EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Imoxat (EMEA/V/C/005597/0000)

INN: imidacloprid / moxidectin

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

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Introduction

The applicant Chanelle Pharmaceuticals Manufacturing Ltd submitted on 24 July 2020 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Imoxat through the centralised procedure under Article 3(3) of Regulation (EC) No 726/2004 (generic).

The eligibility to the centralised procedure was agreed upon by the CVMP on 24 April 2020 as the product would constitute a generic product of a product authorised through the centralised procedure - Advocate (reference product).

At the time of submission, the applicant applied for the following indications:

For cats suffering from, or at risk from, mixed parasitic infections:

- the treatment and prevention of flea infestation (*Ctenocephalides felis*),
- the treatment of ear mite infestation (*Otodectes cynotis*),
- the treatment of notoedric mange (*Notoedres cati*),
- the treatment of the lungworm *Eucoleus aerophilus* (syn. *Capillaria aerophila*) (adults),
- the prevention of lungworm disease (L3/L4 larvae of *Aelurostrongylus abstrusus*),
- the treatment of the lungworm *Aelurostrongylus abstrusus* (adults),
- the treatment of the eye worm *Thelazia callipaeda* (adults),
- the prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*),
- the treatment of infections with gastrointestinal nematodes (L4 larvae, immature adults and adults of *Toxocara cati* and *Ancylostoma tubaeforme*).

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

For ferrets suffering from, or at risk from, mixed parasitic infections:

- For the treatment and prevention of flea infestation (*Ctenocephalides felis*),
- the prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*).

For dogs suffering from, or at risk from, mixed parasitic infections:

- For the treatment and prevention of flea infestation (*Ctenocephalides felis*),
- the treatment of biting lice (*Trichodectes canis*),
- the treatment of ear mite infestation (*Otodectes cynotis*), sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*), demodicosis (caused by *Demodex canis*),
- the prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*),
- the treatment of circulating microfilariae (*Dirofilaria immitis*),
- the prevention of cutaneous dirofilariosis adult stages of *Dirofilaria repens*
- the prevention of cutaneous dirofilariosis (L3 larvae of *Dirofilaria repens*),
- the reduction of circulating microfilariae (*Dirofilaria repens*),
- the prevention of angiostrongylosis (L4 larvae and immature adults of *Angiostrongylus vasorum*),
- the treatment of *Angiostrongylus vasorum* and *Crenosoma vulpis*,

- the prevention of spirocercosis (*Spirocerca lupi*),
- the treatment of *Eucoleus* (syn. *Capillaria*) *boehmi* (adults),
- the treatment of the eye worm *Thelazia callipaeda* (adults),
- the treatment of infections with gastrointestinal nematodes (L4 larvae, immature adults and adults of Toxocara *canis, Ancylostoma caninum* and *Uncinaria stenocephala*, adults of *Toxascaris leonina* and *Trichuris vulpis*).

The product can be used as part of a treatment strategy for flea allergy dermatitis (FAD).
Imoxat contains the active substances imidacloprid, an ectoparasiticide belonging to the chloronicotinyl group of compounds and moxidectin, a parasiticide, a second-generation macrocyclic lactone of the milbemycin family. The target species are cats, dogs and ferrets.

Imoxat spot-on solution is available in the following strengths of imidacloprid / moxidectin: 40 mg/4 mg, 80 mg/8 mg, 40 mg/10 mg, 100 mg/25 mg, 250 mg/62.5 mg, 400 mg/100 mg and is presented in packs containing 3 pipettes.

The rapporteur appointed is Jeremiah Gabriel Beechinor and the co-rapporteur is Cristina Muñoz Madero.

The dossier has been submitted in line with the requirements for submissions under Article 13(1) of Directive 2001/82/EC – a generic application.

On 7 October 2021, the CVMP adopted an opinion and CVMP assessment report.

On 7 December 2021, the European Commission adopted a Commission Decision granting the marketing authorisation for Imoxat.

Scientific advice

Not applicable.

MUMS/limited market status

Not applicable.

Part 1 - Administrative particulars

Detailed description of the pharmacovigilance system

The applicant has provided a detailed description of the pharmacovigilance system (, 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 Chanelle Pharmaceuticals Manufacturing Ltd., Dublin Road, Loughrea, Galway, Ireland which holds a manufacturing authorisation issued on 11 March 2020 by the Health Products Regulatory Authority, Ireland. GMP certification confirms the date of the last inspection (1 March 2019) and shows that the site is authorised for the batch release of such veterinary dosage forms.

GMP declarations for the active substance manufacturing sites were provided from the Qualified Person (QP) at the EU batch release site. The declarations were based on on-site audits of the active substance manufacturing sites.

Overall conclusions on administrative particulars

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

The GMP status of all of the manufacturing sites of the active substances is fully established. The GMP status of the finished product manufacturing site has been satisfactorily established and is in line with legal requirements.

Part 2 - Quality

Composition

The finished product, indicated for cats of varying size and ferrets is presented as a clear colourless to yellow spot-on solution containing two active substances; moxidectin at 10 mg/ml and imidacloprid at 100 mg/ml. The finished product, indicated for dogs of varying size is presented as a clear colourless to yellow spot-on solution containing two active substances; moxidectin at 25 mg/ml and imidacloprid at 100 mg/ml.

Other ingredients are: butylhydroxytoluene (BHT), propylene carbonate and benzyl alcohol.

The product is presented in white polypropylene unit dose pipettes with snap-off cap as described in section 6.5 of the SPC.

Containers

The primary packaging is a unit dose white pipette with snap-off cap consisting of 4 layers: polypropylene (PP)/cyclic olefin copolymer (COC)/ethylene vinyl alcohol (EVOH)/polypropylene (PP). The secondary packaging is a sachet composed of polyethylene (PET)/aluminium foil/nylon/low density polyethylene (LDPE). The materials comply with the relevant European Pharmacopoeia (Ph. Eur.) and EU requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

The product is presented as 3-unit dose pipettes, each individually packed in a foil sachet, packed into a cardboard box. The pack sizes are consistent with the dosage regimen and duration of use.

Development pharmaceutics

The applications for imidacloprid and moxidectin spot-on solutions for cats and ferrets and dogs have been submitted as generic applications under paragraph 1 of Article 13 of Directive 2001/82/EC. The reference products are ‘Advocate Spot-On Solutions” authorised in the EU via the centralised procedure on 2 April 2003. The aim of formulation development was to produce a stable topical solution which is qualitatively and quantitatively pharmaceutically equivalent to the reference products.

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. (butylhydroxytoluene and benzyl alcohol) or USP NF (propylene carbonate) standards. There are no novel

excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC.

In relation to the development of the formulation, a reverse engineering approach combined with publicly available information for the reference products was used to deduce the full quantitative details of the formulation of the reference products. Batches of the reference product (100 mg/10 mg and 100 mg/25 mg) were analysed, alongside the proposed generic products, as part of the quantitative confirmation studies with samples assayed for benzyl alcohol and propylene carbonate content by gas chromatography. The physico-chemical characteristics and other relevant testing parameters of the reference product and generic product were shown to demonstrate compliance with the proposed release specification for the generic product.

In terms of the manufacturing process development, limited information relating to manufacturing development is provided given the simple nature of the manufacturing process. Process development work was conducted separately for both the 100 mg/10 mg (cats/ferrets) and 100 mg/25 mg (dogs) products with the aim of assessing the process of addition and mixing of the active ingredient and excipients. In each case the production of a solution meeting requirements of the proposed finished product release specification was the relevant endpoint. As part of pharmaceutical development, studies were also carried out to determine residual pipette volume.

An exemption from the provision of bioequivalence studies is accepted based on results from the comparative analysis of the candidate and reference formulations, which demonstrate that both formulations can be considered sufficiently similar, to be considered the same, in terms of composition and physico-chemical properties.

Method of manufacture

The finished product is a spot-on solution which is manufactured in a simple process involving sequential addition and dissolution of the product ingredients with mixing between each addition. The bulk material is subsequently filtered before the pipettes are filled, sealed and individually packed into sachets. The different strengths are obtained by filling the pipettes with different volumes of the spot-on solution.

The defined in-process controls are appropriate for this type of manufacturing process and are adequately described within the manufacturing process narrative.

A maximum hold time for bulk product of 3 months is validated for the both the cats/ferrets and dogs products.

Two separate process validation studies were undertaken, one for the 100 mg/10 mg (cats/ferrets) products and one for the 100 mg/25 mg (dogs) products Process validation data was presented for both the bulk solution and the filled product and full details of the sampling and testing plan were provided. Results met the required specification limits for the relevant testing parameters as detailed in the dossier. According to Guideline EMA/CHMP/CVMP/QWP/BPW/70278/2012 *Process validation for finished products – information and data to be provided in regulatory submissions,* the cats/ferrets products fall into the category of "specialised pharmaceutical dose forms" given that moxidectin comprises <2% of this formulation. Whilst provision of supporting data from three batches would normally be required, the receipt of satisfactory data for only 2 batches in support of the cats/ferrets product is accepted given that it is accompanied by a commitment to conduct process validation on the next batch of this product. The dossier includes a commitment to perform process validation on three consecutive batches of the largest of the proposed batch sizes and a process validation scheme for this batch size has also been provided.

Control of starting materials

Active substance

Imidacloprid

The active substance imidacloprid is monographed in the Ph. Eur. and data on the active substance is provided according to the Active Substance Master File (ASMF) procedure.

The active substance specification for the finished product manufacturer includes tests for appearance, identity (IR), solubility, loss on drying, chlorides, assay (HPLC), related substances (HPLC) and residual solvents (GC). The specification is considered to be acceptable. The test methods used for the control of the active substance are as per Ph. Eur. and an in-house GC residual solvents assay method is used. Compliant batch analysis data has been provided from the proposed dosage form manufacturing site for two batches of active substance from the proposed supplier. A declaration is provided that reference standards used for testing the imidacloprid raw materials are the same as those used for finished product analysis.

Moxidectin

There is a monograph for moxidectin in the Ph. Eur., and both manufacturers of the active substance have been granted a Certificate of Suitability of the European Pharmacopoeia (CEP) for moxidectin, copies of which has been provided within the application. The relevant information has been assessed by the EDQM before issuing the Certificate of Suitability. Additional details are included on both CEPs for tests for residual solvents and residual antioxidant, use of water as a solvent in the last steps of the synthesis and container-closure systems. Batch analysis data has been provided from the proposed dosage form manufacturing site for two batches of active substance from both proposed suppliers.

Excipients

All excipients are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. (butylhydroxytoluene and benzyl alcohol) or USP NF (propylene carbonate). Reference to USP NF for the excipient propylene carbonate is acceptable in the absence of a Ph. Eur. monograph. The manufacturing and filling processes takes place under a blanket of nitrogen, low oxygen. The list of excipients is included in section 6.1 of the SPC.

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

None of the starting materials used for the active substance or the finished product are risk materials as defined in the current version of the Note for guidance on minimising the risk of transmitting animal spongiform encephalopathy agents via human and veterinary medicinal products (EMA/410/01 rev 3). The product is therefore out of the scope of the relevant Ph. Eur. monograph and the Note for guidance.

Control tests on the finished product

The finished product release specification controls relevant parameters for the dosage form. Parameters on the specification are: appearance, uniformity of dosage units, identity (active substances), identity (antioxidant), assay (active substances), related substances, assay (antioxidant), condition of packaging, moisture, microbial purity and seal integrity test. The finished product specifications are acceptable. The

test for microbiological quality is proposed to be tested on a skip-test basis and will be applied following the testing of the first 6 commercial batches of product.

Analytical methods are well described and have been validated in accordance with VICH GL2: *Validation of analytical procedures: methodology*. System suitability criteria are well defined and method descriptions are sufficiently detailed.

The test method for total aerobic microbial count determination has been successfully validated however for the total combined yeasts/moulds count and the tests for specified organisms, no recovery of the test organisms in the presence of the product has been demonstrated. This has been attributed to the presence of benzyl alcohol in the formulation and the efforts undertaken with the assay itself to allow the test organisms to be recovered have been described. Batch analysis data is provided and confirms compliance with the finished product release specification thus demonstrating consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Ph. Eur. CRS material for the active substances and the antioxidant is used and working standards are established by standardising a batch of material against the primary Ph. Eur. reference materials.

Stability

Stability data is presented for studies carried out on three production scale batches of the 100 mg/25 mg products (dogs) and two production scale batches of the 100 mg/10 mg product (cats/ferrets), manufactured at the proposed dosage form manufacturing site. Stability data for these batches stored under VICH long term conditions for 24 months at 25 ºC/60% RH and for 6 months under accelerated conditions at 40 ºC/75% RH according to VICH GL3 *Stability testing of new veterinary drug substances and medicinal products* were provided. The stability batches were packaged in the intended commercial packaging. Whilst batches were manufactured using different batches of imidacloprid active substance, the same batch of moxidectin active substance was used for both the cats/ferrets and dog product batches however the commitment in the dossier, to provide additional stability data will address this.

The proposed specification for shelf life is the same as that for release with some exceptions. The analytical procedures used are stability indicating.

For all batches in the stability study, results for all parameters are within specification at all VICH storage conditions however some specific trends were noted and were product-specific.

No photostability study is presented with the application, however, its omission is considered justified on the basis that the product is packaged within a white pipette stored in a multi-ply foil sachet which provides adequate protection from light. Inclusion of a warning to store the original package in order to protect from light on the SPC and product labelling is, however, considered prudent.

The proposed shelf-life of the product as packaged for sale is 2 years based on real time data of 24 months and accelerated data of 6 months with the special storage precaution of "Do not store above 25°C".

Overall conclusions on quality

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

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

Part 3 – Safety

This application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC, as amended (a generic veterinary medicinal product).

Imoxat is a topical spot-on solution containing the active substances imidacloprid and moxidectin. The 40 mg/4 mg strength is intended for use in cats and ferrets, the 80 mg/8 mg strength is intended for use in cats and the remaining strengths (40 mg/10 mg, 100 mg/25 mg, 250 mg/62.5 mg & 400 mg/100 mg) are intended for use in dogs.

The reference product cited is Advocate (EU/2/03/039/001-054), which was first granted a marketing authorisation following a centralised procedure (EMEA/V/C/000076) on 2 April 2003. It can be accepted that the reference product has been authorised in the Union based upon a full dossier for greater than 10 years and is a valid reference product.

Safety documentation

According to Article 13(1) of Directive 2001/82/EC, as amended, the applicant shall not be required to provide the results of the safety and residue tests or of the pre-clinical and clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 5 for not less than eight years in a Member State or the Community.

The reference product cited by the applicant is Advocate spot-on solution and the applicant has claimed an exemption from the requirement to conduct *in vivo* bioequivalence studies in accordance with section 7.1.b of the Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.3-corr.).

The applicant has presented publicly available information on the reference product and also the results of comparative studies, and it can be accepted that the candidate and reference products are the same pharmaceutical form, are intended for administration in the same manner, to the same target species for the same indications and at the same dose rates.

Based upon publicly available information on the reference product, the candidate and reference formulations are qualitatively and quantitatively the same in respect of the active substances and the excipient butylhydroxytoluene and are qualitatively the same in respect of the remaining excipients. With regards to the quantitative composition of the remaining excipients (benzyl alcohol and propylene carbonate) and the physico-chemical properties of the formulations, the applicant has presented the results from comparative analysis of the candidate and reference formulations, which demonstrate that the candidate and reference formulations can be considered sufficiently similar, to be considered the same, in terms of composition and physico-chemical properties.

Pharmacodynamics

Reference is made to the pharmacodynamic properties as detailed in section 5.1 of the SPC of the reference product:

Imidacloprid, 1-(6-Chloro-3-pyridylmethyl)-N-nitro-imidazolidin-2-ylideneamine is an ectoparasiticide belonging to the chloronicotinyl group of compounds. Chemically, it is more accurately described as a

chloronicotinyl nitroguanidine. Imidacloprid is effective against larval flea stages and adult fleas. Flea larvae in the pet's surroundings are killed after contact with a pet treated with the product. Imidacloprid has a high affinity for the nicotinergic acetylcholine receptors in the post-synaptic region of the central nervous system (CNS) of the flea. The ensuing inhibition of cholinergic transmission in insects results in paralysis and death. Due to the weak nature of the interaction with mammalian nicotinergic receptors and the postulated poor penetration through the blood-brain barrier in mammals, it has virtually no effect on the mammalian CNS. Imidacloprid has minimal pharmacological activity in mammals.

Moxidectin, 23-(O-methyloxime)-F28249 alpha is a second-generation macrocyclic lactone of the milbemycin family. It is a parasiticide which is active against many internal and external parasites. Moxidectin is active against larval stages (L3, L4) of *Dirofilaria immitis.* It is also active against gastrointestinal nematodes. Moxidectin interacts with GABA and glutamate-gated chloride channels. This leads to opening of the chloride channels on the postsynaptic junction, the inflow of chloride ions and induction of an irreversible resting state. The result is flaccid paralysis of affected parasites, followed by their death and/or expulsion.

Pharmacokinetics

Reference is made to the pharmacokinetic properties as detailed in section 5.2 of the SPC of the reference product.

After topical administration of the product, imidacloprid is rapidly distributed over the animal's skin within one day of application. It can be found on the body surface throughout the treatment interval. Moxidectin is absorbed through the skin, reaching maximum plasma concentrations approximately 1 to 2 days after treatment in cats. Following absorption from the skin, moxidectin is distributed systemically throughout the body tissues but due to its lipophilicity it is concentrated mainly in the fat. It is slowly eliminated from the plasma as manifested by detectable moxidectin concentrations in plasma throughout the treatment interval of one month.

The mean T½ in cats ranges between 18.7 and 25.7 days. Studies evaluating the pharmacokinetic behaviour of moxidectin after multiple applications have indicated that steady state serum levels are achieved following approximately 4 consecutive monthly treatments in cats.

Toxicological studies

No data was presented. The applicant has presented the results from comparative analysis of the candidate and reference formulations, which demonstrate that the candidate and reference formulations can be considered sufficiently similar, to be considered the same, in terms of both composition and physico-chemical properties. Based upon the comparative data provided, bioequivalence with the reference product can be accepted and the omission of toxicological data can be considered acceptable.

Studies of other effects

No data was presented. The applicant has presented the results from comparative analysis of the candidate and reference formulations, which demonstrate that the candidate and reference formulations can be considered sufficiently similar, to be considered the same, in terms of both composition and physico-chemical properties. Based upon the comparative data provided, bioequivalence with the reference product can be accepted and the omission of the results of dermal irritation, immunotoxicity or sensitisation studies can be considered acceptable.

Excipients

In addition to the active substances, the candidate formulations contain the excipients butylhydroxytoluene, propylene carbonate and benzyl alcohol. These excipients are commonly used in pharmaceutical spot-on solutions and are also included in the reference formulations.

User safety

A user safety assessment has not been provided.

Based upon the information that has been provided, it can be accepted that Imoxat spot-on solution and Advocate spot-on solution are of the same quantitative and qualitative composition in terms of active substances (imidacloprid and moxidectin) and are qualitatively the same in respect of the excipients. Furthermore, it can be accepted that Imoxat and Advocate are of the same pharmaceutical form (spot-on solution), are to be supplied in pipettes of the same fill volume and are intended for administration in the same manner (topical) to the same target species (cats, dogs and ferrets) for the same indications and at the same dose rates. As such, it can be accepted that the risk posed to the user by Imoxat spot-on solution is not expected to differ to that posed by Advocate spot-on solution.

The same user safety warnings as approved by CVMP for the reference product, are proposed for the candidate product:

- Avoid contact with skin, eyes or mouth.
- Do not eat, drink or smoke during application.
- Wash hands thoroughly after use.
- After application do not stroke or groom animals until the application site is dry.
- In case of accidental spillage onto skin, wash off immediately with soap and water.
- People with known hypersensitivity to benzyl alcohol, imidacloprid or moxidectin should administer the product with caution. In very rare cases the product may cause skin sensitisation or transient skin reactions (for example numbness, irritation or burning/tingling sensation).
- In very rare cases the product may cause respiratory irritation in sensitive individuals.
- If the product accidentally gets into eyes, they should be thoroughly flushed with water.
- If skin or eye symptoms persist, or the product is accidentally swallowed, seek medical advice immediately and show the package leaflet or the label to the physician.

This is considered appropriate and provided the product is stored, handled, administered and disposed of in accordance with the recommendations included in the SPC, it can be accepted that Imoxat spot-on solution will not present an unacceptable risk to the user.

Environmental risk assessment

A phase I environmental risk assessment (ERA) was provided according to the relevant CVMP/VICH guidelines. The environmental risk assessment can stop in phase I and no phase II assessment is required because Imoxat is intended for use in cats, dogs and ferrets, which are non-food-producing animals. However, moxidectin has previously been classified as persistent, bioaccumulative and toxic (PBT) in the environment, which is addressed in section 5.2 of the SPC.

The environmental warnings and disposal advice proposed by the applicant for inclusion in SPC sections 4.5 and 6.6 are the same as those previously agreed by the CVMP for the reference products and can therefore be applied to the candidate products.

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 included in the SPC.

Overall conclusions on the safety documentation

This application has been submitted in accordance with Article 3(3), of Regulation (EC) No. 726/2004 (a generic veterinary medicinal product). In accordance with Article 13(1) of Directive 2001/82/EC, as amended, the applicant shall not be required to provide the results of the safety and residue tests or of the pre-clinical and clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 5 for not less than eight years in a Member State or the Community.

The applicant has claimed an exemption from the requirement to conduct *in vivo* bioequivalence studies and has presented publicly available information on the reference product and also the results of comparative studies.

It can be accepted that the candidate and reference products are of the same pharmaceutical form, are intended for administration in the same manner, to the same target species for the same indications and at the same dose rates. Further, the candidate and reference formulations are qualitatively and quantitatively the same in respect of the active substances and the excipient butylhydroxytoluene and are qualitatively the same in respect of the remaining excipients.

With regards the quantitative composition of the remaining excipients (benzyl alcohol and propylene carbonate) and the physico-chemical properties of the formulations, comparative analysis of the candidate and reference formulations, demonstrate that the candidate and reference formulations can be considered sufficiently similar, to be considered the same, in terms of both composition and physico-chemical properties.

Pharmacology

No data in relation to the pharmacological aspects of the product has been presented. Given that the comparative analysis of the candidate and reference formulations has demonstrated that the candidate and reference formulations can be considered sufficiently similar, to be considered the same, in terms of both composition and physico-chemical properties, then bioequivalence can be accepted and the applicant's proposal to include text identical to that of the reference product in sections 5.1 and 5.2 of the proposed SPC can be considered acceptable.

Toxicology

No data in relation to the toxicological profile of the product have been provided. Given that the comparative analysis of the candidate and reference formulations has demonstrated that the candidate and reference formulations can be considered sufficiently similar, to be considered the same, in terms of both composition and physico-chemical properties, bioequivalence with the reference product and the omission of toxicological data can be accepted.

User Safety

No user safety assessment was provided.

Based upon the information provided, it can be accepted that Imoxat spot-on solution and Advocate spot-on solution are of the same quantitative and qualitative composition in terms of active substances (imidacloprid and moxidectin) and are qualitatively the same in respect of the excipients. Furthermore, it can be accepted that Imoxat and Advocate are of the same pharmaceutical form (spot-on solution), are to be supplied in pipettes of the same fill volume and are intended for administration in the same manner (topical) to the same target species (cats, dogs and ferrets) for the same indications and at the same dose rates.

As such, it can be accepted that the risk posed to the user by the candidate product is not expected to differ to that posed by the reference product.

The same user safety warnings as approved by the CVMP for the reference product have been proposed for the candidate product and this is considered appropriate. Provided the candidate product is stored, handled, administered and disposed of in accordance with the recommendations included in the SPC, it can be accepted that Imoxat spot-on solution will not present an unacceptable risk to the user.

Environmental Safety

A Phase I environmental risk assessment (ERA) was provided according to the CVMP/VICH guidelines. Given that the product is intended for use in non-food animals, the ERA can stop at Phase I and a Phase II assessment is not required. 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 included in the SPC.

Part 4 – Efficacy

Bioequivalence

In vivo bioequivalence studies were not conducted. Instead, the applicant claimed an exemption from such studies based on section 7.1.b) of the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.3-corr.): *'For products intended for intramuscular, subcutaneous or systemically acting topical administration, bioequivalence studies are not required in cases when the product is of the same type of solution, contains the same concentration of the active substance and comparable excipients in similar amounts as the reference veterinary medicinal product, if it can be adequately justified that the difference(s) in the excipient(s) and/or their concentration have no influence on the rate and/or extent of absorption of the active substance'.*

However, the exemption from requirements to conduct *in vivo* bioequivalence studies set out in section 7.1.b) of the aforementioned guideline applies specifically to topically-applied products with systemically acting substances and section 5.2 of the SPC for the reference product states the following:

'*After topical administration of the product, imidacloprid is rapidly distributed over the animal's skin within one day of application. It can be found on the body surface throughout the treatment interval. Moxidectin is absorbed through the skin, reaching maximum plasma concentrations approximately 1 to 2 days after treatment in cats. Following absorption from the skin, moxidectin is distributed systemically throughout the body tissues but due to its lipophilicity it is concentrated mainly in the fat. It is slowly eliminated from the plasma as manifested by detectable moxidectin concentrations in plasma throughout the treatment interval of one month.'*

Consequently, it can be accepted that moxidectin is a systemically acting active substance following topical application and therefore the exemption claimed can be accepted for moxidectin. However, the

exemption being claimed is not considered applicable for the active substance imidacloprid, given that systemic bioavailability is not foreseen.

That said, it is noted from the CVMP 'Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats' (EMEA/CVMP/EWP/005/2000-Rev.3), that for locally-acting, topical, generic, ectoparasiticidal products:

'Efficacy or tolerance studies are not considered necessary in the case that the composition (i.e. quality and quantity of the active substance(s) and excipient(s)) and the physico-chemical properties of the generic product and the reference product are identical and the generic is to be administered at the same dose and route of administration as the reference product. If there is a difference in composition of excipients which may affect absorption, rate and extent of distribution and persistence of the active substance, further studies, e.g. dose confirmation and/or field studies, may be necessary.'

The applicant has presented publicly available information on the reference product and also the results of comparative studies, and it can be accepted that the candidate and reference products are the same pharmaceutical form, are intended for administration in the same manner, to the same target species for the same indications and at the same dose rates.

Based upon publicly available information on the reference product, the candidate and reference formulations are qualitatively and quantitatively the same in respect of the active substances and the excipient butylhydroxytoluene and are qualitatively the same in respect of the remaining excipients. With regards the quantitative composition of the remaining excipients (benzyl alcohol and propylene carbonate) and the physico-chemical properties of the formulations, the applicant has presented the results from comparative analysis of the candidate and reference formulations, which demonstrate that the candidate and reference formulations can be considered sufficiently similar, to be considered the same, in terms of composition and physico-chemical properties.

Considering the above, the applicant's claim for an exemption from the requirements to conduct *in vivo* bioequivalence studies is acceptable and consequently bioequivalence between the candidate product Imoxat and the reference product Advocate can be accepted.

Pharmacodynamics

Please refer to Part 3.

Development of resistance

Given the legal basis of this application (generic) and the fact that the candidate and reference formulations are qualitatively and quantitatively the same in respect of the active substances, moxidectin and imidacloprid, and bioequivalence with the reference product is accepted, the resistance profile of the candidate product is expected to reflect that of the reference product.

It can be accepted that the candidate and reference products are of the same pharmaceutical form (spot-on solution) and are intended for administration in the same manner (topical) to the same target species (cats, dogs and ferrets) for the same indications and at the same dose rates and as such the potential for resistance development is not expected to differ between candidate and reference formulations.

The applicant has proposed to include the same information in section 4.4 of the SPC intended to limit the development of resistance to the active substances as has already been agreed for the reference product and this is considered acceptable.

Pharmacokinetics

Please refer to Part 3.

Dose justification/determination

The product is a topical spot-on formulation containing moxidectin and imidacloprid as the active substances. The candidate and reference formulations are qualitatively and quantitatively the same in respect of the active substances. The candidate and reference products are of the same pharmaceutical form (spot-on solution) and are intended for administration in the same manner (topical) to the same target species (cats, dogs and ferrets) for the same indications. In addition, the fill volumes of the different pipette sizes match those already approved for the reference product. Consequently, the applicant proposes that the candidate product be administered at the same dose rates as already approved for the reference product and given that the omission of bioequivalence studies has been accepted, this is considered appropriate.

Target animal tolerance

No target animal tolerance data was presented.

This application has been submitted as a generic application and, in accordance with Article 13(1) of Directive 2001/82/EC, the applicant shall not be required to provide the results of the pre-clinical and clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 5 for not less than eight years in a Member State or the Community.

The applicant has claimed bioequivalence with the reference product cited, Advocate spot-on, and it can be accepted that the candidate and reference products are of the same pharmaceutical form (spot-on solution) and are intended for administration in the same manner (topical) to the same target species (cats, dogs and ferrets) for the same indications and at the same dose rates. Further, the candidate and reference formulations are qualitatively and quantitatively the same in respect of the active substances and the excipient butylhydroxytoluene and are qualitatively the same in respect of the remaining excipients. With regards the quantitative composition of the remaining excipients (benzyl alcohol and propylene carbonate) and the physico-chemical properties of the formulations, the applicant has presented the results from comparative analysis of the candidate and reference formulations, which demonstrate that the candidate and reference formulations can be considered sufficiently similar, to be considered the same, in terms of composition and physico-chemical properties. In addition, the fill volumes of the different pipette sizes match those already approved for the reference products and consequently, no difference in exposure between candidate and reference formulations is anticipated.

Given that the comparative analysis of the candidate and reference formulations has demonstrated that the candidate and reference formulations can be considered sufficiently similar to be considered the same, in terms of both composition and physico-chemical properties, bioequivalence with the reference product and the omission of target animal tolerance data for the candidate formulations can be accepted.

Clinical studies

No clinical study data has been presented.

This application has been submitted as a generic application and, in accordance with Article 13(1) of Directive 2001/82/EC, the applicant shall not be required to provide the results of the pre-clinical and

clinical trials if he can demonstrate that the medicinal product is a generic of a reference medicinal product which is or has been authorised under Article 5 for not less than eight years in a Member State or the Community.

The applicant has claimed bioequivalence with the reference product cited, Advocate spot-on and it can be accepted that the candidate and reference products are of the same pharmaceutical form (spot-on solution) and are intended for administration in the same manner (topical) to the same target species (cats, dogs and ferrets) for the same indications and at the same dose rates. Further, the candidate and reference formulations are qualitatively and quantitatively the same in respect of the active substances and the excipient butylhydroxytoluene and are qualitatively the same in respect of the remaining excipients. With regards the quantitative composition of the remaining excipients (benzyl alcohol and propylene carbonate) and the physico-chemical properties of the formulations, the applicant has presented the results from comparative analysis of the candidate and reference formulations, which demonstrate that the candidate and reference formulations can be considered sufficiently similar, to be considered the same, in terms of both composition and physico-chemical properties.

Given that the comparative analysis of the candidate and reference formulations has demonstrated that the candidate and reference formulations can be considered sufficiently similar, to be considered the same, in terms of both composition and physico-chemical properties, bioequivalence with the reference product and the omission of clinical data for the candidate formulations can be accepted.

Overall conclusion on efficacy

Bioequivalence

In vivo bioequivalence studies were not conducted. Instead, the applicant claimed an exemption from such studies based on section 7.1.b) of the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/2000-Rev.3-corr.). However, the exemption from requirements to conduct *in vivo* bioequivalence studies set out in section 7.1.b) of the aforementioned guideline applies specifically to topically-applied products with systemically acting substances. It can be accepted that moxidectin is a systemically acting active substance following topical application and therefore the exemption claimed can be accepted for moxidectin. However, the exemption being claimed is not considered applicable for the active substance imidacloprid, given that systemic bioavailability is not foreseen.

The CVMP 'Guideline for the testing and evaluation of the efficacy of antiparasitic substances for the treatment and prevention of tick and flea infestation in dogs and cats' (EMEA/CVMP/EWP/005/2000-Rev.3) indicates that for locally-acting, topical, generic, ectoparasiticidal products '*Efficacy or tolerance studies are not considered necessary in the case that the composition (i.e. quality and quantity of the active substance(s) and excipient(s)) and the physico-chemical properties of the generic product and the reference product are identical and the generic is to be administered at the same dose and route of administration as the reference product*'.

Based upon publicly available information on the reference product, and the results from comparative analysis of the candidate and reference formulations, the candidate and reference formulations can be considered sufficiently similar, to be considered the same, in terms of both composition and physico-chemical properties. Therefore, the applicant's claim for an exemption from the requirements to conduct *in vivo* bioequivalence studies and consequently bioequivalence with the reference product can be accepted.

Resistance

No resistance data has been provided. Given the legal basis of this application (generic) and the fact that the candidate and reference formulations are qualitatively and quantitatively the same in respect of the active substances, moxidectin and imidacloprid, the resistance profile of the candidate product is expected to reflect that of the reference product. Additionally, the candidate and reference products are of the same pharmaceutical form and are intended for administration in the same manner, to the same target species, for the same indications and at the same dose rates; as such, the potential for resistance development is not expected to differ between candidate and reference formulations.

Target animal tolerance

No target animal tolerance data was presented. Given that the comparative analysis of the candidate and reference formulations has demonstrated that the candidate and reference formulations can be considered sufficiently similar, to be considered the same, in terms of both composition and physico-chemical properties, bioequivalence with the reference product and the omission of target animal tolerance data for the candidate formulations can be accepted.

Clinical studies

No clinical study data has been presented. Given that the comparative analysis of the candidate and reference formulations has demonstrated that the candidate and reference formulations can be considered sufficiently similar, to be considered the same, in terms of both composition and physico-chemical properties, bioequivalence with the reference product and the omission of clinical study data for the candidate formulations can be accepted.

Part 5 – Benefit-risk assessment

Introduction

Imoxat is a spot-on solution containing imidacloprid and moxidectin. The active substances are well-known and are already authorised in combination (Advocate).

The active substance imidacloprid is an ectoparasiticide belonging to the chloronicotinyl group of compounds. Imidacloprid is effective against larval flea stages and adult fleas. Imidacloprid has a high affinity for the nicotinergic acetylcholine receptors in the post-synaptic region of the central nervous system (CNS) of the flea. Moxidectin is a second-generation macrocyclic lactone of the milbemycin family. It is a parasiticide which is active against many internal and external parasites. Moxidectin interacts with GABA and glutamate-gated chloride channels. This leads to opening of the chloride channels on the postsynaptic junction, the inflow of chloride ions and induction of an irreversible resting state.

The product is intended for use in cats, dogs and ferrets suffering from, or at risk from, mixed parasitic infections.

The proposed minimum doses are 10 mg/kg bodyweight imidacloprid and 1.0 mg/kg bodyweight moxidectin for cats. Ferrets should be administered one pipette containing 40 mg imidacloprid and 4 mg moxidectin. For dogs the proposed minimum doses are 10 mg/kg bodyweight imidacloprid and 2.5 mg/kg bodyweight moxidectin. The route of administration is as a spot-on and the treatment schedule should be based on individual veterinary diagnosis and on the local epidemiological situation.

The application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC (generic application).

Benefit assessment

Direct therapeutic benefit

The product is beneficial in the treatment and/or prevention of ectoparasitic and endoparasitic infestations in cats, dogs and ferrets, caused by *Ctenocephalides felis*, *Otodectes cynotis*, *Trichodectes canis*, *Notoedres cati*, *Sarcoptes scabiei var canis*, *Demodex canis, Eucoleus aerophilus* (adults) *Aelurostrongylus abstrusus* (adults), the L3/L4 larvae of *Aelurostrongylus abstrusus*, *Thelazia callipaeda* (adults), *Angiostrongylus vasorum, Crenosoma vulpis*, *Spirocerca lupi*, *Eucoleus boehmi* (adults), the L3 and L4 larvae of *Dirofilaria immitis*, circulating microfilariae of *D. immitis,* the adult stages, L3 Larvae and circulating microfilariae of *Dirofilaria repens, Toxocara cati*, *Ancylostoma tubaeforme* (the L4 larvae, immature adults and adults), *Toxocara canis, Ancylostoma caninum* and *Uncinaria stenocephala*, L4 larvae, immature adults and adults of *Toxascaris leonina* and the adults of *Trichuris vulpis*.

Additionally, the product can be used as part of a treatment strategy for flea allergy dermatitis (FAD).

Additional benefits

No additional benefits for this generic veterinary medicinal product are expected other than the availability of an alternative product on the market place.

Risk assessment

Quality:

Information on development, manufacture and control of the active substances and finished product has been presented in a generally satisfactory manner.

Safety:

The risks associated with use of the product are expected to be the same as those of the reference product. Therefore, the product is not expected to present an unacceptable risk to the target animal, user or environment when used as recommended.

Risk management or mitigation measures

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

User safety:

User safety risks have been identified, mainly the risks associated with exposure via dermal contact. These risks have been addressed by the safety warnings in the SPC.

Evaluation of the benefit-risk balance

At the time of submission, the applicant applied for the following indication:

For cats suffering from, or at risk from, mixed parasitic infections:

- the treatment and prevention of flea infestation (*Ctenocephalides felis*),

- the treatment of ear mite infestation (*Otodectes cynotis*),
- the treatment of notoedric mange (*Notoedres cati*),
- the treatment of the lungworm *Eucoleus aerophilus* (syn. *Capillaria aerophila*) (adults),
- the prevention of lungworm disease (L3/L4 larvae of *Aelurostrongylus abstrusus*),
- the treatment of the lungworm *Aelurostrongylus abstrusus* (adults),
- the treatment of the eye worm *Thelazia callipaeda* (adults),
- the prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*),
- the treatment of infections with gastrointestinal nematodes (L4 larvae, immature adults and adults of *Toxocara cati* and *Ancylostoma tubaeforme*).

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

For ferrets suffering from, or at risk from, mixed parasitic infections:

- For the treatment and prevention of flea infestation (*Ctenocephalides felis*),
- the prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*).

For dogs suffering from, or at risk from, mixed parasitic infections:

- For the treatment and prevention of flea infestation (*Ctenocephalides felis*),
- the treatment of biting lice (*Trichodectes canis*),
- the treatment of ear mite infestation (*Otodectes cynotis*), sarcoptic mange (caused by *Sarcoptes scabiei* var. *canis*), demodicosis (caused by *Demodex canis*),
- the prevention of heartworm disease (L3 and L4 larvae of *Dirofilaria immitis*),
- the treatment of circulating microfilariae (*Dirofilaria immitis*),
- the prevention of cutaneous dirofilariosis adult stages of *Dirofilaria repens*
- the prevention of cutaneous dirofilariosis (L3 larvae of *Dirofilaria repens*),
- the reduction of circulating microfilariae (*Dirofilaria repens*),
- the prevention of angiostrongylosis (L4 larvae and immature adults of *Angiostrongylus vasorum*),
- the treatment of *Angiostrongylus vasorum* and *Crenosoma vulpis*,
- the prevention of spirocercosis (*Spirocerca lupi*),
- the treatment of *Eucoleus* (syn. *Capillaria*) *boehmi* (adults),
- the treatment of the eye worm *Thelazia callipaeda* (adults),
- the treatment of infections with gastrointestinal nematodes (L4 larvae, immature adults and adults of Toxocara *canis, Ancylostoma caninum* and *Uncinaria stenocephala*, adults of *Toxascaris leonina* and *Trichuris vulpis*).

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 is considered 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 Imoxat 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.