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Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for the extension of a community marketing authorisation for Comfortis (EMEA/V/C/002233/X/0010)

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

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Introduction

An application for an extension to the Community marketing authorisation for Comfortis was submitted by Eli Lilly and Company Limited to the European Medicines Agency (the Agency) on 24 May 2013 in accordance with Article 19 of Commission Regulation (EC) No. 1234/2008 and Annex I point 2(c) thereof.

The product Comfortis chewable tablets for dogs and cats was first authorised for use in the Community on 11 February 2011. The tablets contain the active substance spinosad, and are available in 7 strengths for dogs and 4 for cats.

The CVMP adopted an opinion and CVMP assessment report on 12 September 2013.

On 13 November 2013, the European Commission adopted a Commission Decision for this application.

The veterinary medicinal product is authorised for the following indication:

Dogs and cats: Treatment and prevention of flea infestations (*Ctenocephalides felis*).

The preventive effect against re-infestations is a result of the adulticidal activity and the reduction in egg production and persists for up to 4 weeks after a single administration of the product.

The veterinary medicinal product can be used as part of a treatment strategy for the control of flea allergy dermatitis (FAD).

This extension application for Comfortis chewable tablets is to add a new strength (180 mg) for both target species dogs and cats.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (current version September 2012) which fulfils the requirements of Directive 2001/82/EC, as amended. 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

Comfortis tablets for cats and dogs are manufactured in the USA and shipped to Europe. Secondary packaging and batch release for the EU will be carried out by Eli Lilly and Company, Speke Operations, Liverpool, UK. An additional site for secondary packaging is in the United Kingdom.

Copies of manufacturer's/importer's authorisation for the Speke site and secondary packaging site have been submitted. The manufacturing site in the USA was inspected by the Irish Medicines Board (IMB) and GMP certificate issued in October 2011 has been presented.

Since this procedure is an extension application no further inspection action is deemed necessary.

Overall conclusions on administrative particulars

The detailed description of the pharmacovigilance system and the GMP certification of the manufacturing sites were considered in line with legal requirements.

Part 2 - Quality

Composition

Seven different strengths of Comfortis tablets are currently approved (strengths range from 90 mg up to 1,620 mg at a percentage content of active substance of 53.33%). With this application a new strength (180 mg) within the range of the already approved ones is requested.

The active substance is spinosad (INN). Approximately 90% of spinosad is comprised of spinosyns A and D. Of that 90%, the ratio of spinosyn A to A+D is 0.85 when calculated as spinosyn A/(spinosyn A+D). Spinosad is a fermentation product derived from strains of *Saccharopolyspora spinosa*.

Well established excipients are used in the manufacture of Comfortis tablets, that is, pharmaceutical grade microcrystalline cellulose and hydroxypropyl cellulose (serving as diluent and binder), crosscarmellose sodium (disintegrant), colloidal silicon dioxide (glidant) and magnesium stearate (lubricant).

Artificial powdered beef flavour is used to achieve palatability.

Container

The finished product is presented in blister packs (3 or 6 tablets per blister) inside a folding carton. The blister foil (clear polychlorotrifluoroethylene/polyethylene/polyvinylchloride (PCTFE/PE/PVC) laminate) is sealed with a PVC based heat seal coating (lacquered) aluminium foil (product contact surface is PVC).

Development pharmaceutics

This is an extension application to the approved immediate release palatable tablet formulation for use in dogs and cats. The different tablet sizes are manufactured using the same bulk mix. The potency (amount of spinosyn factors A and D within a given lot of spinosad) of the final blend is adjusted to 53.33%.

As the additional strength proposed (180 mg) is obtained by compressing different weights of the approved common blend, no supplemental development work was conducted with the exception of compression studies.

To accommodate the target species (dogs and cats) weight ranges eight strengths (90, 140, 180, 270, 425, 665, 1,040 and 1,620 mg) are presented. The choice of the excipients was adequately justified within the initial marketing authorisation application.

Method of manufacture

The manufacturing formula is given for an 800 kg batch. The theoretical number of tablets depends on how the blends are split which will depend on marketing needs.

A comprehensive description of the utilised equipment and the manufacturing method is given in the documentation. The wet granulation technique employed with subsequent blending and compression of tablets is regarded to be a standard manufacturing process.

Control of starting materials

Active substance

Spinosad (INN, pharmaceutical grade) is not the subject of a monograph in either the European Pharmacopoeia (Ph. Eur.), or any other pharmacopoeia of the EU.

The data for this active substance were presented within the initial marketing authorisation application in the form of an ASMF. The manufacturing site of the active substance manufacturer is in the USA.

Specification for pharmaceutical grade spinosad:

The specification distinguish between spinosyn factors exhibiting greater than 90% activity, "Active Substances", and the spinosyn factors with less than 90% activity, "Related Substances".

The spinosyn factors in addition to A and D included in the "Active Substances" specification are: B, C, E, F, H, J, K, L and N-demethyl spinosyn D (also termed B of D).

The spinosyn factors included in the "Related Substances" specification are: G, PSA(A), PSA(D), Spinactin, 23 methyl spinosyn (also termed isomer of D and formerly unknown 6), and unknowns.

The proposed re-test period of 24 months is acceptable.

Excipients

The following excipients used in the manufacture of the tablets comply with the Ph. Eur. monographs:

- Cellulose microcrystalline (Ph. Eur.)
- Hydroxypropylcellulose (Ph. Eur.)
- Crosscarmellose Sodium (Ph. Eur.)
- Silica, colloidal anhydrous (Ph. Eur.)
- Magnesium stearate (Ph. Eur.).

There is no pharmacopoeia monograph for the artificial powdered beef flavour PC-0 125 (gamma irradiated). It is manufactured according to an in-house reference standard. This excipient is an established flavouring product that has been used in several veterinary medicinal products since the 1990s. It consists of hydrolysed vegetable protein (from soybeans), hydrogenated vegetable oil (from soybeans) and desiccated pork liver powder (from pork livers of swine raised in the USA). The vegetable components of the artificial powdered beef flavour are sourced from non-genetically modified soybeans only. All three ingredients of the flavour are FDA approved human food ingredients (complying with FDA law and regulations). Gamma irradiation of the artificial powdered beef flavour is carried out and the limits established for microbiological purity are sufficient to guarantee the quality of the tablets.

The data provided for the excipients are considered acceptable.

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

The risk of transmission of animal spongiform encephalopathies (TSE) of the components of this veterinary medicinal product was assessed during the initial marketing authorisation application.

The TSE risk associated with the use of artificial powdered beef flavour is negligible. Only one component

used to manufacture this excipient is of animal origin (desiccated pork liver powder). The livers used to obtain the desiccated pork liver powder are from swine raised in the USA only. The other two components of the artificial powdered beef flavour (hydrolysed vegetable protein and hydrogenated vegetable oil) are from vegetable origin. Both are sourced from non-GMO soybeans only.

Magnesium stearate used as lubricant in the manufacture of the tablets is of vegetable origin.

None of the starting materials used in the manufacture of the active substance spinosad 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).

TSE declarations for the Comfortis components were submitted accordingly.

Control tests during production

Blending – prior to drying

Purified water is added to the granulation mixture to achieve a defined torque. After the marketing authorisation was granted a minor variation to the manufacturing process was accepted. This led to a change in the granulation endpoint, from a fixed water addition amount to a torque endpoint.

Blending – after drying

Each granulation sub-batch is checked for moisture content. If the loss on drying (LOD) is ≤ 2.0%, the drying cycle is complete.

Compression

Limits for the following parameters have been established for each tablet strength: weight, hardness, thickness and friability.

Control tests on the finished product

Adequate specifications and routine tests have been described to ensure appropriate and constant quality of the finished product. The following methods are employed which comply with the Ph. Eur.:

- Uniformity of dosage units,
- Dissolution is performed in 0.1 N HCL with 0.02% Tween 80 at 75 rpm for the low strengths including the 180 mg tablets and 100 rpm for 1,040 mg and 1,620 mg tablets. The equipment used is the United States Pharmacopeia (USP) apparatus 2 (paddles),
- Microbial limit tests (Ph. Eur., 5.1.4),
- Moisture content.

The identity of spinosad is confirmed by two independent tests (IR and (spinosyn factors A + D assay) HPLC retention time).

The content of spinosyn factors A + D and of related substances is determined by a reversed phase (RP) HPLC method with isocratic elution and UV detection at 250 nm. The method is also stability indicating.

Stability

The stability of the active substance was assessed within the original marketing authorisation application.

A retest period of 24 months is approved.

No stability data has been presented for the new tablet strength (180 mg). A bracketing approach in accordance with VICH guideline GL45 Bracketing and matrixing designs for stability testing of new veterinary drug substances and medicinal products (EMEA/CVMP/VICH/581467/2007) has been employed to claim the 36-month shelf-life approved for the other tablet strengths. This is acceptable.

Overall conclusions on quality

Data were presented in the form of an ASMF in the initial marketing authorisation application.

Comprehensive information on manufacture and characteristics is provided for the active ingredient spinosad, pharmaceutical grade. Routine tests and specifications are considered sufficient to assure constant quality of the active substance. The proposed re-test period of 24 months is acceptable.

The excipients used are considered acceptable, as well as the packaging materials. All excipients contained in the tablet except the artificial powdered beef flavour (containing pig liver powder) are of pharmacopoeial grade quality. There are no concerns in relation to TSE with any of the ingredients of the product.

The rationale for the choice of the formulation is acceptable.

A specification has been developed for release of the tablets which is considered acceptable. Control methods have been validated and the specification is considered to be relevant for a product of this type.

The stability data provided reflect the VICH recommendations. A shelf life of 3 years has been approved, and the stability data on the finished product provided are acceptable as primary stability information. Data demonstrate stability at long term and accelerated conditions.

Part 3 – Safety

This application is for the introduction of a new tablet strength (180 mg) to the existing Comfortis chewable tablets which is intended for use in dogs with a bodyweight between 3.1 kg and 3.8 kg and cats with a bodyweight between 2.9 kg and 3.6 kg.

The safety of the product has already been assessed by the Committee for Medicinal Products for Veterinary Use (CVMP) during the initial marketing authorisation application and a later variation to add cats as target species. Appropriate measures to ensure the safe use of the product are included in the product information.

No new safety data have been presented with this application. This is considered acceptable.

Safety documentation

User safety

The user safety was adequately demonstrated in the initial dossier of Comfortis and measures to ensure the safety of the user are adequately reflected in the product information.

Environmental risk assessment

An increase of the overall use of the product is not expected with the introduction of a new strength.

A Phase I environmental risk assessment (ERA) was provided according to the VICH guidelines with the marketing authorisation application and a later variation to add cats as target species.

The environmental risk assessment can stop in Phase I and no Phase II assessment is required because the veterinary medicinal product will only be used in non-food producing animals.

Based on the data provided, Comfortis is not expected to pose a risk for the environment when used according to the Summary of product characteristics (SPC).

Overall conclusions on safety

This application is for the introduction of a new tablet strength (180 mg) to the existing Comfortis chewable tablets which is intended for use in dogs with a bodyweight between 3.1 kg and 3.8 kg and cats with a bodyweight between 2.9 kg and 3.6 kg. Appropriate measures to ensure the safe use of the product are included in the product information.

Residues documentation

Not applicable.

Part 4 – Efficacy

This application is for the introduction of a new tablet strength (180 mg) to the existing Comfortis chewable tablets which is intended for use in dogs with a bodyweight between 3.1 kg and 3.8 kg and cats with a bodyweight between 2.9 kg and 3.6 kg. The efficacy and target animal safety of the product was assessed by the CVMP during the initial marketing authorisation application and a later variation to add cats as target species. Appropriate measures to ensure the effective and safe use of the product in dogs and cats are included in the product information.

No new efficacy data have been presented with this application. This is considered acceptable.

Part 5 – Benefit-risk assessment

Introduction

This application is for the introduction of a new tablet strength (180 mg) to the existing Comfortis chewable tablets and intended for use in dogs with a bodyweight between 3.1 kg and 3.8 kg and cats with a bodyweight between 2.9 kg and 3.6 kg.

Benefit assessment

Direct therapeutic benefit

The therapeutic benefit assessment for the new tablet strength remains the same as that established for Comfortis during the assessments of the initial dossier and the variation to add cats as target species.

Additional benefits

The addition of a new tablet strength (180 mg) simplifies the dosing scheme in dogs and cats of the appropriate bodyweight categories as they are currently dosed with 2 x 90 mg tablets.

Risk assessment

The dossier takes into account current guidelines on pharmaceutical quality and the provisions of the pharmacopoeias. The formulation development and the manufacture of the tablets are well described. The manufacturing process has been established and leads to a product of consistent quality. Specifications set are relevant to control the quality of the product. The proposed shelf life of 36 months has been substantiated by the findings of the stability study.

All other potential risks with regard to the target animal, the user and the environment have been adequately characterised during the initial dossier assessment of Comfortis and a subsequent variation to add cats as target species, and the appropriate information and warnings included in the product information for the already authorised tablet strengths are applicable to the proposed strength.

Risk management or mitigation measures

Appropriate warnings have been included in the SPC to inform on the potential risks to the target animals and the user and the environment and to provide advice for reducing these risks.

Evaluation of the benefit-risk balance

The formulation and manufacture of Comfortis is well described and specifications set ensure that product of consistent quality will be produced. The benefit-risk balance for the proposed tablet strength is favourable, and in line with the authorised Comfortis chewable tablet strengths.

Conclusion

The overall benefit-risk evaluation is deemed positive with a sufficiently clear and complete product information.

Based on the original and complementary data presented the CVMP concluded that the quality, safety and efficacy of Comfortis, including the new strength, are considered to be in accordance with the requirements of Directive 2001/82/EC, as amended.