatment only' and 'Keep out of sight and reach of children'.
- The product is presented in bottles with a syringe plug-in adapter, thus limiting the potential for user exposure. Section 15 of the package leaflet includes the direction 'Don't leave the filled dosing syringe unattended while preparing the cat for administration. Replace the cap and rinse the syringe with water when finished'.
- The following user safety statements were agreed: 'Exposure to pregabalin may cause adverse effects such as dizziness, tiredness, ataxia, blurred vision and headache.'

Avoid skin, eye or mucosal contact. Thoroughly wash hands immediately after administration of the veterinary medicinal product.

In case of accidental eye or mucosal contact, flush with water. Seek medical advice if symptoms (dizziness, tiredness, ataxia or blurred vision) occur.

In case of skin contact, wash with soap and water. Remove contaminated clothing.

In case of accidental ingestion, seek medical advice immediately and show the package leaflet or the label to the physician. Do not drive as tiredness may occur.'

The proposed risk mitigation measures and user warnings are considered prudent and can be accepted. The product, when used as directed in the SPC, will not pose an unacceptable risk to the user.

Environmental risk assessment

Bonqat 50 mg/ml oral solution is indicated for the alleviation of acute anxiety and fear in cats associated with transportation and veterinary visits. The product will therefore only be administered to individual cats.

An environmental risk assessment (ERA) was provided according to relevant CVMP/VICH guidelines (VICH GL 6). Based on the data provided, the ERA can stop at phase I, as none of the phase II criteria are met. Pregabalin is not expected to pose a risk for the environment when used according to the SPC.

It can be concluded that the product will not present an unacceptable risk for the environment when handled, administered, stored and disposed of in accordance with the recommendations proposed for inclusion in the SPC.

Residues documentation

Not applicable.

Overall conclusions on the safety documentation

For pharmacological properties, see part 4.

The single and repeat dose toxicity profiles of pregabalin have been supported by way of reference to literature data including summaries of toxicology studies reported in a product monograph and a publicly available FDA document for Lyrica, in addition to results from a dose range-finding study and a 28-day repeat dose safety study in dogs. Based on the totality of information presented, the acute toxic potential of pregabalin in laboratory animal species appears to be low. Whilst the data provided fulfils the repeat dose toxicity requirements for the active substance (as detailed in annex I to Directive 2001/82/EC), the information is generally of limited value to derive a TRV for the purpose of user risk assessment.

The applicant has cited studies from published literature and summaries of toxicological studies reported in a publicly available FDA document to describe the reproductive and developmental toxicity of pregabalin. Based on the totality of data presented, there is no evidence that pregabalin has teratogenic potential. Signs of reproductive toxicity in rats and developmental toxicity in rats and rabbits generally associated with maternal toxicity were observed at doses significantly higher than the proposed treatment dose of Bonqat 50 mg/ml oral solution for cats. Suitable text has been included in section 4.7 of the SPC. The data published by Morse (2016) can be used to derive a TRV for developmental toxicity

for the purposes of the user risk assessment. Based on these data, the proposed NOAEL of 500 mg/kg bw can be accepted for developmental (embryo-foetal) toxicity.

Concerning genotoxicity, the applicant conducted a bacterial reverse mutation assay and a human lymphocyte micronucleus assay. Further data on in vitro and in vivo genotoxicity testing and carcinogenicity are derived from published literature. The available data can be accepted as convincing evidence that pregabalin lacks genotoxic potential. Whilst pregabalin can be considered a single-species, single-tumour type, non-genotoxic mouse carcinogen, there is no evidence to suggest an associated carcinogenic risk to humans.

Local effect studies conducted according to GLP specifications and in accordance with OECD guidance demonstrate that the final formulation has low percutaneous absorption (mean total absorption of 0.12% in 24 hours), is not irritant to the skin or eyes and has no potential to induce skin sensitisation.

The user risk assessment provided is broadly in accordance with the CVMP guideline on user safety for pharmaceutical medicinal products (EMA/CVMP/543/03-Rev.1). While there are a number of deficiencies pertaining to the applicant's approach to quantifying the risk to user safety following oral ingestion, the CVMP concludes on an absence of risk for adult users including pregnant women handling the product.

The product is supplied in containers with child-resistant packaging. Taking into account the presentation of the product, it is unlikely that children will have access to the product or will be able to open the product if they gain access under normal conditions of use.

Based on the risk assessment provided and the user safety statements proposed for inclusion in the product information, it is accepted that the product, when used as directed in the SPC, will not pose an unacceptable risk to the user.

The product, under normal conditions of use, does not pose a risk to the environment.

Part 4 – Efficacy

Bonqat 50 mg/ml oral solution for cats contains the active substance pregabalin. This product has been developed for the alleviation of acute anxiety and fear associated with transportation and veterinary visits. Pregabalin is a new active substance not authorised in a veterinary medicinal product in the EU before.

Pharmacodynamics

The applicant used published literature to demonstrate the mechanism of action of pregabalin in rats, mice, monkeys, dogs and humans.

Pregabalin is a structural analogue of the neurotransmitter GABA and has a mechanism of action that is similar to that of gabapentin but different from that of benzodiazepines and other anxiolytic agents. Pregabalin is a pure (*S*)-enantiomer of a chiral compound, and about 10-fold more potent than the corresponding (*R*)-enantiomer (Field et al. 2001; Taylor et al. 1993). Pregabalin selectively binds to two auxiliary subunits of the P/Q type of voltage-gated calcium channels, alpha2-delta-1 and alpha2-delta-2, and decreases the release of several neurotransmitters, including glutamate and monoaminergic neurotransmitters, which are implicated in the pathophysiology of anxiety (Mico and Prieto 2012). The alpha2-delta subunits are widely expressed in the nervous system, with the alpha2-delta-1 subunit being mainly present in terminal endings of the excitatory neurons (Cole et al. 2005; Dolphin 2016). Accordingly, an extensive [³H]-pregabalin binding was demonstrated throughout the CNS, with high-level binding in the cortex, hippocampus, cerebellum, dorsal horn of the spinal cord and amygdala (Li et

al. 2011). In addition to the CNS, these auxiliary subunit types are found in heart, lung, skeletal muscle, testis, pancreas and prostate (Arikkath et al. 2003).

In human medicines, pregabalin is recognised as an anxiolytic, anti-nociceptive and antiseizure compound. In addition to the therapeutic effect, the reduction in the levels of excitatory neurotransmitters in the CNS may also lead to signs of sedation, e.g. ataxia and drowsiness, due to an exaggerated pharmacological effect. Pregabalin has been authorised for human use for over 15 years. In humans, pregabalin has fewer side effects when compared to benzodiazepines, trazodone and gabapentin and may be more potent than gabapentin.

Clinical effects in the target species, cats, were evaluated in 5 nonclinical studies and 2 field studies conducted by the applicant and are described later in this assessment report (clinical studies). In accordance with the applicant's objective, studies were conducted to determine a dose of pregabalin which would have an anxiolytic effect but not a sedative effect. However, at the recommended treatment dose of 5 mg/kg bw, signs of sedation including drowsiness and ataxia were noted. These effects are directly related to the pharmacological effects of pregabalin. In addition, secondary pharmacological effects relating to other body systems were noted, including a decrease in heart and respiratory rate as well as body temperature. However, in general, the values remained within the normal range for cats.

In other species (rats, mice and monkeys), secondary pharmacological effects were noted of the neurological system (ataxia) at doses above 30 mg/kg bw and of the gastrointestinal system (decreased gastric emptying and intestinal transit time) at doses above 100 mg/kg bw. Cardiovascular effects have not been reported in rats, dogs, or monkeys, which were administered much higher doses.

Based on the data presented, it is accepted that the basic pharmacodynamic effects (primary and secondary) have been adequately described.

The text proposed for the SPC is generally acceptable. The applicant has included a warning on the potential interaction of pregabalin with the other central nervous system depressants, and the need for appropriate dose adjustment. This is relevant information for the veterinarian who may need to administer other medicinal products to cats once they arrive at the clinic (e.g. for the purposes of diagnostic investigation and/or treatment).

Pharmacokinetics

The applicant has provided the results of a pivotal pharmacokinetic study and metabolite profiling study to investigate the absorption, distribution, metabolism and excretion (ADME) of pregabalin in cats. In addition, further pre-clinical studies investigating the pharmacokinetic parameters of pregabalin in cats in fasted and fed states have been provided. Data in the published literature related to other species have also been provided.

Absorption

Oral bioavailability, as studied in the rat, dog, monkey and in humans is high (> 90%). Absorption is fast, with peak plasma concentrations achieved in about one hour after oral administration. In a study using 6 dogs, a dose of 5 mg/kg bw resulted in a C_{max} of 6.9 µg/ml, T_{max} of 1 hour, $AUC_{0-24 h}$ of 51.5 µg/h/ml and $t_{1/2}$ of 4 hours. In humans, a dose of 3.9 mg/kg bw resulted in a C_{max} of 9 µg/ml, T_{max} of 0.8 hours, $AUC_{0-\infty}$ of 66 µg/h/ml and $t_{1/2}$ of 6 hours.

In cats, the pivotal PK study demonstrated that almost complete absorption of pregabalin occurs following oral administration of the final formulation in the fasted state. Mean oral bioavailability of between 88–101% was reported in cats following administration of 2.5–7.5 mg/kg bw.

Systemic exposure (AUC_{∞} and C_{max}) to pregabalin increased in a dose-dependent manner following administration of 2.5 to 7.5 mg/kg bw.

Single administration of the proposed dose of 5 mg/kg bw of the final formulation resulted in fast absorption ($T_{max} = 0.5\text{--}1$ hour) and a C_{max} in plasma of 10.1 µg/ml. The area under plasma concentration-time curve (AUC_{0-24h}) in fasted state was 129 µg*h/ml. The mean absolute oral bioavailability of pregabalin was 94.3%.

Following product administration on two consecutive days, absorption increased slightly (as measured by AUC and C_{max}) and time to peak plasma concentration was delayed ($T_{max} = 0.5\text{--}4$ hours) on the second day of dosing. This indicates a potential for accumulation upon repeated daily dosing for a number of days, however, after a single repeated dose at 24 hours, values were comparable. That said, no safety concerns were noted in this study or in the target animal safety study, where the product was administered up to 6 days. However, while available data do not raise any safety concerns when the product is administered on two consecutive days, the safety and efficacy of such use has not been established in the field and the product is therefore only indicated for single use.

Food effect studies:

The effect of feeding on basic pharmacokinetic parameters was investigated in two non-GLP-compliant studies in the cat.

In the first study, pharmacokinetic parameters were determined following administration of a development formulation at a dose of 5 mg pregabalin/kg bw to four female cats in both fed and fasted states. Based on the findings of this study, it does appear that feeding does impact on absorption, leading to a reduction in maximum plasma concentrations achieved and a delay in T_{max} . However, there appears to be minimal impact on the extent of absorption as measured by AUC.

In the second study, pharmacokinetic parameters were determined following administration of a development formulation at a dose of 5 mg pregabalin/kg bw to four male cats under fasted conditions and when fed according to four different feeding regimens. No significant differences were observed between the fasted and the four different fed states in terms of overall absorption (AUC). Although the sample size was small, it is accepted that there is no evidence of a significant impact of different feeding regimens on overall systemic exposure to pregabalin.

Although administration of food results in a longer T_{max} and lower C_{max} , in terms of overall systemic exposure (as determined by AUC), there is no evidence of significant differences between the fed and fasted states, and Bonqat can be administered with or without food (although large amounts of food may delay the onset of effect).

Distribution

Based on the data provided in the pivotal pharmacokinetic study with a volume of distribution in steady state (V_{ss}) of 0.4 l/kg in cats of both sexes, it is accepted that pregabalin is widely distributed in tissues. ^{14}C -pregabalin is widely distributed in most tissues and crosses the blood-brain barrier in the mouse, rat and monkey after oral administration. *In vitro*, pregabalin is not bound to mouse, rat, monkey or human plasma proteins. Though not studied, the same is likely true also for cats.

Metabolism

In a study conducted to profile the metabolites of pregabalin in cats following the administration of a 20 mg pregabalin/ml oral solution, a total of eight metabolites were identified using UPLC-MS. Based on ion abundances, glycosylated pregabalin (M5, glucose or galactose conjugation) was identified as the only major metabolite, with the others being considered minor or trace metabolites. It is noted that *N*-methylation (M3) was considered a minor metabolite. This metabolite is further profiled in the pivotal

pharmacokinetics study, three non-GLP-compliant pharmacokinetic studies and the pivotal target animal safety study.

Excretion

The elimination of pregabalin from the plasma of the cat was studied after single intravenous (dose 2.5 mg/kg bw) and oral administration (dose 5 mg/kg bw). Based on these data, it is concluded that pregabalin is a slowly cleared compound with total plasma clearance of 0.03 l/h/kg. The mean $t_{1/2}$ was 12.3 h after intravenous and 14.7 h after oral administration, suggesting a somewhat slower rate of elimination compared to other species.

No studies were conducted to evaluate the route of excretion of pregabalin or its metabolites in cats. In the rat, monkey and in humans, radiolabelled studies indicated that pregabalin is excreted in the urine, with unchanged parent representing $\geq 90\%$ of drug-derived material. In dogs, approximately 45% of the pregabalin dose is excreted in urine as the *N*-methyl metabolite.

The pharmacokinetic studies provided are generally of a good standard and, overall, the pharmacokinetics are well described and in line with knowledge on other species.

The text proposed for inclusion in section 5.2 of the SPC is considered adequate.

Dose determination / finding studies

The dose finding study was a PK/PD study in a cross-over design in healthy cats (two male and two female) investigating the plasma profiles and appropriate absorption parameters of pregabalin together with sedative effects and safety. In this study, four different doses were evaluated; 2, 5, 10 and 20 mg/kg bw. Based on published literature cited by the applicant, this was considered an appropriate range of doses for investigation. The test item used was not the final product formulation but an authorised human product, Lyrica 20 mg/ml oral solution. Each cat received a single oral administration of each of the four different doses at weekly intervals. On dosing days, animals were fasted prior to treatment, and food was given 4 hours after dosing.

Dose dependent clinical signs of sedation, ataxia and mydriasis were observed increasing in frequency and severity with increasing dose levels. Duration of sedation was also observed to be dose dependent, increasing with increasing dose. It is accepted that sedation, ataxia and partially dilated pupils are likely directly associated with the pharmacodynamic effects of pregabalin. The former effects represent obvious difficulties in achieving a non-sedative but anxiolytic dose as proposed by the applicant.

In terms of other reported adverse events related to the product, slight to severe salivation was noted at doses of 10 mg/kg bw and 20 mg/kg bw. In addition, a reduced rectal temperature and a decrease in blood pressure was noted for all doses. While all values remained in the normal physiological range, this study was conducted in healthy cats and it is unclear how these clinical signs would affect health compromised cats, with various comorbidities.

The ability to take blood samples and ease of handling were scored according to a numerical rating scale and can be considered as suitable further parameters to indicate the efficacy of the anxiolytic treatment. However, no effect was noted on these parameters at any of the doses, and therefore this study has not provided support for the efficacy of pregabalin for the proposed indication. That said, it is accepted that the sample size was small, and laboratory cats (as used in this study) are accustomed to undergoing frequent handling and blood sampling.

The results of the study indicate though that there were challenges in administering the necessary volumes associated with the 20 mg/ml concentration of the human medicinal product, including the need to administer the dose in repeated small increments. At doses of 10 mg/kg bw and 20 mg/kg bw,

there were concerns as to whether the entire amount of product was swallowed due to the severity of salivation that occurred. The applicant therefore chose a 50 mg/ml concentration for the final formulation, in order to overcome the problem related to administration of larger doses.

Based on these results (mild signs of sedation in a number of cats after oral doses of 2 and 5 mg/kg bw), and notwithstanding the fact that no effect on ability to take blood samples or ease of handling was noted, the 5 mg/kg bw and 2.5 mg/kg bw were both considered to be appropriate dose regimens to be tested under field conditions to determine an anxiolytic dose.

Data on clinical effects evaluated in the context of the food effect studies

Two studies were primarily designed to evaluate the effect of food on pharmacokinetic parameters at 5 mg/kg bw dose. However, in these studies also the safety was evaluated and clinical signs were recorded.

In the first study, clinical signs included mild sedation, reduced body temperature, decreased heart rate and changes in blood pressure (within normal limits).

In the second study, sedation, ataxia, lethargy was observed 1-2 hours after product administration in most cats, in all feeding regimens. Diarrhoea and moderate salivation were also noted.

Based on the safety findings of the dose determination study and the food effect studies it is accepted that the 2.5 mg/kg bw and 5 mg/kg bw represent appropriate dose regimens suitable for further evaluation of pregabalin in the pivotal field study as an anxiolytic agent. While mild signs of sedation and ataxia are noted at the proposed dose of 5 mg/kg bw, there are no unacceptable safety concerns evident at this dose. Given that the severity, frequency and duration of adverse clinical effects increases with increasing dose, treatment doses greater than 5 mg/kg bw were not considered appropriate for evaluation in the field, as they are not suited to the proposed indication.

Target animal tolerance

One pivotal GLP-compliant study and four non-clinical studies were provided to investigate target animal safety of the product, in addition to the safety data obtained from the clinical safety and efficacy trials.

Pivotal Target Animal Safety Study

This study was a GLP-compliant study in which the final formulation was administered to healthy cats (n=32, four study groups with four males and four females per group) aged 7 months old (weight range 2.7 – 5.2 kg). In accordance with the Guideline on Target Animal Safety For Veterinary Pharmaceutical Products (VICH GL43 EMEA/CVMP/VICH/393388/2006, September 2008) Bonqat was administered at 1x, 3x and 5x the proposed recommended treatment dose (RTD) at 3 times the proposed duration. In order to ensure the safety of proposed use of the veterinary medicinal product at two consecutive days, the duration of dosing was six days. While the animals used in this study can be considered to satisfy guideline requirements (young, healthy), the study animals are not fully reflective of the intended target population (age 5 months to 15 years). Consequently, systemic tolerance to overdose of the product in animals younger than 7 months, older animals or those with co-morbidities will not have been characterised in this study.

It can be accepted that a sufficiently comprehensive range of safety parameters was assessed in this study. Clinical signs were noted in all pregabalin-treated groups and were considered exaggerated pharmacological effects.

Following repeated administration of 5 mg/kg bw/day (1x RTD), clinical signs of sedation were noted comprising of limited usage of hind limbs, uncoordinated behaviour (severity up to moderate), abnormal gait, decreased activity, lying on side, and/or sedated appearance (grade 1; i.e., mild signs of depression, drowsiness or ataxia) in males on Day 1. Level of sedation was recorded on a 4 point scale (0=not sedated, 3=deep sedation). Abnormal gait was noted in two females on Day 5, 2 hours after dosing. Additionally, slight vomiting was observed in one male on Day 1. Reduced body temperature was observed in 2/8 animals (up to -2.2 °C).

At 3x RTD and 5x RTD (i.e. 15 and 25 mg/kg bw/day), signs were more severe and were observed at a higher frequency (i.e., in more animals and/or recorded at more times). Clinical signs included limited usage of hindlimbs or paws, uncoordinated behaviour, abnormal gait, decreased activity, lying on side, partly up to completely closed eyes, sedated appearance, dilated pupils, quiet but alert behaviour, decreased mental alertness, cold to touch, sedated appearance (up to grade 3; i.e., depressed, drowsy and sleepy) and/or loss of consciousness (in one male on Day 1 at 25 mg/kg bw/day). Additionally, slight to severe salivation was seen directly after dosing in animals treated at 3x RTD and 5x RTD (15 and 25 mg/kg bw/day) on multiple dosing days, which was considered to be related to the taste of the test item.

Clinical signs were only or predominantly observed on the first day of dosing and generally persisted longer at higher doses: that is, up to 8 hours after dosing on Day 1 (generally up to 2 hours at the RTD of 5 mg/kg bw/day), while mostly up to 2 hours after dosing on other dosing days. This may suggest that cats receiving repeated daily doses can develop tolerance to the sedative effect of the active substance. However, it is noted that the product will be authorised for single use only.

Sedation, ataxia and reduced body temperature may impede accuracy of the clinical veterinary examination (for example, a reduction of 2.2 °C may cause a previously pyrexia cat to appear normothermic). The applicant has included this information in section 4.5 of the SPC as the above-mentioned clinical signs may impact on the accuracy of the veterinary clinical examination.

No treatment-related effects on physical examination, body weight, food consumption, haematology, clotting, clinical biochemistry, urinalysis, ophthalmologic evaluation, macroscopic pathology or histopathology of examined tissues were noted. No treatment related change in blood pressure and heart rate was observed, contrary to the findings of other non-clinical studies.

In conclusion, the findings of the pivotal target animal safety study indicate that adverse events relating to the pharmacological effects of pregabalin are possible in a dose-dependent manner, already at repeated administrations of the recommended treatment dose of 5 mg/kg bw. The main effects observed were sedation and ataxia/incoordination, suggesting that the applicant has not determined a non-sedative dose of pregabalin for the proposed indication in the laboratory cats. However, signs of mild sedation and ataxia noted at the RTD of 5 mg/kg bw do not pose an unacceptable safety concern. Adverse clinical effects were more severe and were observed at a higher frequency with increasing dose.

Summary of animal tolerance findings from the non-clinical and field studies

The typical clinical signs at the proposed dose have been very similar in all non-clinical studies and relate to the pharmacological action of pregabalin. Clinical signs consisted primarily of central nervous system signs (lethargy, mild sedation, mild ataxia, decreased activity, abnormal movement, mydriasis). Other clinical signs considered possibly treatment related included signs of nausea (salivation, vomiting), and a decrease in body temperature. These signs including those related to reduction in heart rate and body temperature have been included in section 4.5 of the SPC.

Most of the reported clinical signs have been mild or moderate and all of them transient in nature. Although these signs do not indicate an unacceptable safety concern, the impact of such effects on the accuracy of the veterinary clinical examination may need to be considered and as such appropriate warnings are included in the SPC.

The duration of clinical effects has been reported as lasting up to 4 hours in the target animal safety study and greater than 9 hours in a number of cats in the field studies, with a median of 7 hours overall. Suitable mitigation measures to ensure the safety of the animal in the home environment while experiencing clinical signs are included in section 4.5 of the SPC.

In humans, cardiovascular effects have been documented. However, such effects have not been detected in other species (rat, dog or monkey) at higher doses. In the cat, no effects on cardiovascular parameters were noted in the target animal safety study, while in a number of other non-clinical studies decreases in heart rate and respiratory rate were noted. However, all values tended to remain within the physiological reference range. That said, these studies were conducted in healthy animals. Further, while no concerns of adverse cardiovascular effects were raised in the field studies which evaluated a large number of cats from a wide age range, only cats of American Society of Anaesthesiologists (ASA) status I or II (healthy or with mild systemic disease) were included in the field study. Therefore, it is unclear if the cardiovascular effects noted in a number of studies will pose any concern in cats with moderate to severe systemic health issues. An appropriate warning has therefore been included in section 4.5 of the SPC.

The use of pregabalin has not been studied during pregnancy and lactation in the target species. Relevant warnings are included in the SPC section 4.7 (see part 3).

Clinical field trials

Dose confirmation

Pilot Field Study

This pilot study was a GCP-compliant pilot study investigating the anxiolytic effects of different doses of pregabalin (not the final formulation) administered on a single occasion in 13 client owned cats in Finland. The study was designed as a placebo-controlled crossover study, with four treatment days. The cats were randomised to receive an oral dose of 5 mg/kg bw, 10 mg/kg or placebo in one of six treatment sequence orders, determined on the basis of a 3-period, 3-treatment design. The fourth dose was an individually adapted dose of pregabalin between 2 and 15 mg/kg bw.

In total 11 cats received the placebo, 12 cats received 5 mg/kg bw and 12 cats received the 10 mg/kg bw dose for periods 1-3. Taking account of the doses administered to cats in period 4, five cats received 5 mg/kg bw during this period (that is, during the study as a whole, 5 mg/kg bw was administered to cats on 17 occasions).

Efficacy was determined based on a number of different numerical rating scoring systems for the primary efficacy variable: Owner's assessment of the effect of the study treatment. In addition, a number of secondary efficacy variables were evaluated:

- Owner's assessment of the ability to perform the procedures (placing the cat into the carrier at home and transportation in a car), the cat's activity, signs of stress, anxiety and/or fear, duration of the treatment effect, and ease of administration of the product; as well as an external observer's (trained to observe behaviour) assessment of the effect of the study treatment and assessment of stress.

The applicant's decision to focus the response to treatment in two situations which are commonly associated with the demonstration of anxious and/or fearful behaviour in cats (placing the cat in a cat carrier and travel) is considered appropriate and likely to provide good indicators of the anxiolytic efficacy of the product.

For the primary efficacy variable, 58% of owners reported an excellent or good effect with the test product (data for all treatment doses pooled) compared to 9% of the placebo treated cats. Further descriptive analysis indicates there is a tendency towards a slightly higher efficacy with the 10 mg/kg bw dose compared to the 5 mg/kg bw dose. Notably, no significant difference is seen for the 5 mg/kg bw versus placebo group, or the 5 mg/kg bw versus 10 mg/kg bw dose options. That said, it is acknowledged that the group size was small and will not have been powered to detect a statistically significant difference between groups.

Safety data obtained from the study highlighted ataxia and sedation as the most frequently reported adverse events. A total of 28 adverse events (AEs) were reported in 12 cats (92.3%) during the study. No AEs were reported for placebo. Causality was considered possible or probable related to study treatment for 27 AEs in 12 cats. 19 AEs were assessed as being mild, eight as moderate and one as severe. The number of AEs with the dose 5 mg/kg bw was 11 out of 17 administrations, and with the dose of 10 mg/kg bw 15 out of 12 administrations. All but one of the AEs related to the dose 5 mg/kg bw were assessed as mild, compared to the dose of 10 mg/kg bw for which one AE was classified as severe, seven as moderate and seven as mild. Two AEs in one cat led to dosage reduction. The most common AE was ataxia with 25 events in 12 (92%) cats. The majority of AEs (19 cases) were assessed as mild. Eight cases of ataxia were assessed as moderate, one in the 5 mg/kg bw dose group, and seven in the 10 mg/kg bw dose group, and one case of behavioural disorder, not otherwise specified (NOS) was assessed as severe in the 10 mg/kg bw dose group.

A full evaluation of safety to include investigation of parameters such as haematology, biochemistry, heart rate, blood pressure and temperature was not carried out.

Duration of the effect (based on owner's assessment and ability to recognise when the cat was behaving again normally after noticed treatment effect) was related to the dose. The median duration of effect was approximately 10 and 17 hours at doses of 5 and 10 mg/kg bw, respectively. With the dose of 10 mg/kg bw the duration was more variable and longer (up to 34 h) compared to the 5 mg/kg bw dose.

To conclude, while the findings in terms of efficacy are not conclusive (as the study was low powered it is not possible to draw any firm conclusions regarding efficacy of a specific dose), the study provides some evidence that the use of 5 mg/kg bw pregabalin may be beneficial in the reduction of fear and anxiety in cats. However, it is clear from the findings of this study that the 5 mg/kg bw dose demonstrated a better safety profile than the 10 mg/kg bw group in that the number and severity of ataxic and sedation adverse events were significantly lower, as well as the duration of effect. For this reason, it is appropriate that doses of up to 5 mg/kg bw are selected for evaluation in the pivotal field study (noting that the primary objective is to select a dose that is anxiolytic with minimal sedative effects). It is accepted that the numerical rating scoring system to determine the primary efficacy variable 'Owner's assessment of the effect of the study treatment' can be considered reliable and valid.

Clinical studies

Pivotal Field Study

One pivotal study was provided to investigate the efficacy and clinical safety of the product for the proposed indication. This was a multi-site, randomised, blinded, GCP-compliant, adaptive seamless

design (ASD) efficacy study investigating the anxiolytic effects of a single dose of 2.5 mg/kg bw or 5 mg/kg bw of pregabalin compared to a placebo. It was conducted in the EU using client owned cats from 20 veterinary practices in Portugal, Hungary, Finland, Ireland and Germany.

As an ASD study, it was completed in two stages. The first stage can be considered a dose determination study comparing doses of 2.5 mg/kg bw, 5 mg/kg bw and a placebo treatment. Interim analysis was performed after 89 cats (29 in the 2.5 mg/kg group, 30 in the 5 mg/kg group and 31 in the placebo group) had completed the study. In the interim analysis, the two test item doses were evaluated against placebo and each other to find the appropriate dose for the proposed indication in cats. An independent data monitoring committee was established to evaluate efficacy and safety data based on the interim analysis and to make the dose selection for stage 2. Following evaluation of the efficacy (based on the primary efficacy variables) and safety of both doses, it was determined that the results indicated superior efficacy at the 5 mg/kg bw dose. Based on the stage 1 findings, the CVMP is in agreement with this determination.

Stage 2 of the study was a continuation of stage 1 and additional cats were recruited to the 5 mg/kg bw group or the placebo group in accordance with the randomisation protocol. Efficacy and safety of the 5 mg/kg bw dose was analysed based on the data from the full analysis set (FAS) (combined stage 1 and 2), per protocol data set (PP).

A total of 254 client-owned cats were screened and 243 cats with a history of being stressed, anxious and/or fearful when transported by a car and during the veterinary visit entered into the study. 238 cats received pregabalin or placebo treatment. 57.1% of cats were females and 42.9% males. The mean age was 5.47 years (range 0.4-15.6 years). The median weight was 4.25 kg (range 1.8-10.3 kg). The cats represented several breeds, most commonly domestic cats (138 cats, 58%) and European shorthairs (59 cats, 24.8%). 201 cats (84.5%) were neutered. None of the cats were pregnant or lactating. Cats were randomly allocated to a treatment group. The demographics in each group were acceptably balanced and representative of the broader population in terms of breed, weight, sex and age. Treatment was administered approximately 90 minutes prior to placement in the cat carrier and transported for a minimum of 20 minutes, on one occasion.

Efficacy:

Efficacy endpoints were assessed by the owner, veterinary investigator and external observer (based on video footage and clinical assessment) using numerical rating scales. An acceptable number of cats were included in the FAS; 108 cats in the treatment group of 5 mg/kg bw and 101 cats in the placebo group completed the study.

The primary efficacy variables were:

- Owners assessment of the treatment effect based on cat's stress, anxiety and/or fear during the transportation in a car, and
- Investigator's assessment of the treatment effect based on cat's stress, anxiety and/or fear during the clinical examination at the clinic.

During the 16 point clinical assessment of the cat the investigator carried out an assessment of alertness according to a specific rating scale (ranging from 1 (=normal) to 4 (=mild sedation)). Any animals allocated a score 4 (demonstrating signs of mild sedation) were excluded from the efficacy analyses.

The results of the owners and the investigators assessment of the primary efficacy variables were similar; excellent/good response from the 5 mg/kg bw dose was reported as 51.4% and 55.2%, respectively, versus a placebo effect of 26.7% and 29.7%, respectively. A statistically significant effect in favour of the 5 mg/kg bw dose was reported for the full analysis set (FAS) combining stage 1 and 2

population, and a high overall response (OR) rate was also reported for this dose. Furthermore, these findings were supported by statistically significant effects in the dichotomised analysis (FAS) (success = excellent or good effect vs. failure = fair, poor or very poor effect), PP results and analysis of the stage 2 only data.

The statistical analysis employed by the applicant to evaluate the primary efficacy parameters can be considered appropriate. In particular, it is noted that an appropriate adjustment was made to control the error rate due to the interim analysis.

For the following secondary variables (rated by the owner or external observer), statistically significant differences were found in favour of the 5 mg/kg bw dose over the placebo:

- Owner's assessment of ability of placing the cat into the carrier at home for the FAS (combined stage 1 and 2) - Excellent/good result: 68.6% (5 mg/kg bw) versus 57.4% (placebo).
- Owner's assessment of signs and extent of stress, anxiety and/or fear for the FAS (combined stage 1 and 2) - The mean change from baseline between the 5 mg/kg bw dose and placebo during transportation and clinical examination was approximately 2.5 and 3.3, respectively (based on a scale of 1-5, with 1 being excellent/low stress and 5 very poor/high stress).
- External observer's assessment of the treatment effect based on cat's stress, anxiety and/or fear during the transportation in a car - Excellent/good result: 53.5% (5 mg/kg bw) versus 43.3% (placebo).

For selected other variables, the following effects were noted;

- Owner's assessment of the duration of effect – the range for the 5 mg/kg bw dose is very wide; from 1.3 to 28.5 hours, and the mean is 8.4 hours. This is a long period of time and comparable to the mean duration of effect of 9 hours noted in the pilot study and up to 8 hours noted in the non-clinical studies. Duration of effect was based on the onset and duration of any signs related to use of the product such as tiredness, dilated pupils etc. The applicant has included appropriate advice in relation to the management of those cats experiencing prolonged effects of the product.
- Owner's assessment of the usability of the product – The data indicates the product demonstrated good usability and the importance of this is acknowledged in relation to owner compliance and the challenges often presented with administering medicines to cats. It is noted that in the pilot study the owners described 60% of administrations of the product to be somewhat difficult; however, the change in formulation and lower volume of the final formulation used in the pivotal study resulted in improved usability of the product compared to the pilot field study. Approximately 79% of the owners in the pivotal study assessed that it was very easy or easy to administer the formulation.

When stage 2 is evaluated in isolation the results are not statistically significant between the 5 mg/kg bw treatment and the placebo. This is most likely due to the fact that neither group would be sufficiently powered to detect a statistically significant effect. The applicant has stated in the study protocol that sufficient power would be achieved by the inclusion of at least 90 cats in both the treatment and placebo group in total. During stage 2, 77 cats were administered the 5 mg/kg bw treatment dose and 70 cats were administered the placebo.

Safety:

Appropriate safety variables were monitored throughout the study;

- Adverse events (AEs).
- Veterinary investigator's assessment of alertness.

- Owner's assessment of the cat's activity.
- Owner's assessment of the cat's ability to stand up and walk.
- Laboratory safety variables.

Overall, the product was demonstrated to be safe at the dose of 5 mg/kg bw in cats of American Society of Anaesthesiologists (ASA) status I or II (healthy or with mild systemic disease). The main reported adverse events related to the known effects of the active substance were sedation (lethargy) and/or ataxia. It is noted that only three cats were reported as sedated, one by the veterinarian and two by the owners. Other adverse clinical effects reported included: four cats having signs of lethargy, five with ataxia and two with proprioceptive deficits. Assessment of alertness undertaken in the study did not use the same sedation scoring system as used in the non-clinical studies.

The sedation scale used as a clinical scoring system and its descriptions were developed based on the experience received from the clinical pilot field study, and the score describing mild sedation (clinical score 4) was made to identify clinically relevant and unwanted sedation in anxious cats at the veterinary clinic. Based on the results of the alertness assessed by the veterinarians, it seems that the description of the clinical scores and division of the scores from 1 (normal) to 4 (mild sedation) was successful to sensitively detect clinically relevant and unwanted sedation. This can be concluded based on the fact that there were cats in the placebo group that scored a score 2 (slightly less active) and a score 3 (clearly less active) with this scoring system, but none of them scored a score 4 (mild sedation). Thus, it can be concluded that a clinically anxiolytic but non-sedative dose of pregabalin for the proposed indication has been determined.

Heart rate and respiratory rate were reduced in the treated animals. No relevant change in body temperature was noted from the screening visit to the treatment visit. It is unclear if the cardiovascular or respiratory effects noted will pose any concern in cats with moderate to severe systemic health issues. A suitable warning has been included in section 4.5 of the SPC. In addition, it is stated that the cat should undergo an assessment of the current health status prior to prescribing the product.

Efficacy of pregabalin was evaluated using a range of scoring systems for the primary, secondary and other efficacy variables. The scoring system used by the owner to rate the primary efficacy variable, 'treatment effect', was validated in the pilot study. The scoring system was modified slightly for the pivotal study by the inclusion of descriptors to ensure the changes between scores were more constant. This has enhanced the scoring system and not negatively impacted the reliability or validity. The applicant has advised that the other primary efficacy variable, rated by the veterinarian, was based on the scoring system used in published studies and has been modified based on expert advice. This is considered acceptable and, as the findings broadly reflect that of the owner assessment, it is accepted that the results from these scoring systems can be considered reliable and valid.

The product has demonstrated acceptable efficacy for the proposed indication when administered on a single occasion at a dose of 5 mg/kg bw 90 ± 15 minutes before the cat is placed in the cat carrier for transportation. In addition, safety at the recommended treatment dose has been adequately characterised and it is accepted that the product is well tolerated (has an acceptable safety profile) when administered on a single occasion.

The candidate product was administered on a single occasion only in this field trial. While it is acknowledged that data provided in the pivotal pharmacokinetics and target animal safety studies support the safety of use on two consecutive days, no field data to support the safety and efficacy of the product when administered on two consecutive days has been provided. Therefore, the initial proposal by the applicant to include reference to the use of the product on two consecutive days in section 4.9 of the SPC was not considered acceptable.

Overall conclusion on efficacy

Pharmacodynamics:

Pregabalin is a structural analogue of the neurotransmitter GABA. The therapeutic effects of pregabalin are mediated via binding to the $\alpha 2$ -delta auxiliary subunit of voltage-gated calcium channels in the central nervous system. The resultant reduction in calcium flux in synaptic terminals reduces the release of several neurotransmitters, including glutamate and monoaminergic neurotransmitters. The reduction of glutamate and monoaminergic neurotransmitters likely contributes to the anxiolytic effect.

The applicant conducted a number of studies to determine a dose of pregabalin which would have an anxiolytic effect but not a sedative effect. However, it is noted that even at the recommended treatment dose of 5 mg/kg bw signs of sedation including drowsiness and ataxia were noted. These effects are directly related to the pharmacological effects of pregabalin. In addition, secondary pharmacological effects relating to other body systems were noted, including a decrease in heart rate, respiratory rate and body temperature.

Pharmacokinetics:

Absolute oral bioavailability was approximately 88-101% with a mean T_{max} of 0.5-1 hour. Systemic clearance was slow with an average systemic clearance of 0.03 l/h/kg. The volume of distribution was 0.4 l/kg and indicates that pregabalin is highly distributed into the tissues. The elimination half-life is 14.7 hours.

In general, administration of food results in a longer T_{max} and lower C_{max} . However, in terms of overall systemic exposure (as determined by AUC), there is no evidence of significant differences between the fed and fasted states.

Metabolic analysis identified 8 metabolites, with glycosylated pregabalin (M5, glucose or galactose conjugation) identified as the only major metabolite. N-methylation (M3) was considered a minor metabolite.

The pharmacokinetic studies provided are generally of a good standard and, overall, the pharmacokinetics are well described and in keeping with that known for other species.

Dose determination:

Dose justification was based on PK/PD calculations and safety evaluation. Based on the safety results, doses of 2.5 to 5 mg/kg bw were considered appropriate dose regimens to be tested under field conditions to determine an anxiolytic dose with only mild signs of sedation. Given that the severity, frequency and duration of adverse clinical effects increases with increasing dose, treatment doses greater than 5 mg/kg bw were not considered appropriate for evaluation in the field.

Tolerance:

In the target animal safety study, pregabalin was well-tolerated in repeated doses up to 3x the recommended dose. In higher doses, reduced body temperature, severe sedation and loss of consciousness were noted. The main findings at the proposed dose of 5 mg/kg bw suggest the applicant has not determined an anxiolytic and non-sedative dose of pregabalin in laboratory cats for the proposed indication. However, the mild and transient adverse clinical effects noted at the dose of 5 mg/kg bw do not pose an unacceptable safety concern in healthy cats.

Efficacy:

The results from one pivotal clinical field trial show that the product is effective for alleviation of acute anxiety and fear associated with transportation and veterinary visits, at the proposed dose of 5 mg/kg

bw, when administered orally on a single occasion 90 ± 15 minutes before being placed in the cat carrier for transportation, in cats of American Society of Anaesthesiologists (ASA) status I or II (healthy or with mild systemic disease).

Part 5 – Benefit-risk assessment

Introduction

Bonqat is an oral solution containing 50 mg/ml pregabalin as the active substance. It is available in a box containing one 5 ml bottle with 2 ml of product. An oral dosing syringe is included in the box.

The active substance, pregabalin, acts in the central nervous system by reducing the release of various neurotransmitters (glutamate and monoaminergic neurotransmitters), resulting in an anxiolytic effect. The product is intended for use in cats for the following indication: "Alleviation of acute anxiety and fear associated with transportation and veterinary visits". The product is to be administered orally as a single dose of 5 mg/kg bw (0.1 ml/kg bw) approximately 1.5 hours before the start of the transportation.

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

Benefit assessment

Direct therapeutic benefit

The proposed benefit of Bonqat is its efficacy in alleviation of acute anxiety and fear associated with transportation and veterinary visits.

The proposed indication was investigated in one pilot field efficacy study and a pivotal efficacy field trial.

The results from the pivotal clinical field trial show that the product is effective for alleviation of acute anxiety and fear associated with transportation and veterinary visits, at the proposed dose of 5 mg/kg bw, when administered orally on a single occasion 90 ± 15 minutes before being placed in the cat carrier for transportation

Additional benefits

Bonqat provides a treatment option for the alleviation of anxiety and fear in cats. No such product is authorised for use in cats in the EU.

Risk assessment

Quality:

Information on development, manufacture and control of the active substance and 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.

Safety:

Risks for the target animal:

Administration of Bonqat in accordance with SPC recommendations is generally well tolerated. The main reported adverse reactions include mild signs of sedation (characterised by lethargy, proprioception abnormality and ataxia), emesis and hypothermia. Typically, clinical signs are mild and transient.

Taking into account the totality of data, the product has demonstrated acceptable safety profile in respect of the target animal species, cats.

Risk for the user:

Taking into account the presentation of the product, it is unlikely under normal conditions of use that children will have access to the product or will be able to open the product if they gain access.

The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations. Standard safety advice is included in the SPC.

Risk for the environment:

The product 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 and environment, and to provide advice on how to prevent or reduce these risks.

User safety:

User safety risks have been identified, mainly the risks associated with exposure in children. These risks are mitigated by the presentation of the product in child-resistant packaging.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication: Alleviation of acute anxiety and fear associated with transportation and veterinary visits. The product has been shown to be efficacious for these indications, and the CVMP accepted the indications as proposed by the applicant.

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.

Based on the data presented, the overall benefit-risk balance of the application is considered to be positive.

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 Bonqat 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.