

## **Annex I**

**List of the names, pharmaceutical form, strengths of the veterinary medicinal product, animal species, route of administration, marketing authorisation holder in the Member States**

Member State EU/EEA	Applicant/Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Austria <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex CAT 52,5 mg Lösung zum Auftropfen für Katzen	Fipronil	52.5 mg	Spot-on solution	Spot-on use	Cats
Austria <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex S 75 mg Lösung zum Auftropfen für Hunde	Fipronil	75 mg	Spot-on solution	Spot-on use	Dogs
Austria <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex M 150 mg Lösung zum Auftropfen für Hunde	Fipronil	150 mg	Spot-on solution	Spot-on use	Dogs
Austria <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex L 300 mg Lösung zum Auftropfen für Hunde	Fipronil	300 mg	Spot-on solution	Spot-on use	Dogs
Austria <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex XL 412,5 mg Lösung zum Auftropfen für Hunde	Fipronil	412.5 mg	Spot-on solution	Spot-on use	Dogs
Belgium	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex CAT 52,5 mg spot-on oplossing voor katten	Fipronil	52.5 mg	Spot-on solution	Spot-on use	Cats
Belgium	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex S 75 mg spot-on oplossing voor honden	Fipronil	75 mg	Spot-on solution	Spot-on use	Dogs
Belgium	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex M 150 mg spot- on oplossing voor honden	Fipronil	150 mg	Spot-on solution	Spot-on use	Dogs

<sup>1</sup> Marketing authorisation granted

Member State EU/EEA	Applicant/Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Belgium	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex L 300 mg spot-on oplossing voor honden	Fipronil	300 mg	Spot-on solution	Spot-on use	Dogs
Belgium	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex XL 412,5 mg spot-on oplossing voor honden	Fipronil	412.5 mg	Spot-on solution	Spot-on use	Dogs
Czech Republic <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex CAT 52,5 mg roztok pro nakapání na kůži spot-on pro kočky	Fipronil	52.5 mg	Spot-on solution	Spot-on use	Cats
Czech Republic <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex S 75 mg roztok pro nakapání na kůži spot-on pro psy	Fipronil	75 mg	Spot-on solution	Spot-on use	Dogs
Czech Republic <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex M 150 mg roztok pro nakapání na kůži spot-on pro psy	Fipronil	150 mg	Spot-on solution	Spot-on use	Dogs
Czech Republic <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex L 300 mg roztok pro nakapání na kůži spot-on pro psy	Fipronil	300 mg	Spot-on solution	Spot-on use	Dogs
Czech Republic <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex XL 412,5 mg roztok pro nakapání na kůži spot-on pro psy	Fipronil	412.5 mg	Spot-on solution	Spot-on use	Dogs
Denmark	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex CAT 52,5 mg spot-on løsning for katte	Fipronil	52.5 mg	Spot-on solution	Spot-on use	Cats
Denmark	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex S 75 mg spot-on løsning for hunde	Fipronil	75 mg	Spot-on solution	Spot-on use	Dogs

Member State EU/EEA	Applicant/Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Denmark	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex M 150 mg spot-on løsning for hunde	Fipronil	150 mg	Spot-on solution	Spot-on use	Dogs
Denmark	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex L 300 mg spot-on løsning for hunde	Fipronil	300 mg	Spot-on solution	Spot-on use	Dogs
Denmark	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex XL 412,5 mg spot-on løsning for hunde	Fipronil	412.5 mg	Spot-on solution	Spot-on use	Dogs
Greece	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex CAT 52,5 mg Διάλυμα για επίχυση σε σημείο (spot-on) για γάτες	Fipronil	52.5 mg	Spot-on solution	Spot-on use	Cats
Greece	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex S 75 mg Διάλυμα για επίχυση σε σημείο (spot-on) για σκύλους	Fipronil	75 mg	Spot-on solution	Spot-on use	Dogs
Greece	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex M 150 mg Διάλυμα για επίχυση σε σημείο (spot-on) για σκύλους	Fipronil	150 mg	Spot-on solution	Spot-on use	Dogs
Greece	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex L 300 mg Διάλυμα για επίχυση σε σημείο (spot-on) για σκύλους	Fipronil	300 mg	Spot-on solution	Spot-on use	Dogs
Greece	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex XL 412,50 mg Διάλυμα για επίχυση σε σημείο (spot-on) για σκύλους	Fipronil	412.5 mg	Spot-on solution	Spot-on use	Dogs
Ireland	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex CAT 52.5 mg spot-on solution for cats	Fipronil	52.5 mg	Spot-on solution	Spot-on use	Cats

Member State EU/EEA	Applicant/Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Ireland	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex S 75 mg spot-on solution for dogs	Fipronil	75 mg	Spot-on solution	Spot-on use	Dogs
Ireland	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex M 150 mg spot-on solution for dogs	Fipronil	150 mg	Spot-on solution	Spot-on use	Dogs
Ireland	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex L 300 mg spot-on solution for dogs	Fipronil	300 mg	Spot-on solution	Spot-on use	Dogs
Ireland	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex XL 412.5 mg spot-on solution for dogs	Fipronil	412.5 mg	Spot-on solution	Spot-on use	Dogs
Italy	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex CAT 52,5 mg soluzione spot-on per gatti	Fipronil	52.5 mg	Spot-on solution	Spot-on use	Cats
Italy	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex S 75 mg soluzione spot-on per cani	Fipronil	75 mg	Spot-on solution	Spot-on use	Dogs
Italy	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex M 150 mg soluzione spot-on per cani	Fipronil	150 mg	Spot-on solution	Spot-on use	Dogs
Italy	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex L 300 mg soluzione spot-on per cani	Fipronil	300 mg	Spot-on solution	Spot-on use	Dogs
Italy	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex XL 412,5 mg soluzione spot-on per cani	Fipronil	412.5 mg	Spot-on solution	Spot-on use	Dogs

<b>Member State EU/EEA</b>	<b>Applicant/Marketing authorisation holder</b>	<b>Name</b>	<b>INN</b>	<b>Strength</b>	<b>Pharmaceutical form</b>	<b>Route of administration</b>	<b>Animal species</b>
The Netherlands <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex CAT 52,5 mg spot-on oplossing voor katten	Fipronil	52.5 mg	Spot-on solution	Spot-on use	Cats
The Netherlands <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex S 75 mg spot-on oplossing voor honden	Fipronil	75 mg	Spot-on solution	Spot-on use	Dogs
The Netherlands <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex M 150 mg spot-on oplossing voor honden	Fipronil	150 mg	Spot-on solution	Spot-on use	Dogs
The Netherlands <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex L 300 mg spot-on oplossing voor honden	Fipronil	300 mg	Spot-on solution	Spot-on use	Dogs
The Netherlands <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex XL 412,5 mg spot-on oplossing voor honden	Fipronil	412.5 mg	Spot-on solution	Spot-on use	Dogs
Spain <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex GATOS 52,5 mg solución spot-on para gatos	Fipronil	52.5 mg	Spot-on solution	Spot-on use	Cats
Spain <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex75 mg solución spot-on para perros pequeños	Fipronil	75 mg	Spot-on solution	Spot-on use	Dogs
Spain <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex 150 mg solución spot-on para perros medianos	Fipronil	150 mg	Spot-on solution	Spot-on use	Dogs

Member State EU/EEA	Applicant/Marketing authorisation holder	Name	INN	Strength	Pharmaceutical form	Route of administration	Animal species
Spain <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex 300 mg solucióń spot-on para perros grandes	Fipronil	300 mg	Spot-on solution	Spot-on use	Dogs
Spain <sup>1</sup>	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex 412,5 mg solucióń spot-on para perros muy grandes	Fipronil	412.5 mg	Spot-on solution	Spot-on use	Dogs
Slovak Republic	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex CAT 52,5 mg na vonkajšiu aplikácii na kožu mačiek	Fipronil	52.5 mg	Spot-on solution	Spot-on use	Cats
Slovak Republic	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex S 75 mg na vonkajšiu aplikácii na kožu pre psov	Fipronil	75 mg	Spot-on solution	Spot-on use	Dogs
Slovak Republic	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex M 150 mg na vonkajšiu aplikácii na kožu pre psov	Fipronil	150 mg	Spot-on solution	Spot-on use	Dogs
Slovak Republic	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex L 300 mg na vonkajšiu aplikácii na kožu pre psov	Fipronil	300 mg	Spot-on solution	Spot-on use	Dogs
Slovak Republic	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex XL 412,5 mg na vonkajšiu aplikácii na kožu pre psov	Fipronil	412.5 mg	Spot-on solution	Spot-on use	Dogs
United Kingdom	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex CAT 52.5 mg spot-on solution for cats	Fipronil	52.5 mg	Spot-on solution	Spot-on use	Cats
United Kingdom	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex S 75 mg spot-on solution for dogs	Fipronil	75 mg	Spot-on solution	Spot-on use	Dogs

<b>Member State EU/EEA</b>	<b>Applicant/Marketing authorisation holder</b>	<b>Name</b>	<b>INN</b>	<b>Strength</b>	<b>Pharmaceutical form</b>	<b>Route of administration</b>	<b>Animal species</b>
United Kingdom	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex M 150 mg spot-on solution for dogs	Fipronil	150 mg	Spot-on solution	Spot-on use	Dogs
United Kingdom	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex L 300 mg spot-on solution for dogs	Fipronil	300 mg	Spot-on solution	Spot-on use	Dogs
United Kingdom	VET-AGRO TRADING Sp. z o.o. Mełgiewska str. 18, 20-234 Lublin, Poland	Fiprex XL 412.5 mg spot-on solution for dogs	Fipronil	412.5 mg	Spot-on solution	Spot-on use	Dogs



## **Annex II**

**Scientific conclusions and grounds for the refusal of the marketing authorisation and for suspension of the existing marketing authorisations**

# **Overall summary of the scientific evaluation of Fiprex CAT 52.5 mg spot-on solution for cats, Fiprex S 75 mg spot-on solution for dogs, Fiprex M 150 mg spot-on solution for dogs, Fiprex L 300 mg spot-on solution for dogs and Fiprex XL 412.5 mg spot-on solution for dogs (see Annex I)**

## **1. Introduction**

Fiprex is a spot-on formulation containing fipronil as the active substance (pharmacotherapeutic group: ectoparasiticides for topical use). There are five presentations, one for cats (52.5 mg) and four for different sizes of dogs (S, M, L, XL) corresponding to 75, 150, 300 and 412.5 mg, respectively. In each case, the concentration of the active substance, fipronil, is 75 mg/ml but the single-dose pipette volume differs.

The presentations for use in dogs have already been authorised in the reference Member State, the Czech Republic, since December 2011 and the cat product was more recently authorised there in May 2012. Applications for marketing authorisation were submitted to the concerned Member States using the mutual recognition procedure. The legal basis of the application was Article 13a of Directive 2001/82/EC i.e. citing well-established use. During the procedure, there was disagreement between the reference Member State and a concerned Member State, Ireland, on the adequacy of the data presented by the marketing authorisation holder (MAH) in support of efficacy and target animal safety. The objecting concerned Member States considered that the authorisation of Fiprex may present a potential serious risk to animal health since the target animal safety and efficacy of the product had not been sufficiently demonstrated. Consequently the matter was referred to the CVMP.

The CVMP was asked to give its opinion on the concerns raised by the objecting concerned Member State and to conclude on the benefit-risk balance for Fiprex.

## **2. Assessment of the data submitted**

### **2.1. Target animal safety**

Based on the accepted well-established use substantiated by the MAH through public literature within their application, the Committee was able to conclude that the target animal safety was adequately supported. Despite differences in formulation and dose between Fiprex and other fipronil-containing spot-on products cited in the published literature, it is accepted that such products are generally well tolerated and have a wide margin of safety. It was not possible to consider the post-authorisation safety data presented by the MAH (related to periodic safety update reports and sales volume data) since these data included reference to products that were not included in the scope of this referral procedure.

### **2.2. Evidence in support of efficacy**

In accordance with the legal basis of the application, i.e. well established use, the MAH has cited published literature to support the efficacy of the product. The literature cited by the MAH relates to products that are quantitatively different in terms of the active substance and both qualitatively and quantitatively different in terms of the excipients. The CVMP considers that differences in formulation between spot-on products may impact on efficacy, particularly in terms of duration of efficacy. These differences may at least partly be attributable to the effect of the formulation on the rate and/or extent of dermal absorption and distribution of fipronil. The CVMP is of the opinion that the MAH has

inadequately bridged the difference between the formulations of the products cited in the published literature and the formulation of Fiprex. Therefore the CVMP concludes that it is not possible to establish the efficacy profile of Fiprex through extrapolation of data from the published literature.

The MAH presented proprietary clinical studies investigating the efficacy of Fiprex spot-on (the product concerned) and Fiprex spray (not concerned by this procedure) against fleas and ticks in dogs and cats. The study reports were significantly re-worked by the MAH for review during this referral procedure. The raw data were made available as separate documentation. Following a review of these data, the CVMP concluded that the conduct of the studies was not sufficiently robust and the results not sufficiently reliable to take the MAH's proprietary data in account as regards the clinical efficacy of Fiprex spot-on.

The MAH additionally presented a study to compare the physicochemical properties of a number of different fipronil-containing spot-on products, including Fiprex and the pioneer product. This study included basic tests to evaluate characteristics such as drying time and surface spreading of the different products *in vitro*. The MAH did not adequately justify why the outcome of this study was of particular relevance in defining the pharmacological properties, and thereby clinical efficacy, of Fiprex in relation to other fipronil spot ons. Consequently, the CVMP cannot conclude that the findings of the MAH's *in vitro* investigations can be applied to the *in vivo* situation or to the expected efficacy of the products.

### **3. Benefit-risk assessment**

#### ***Introduction***

Fiprex spot-on solutions for dogs and cats contain fipronil. The application was submitted for a mutual recognition procedure, using the legal basis of well-established use (Article 13a of Directive 2001/82/EC).

#### ***Direct therapeutic benefit***

Fipronil is an ectoparasiticide that, depending on the approved product, can be used to prevent and treat flea infestations in dogs and cats, to control flea allergic dermatitis as part of a treatment strategy and also to control infestations of biting lice. Depending on the approved product, Fipronil can also be used to treat and prevent tick infestations in dogs. Fleas are obligate parasites commonly brought into homes by pet cats and dogs. Ticks are obligate parasites that are vectors for diseases to animals and humans e.g. Lyme disease. Spot-on products containing fipronil provide a user-friendly means of targeting flea and tick infestations in the aforementioned companion animal species, as well as the consequential complications that these parasites can cause to both their hosts and pet owners.

Whilst the efficacy of fipronil is well-documented, the MAH has not been able to refine the claims for efficacy of their formulation due to quantitative and qualitative differences compared to those products cited in the product literature. The CVMP considers that differences in formulation between spot-on products may impact on efficacy and this is reflected in the range of customised claims regarding immediate and persistent efficacy for other approved spot-on products. As significant deficiencies were noted in the proprietary clinical studies conducted with Fiprex, these data were not considered reliable. It has therefore not been possible to establish the efficacy profile of the formulation for Fiprex spot-on.

#### ***Risk assessment***

The quality and safety (apart from target animal safety) of Fiprex were not assessed in this referral procedure.

Based on the accepted well-established use substantiated by the MAH through public literature within their application, the Committee was able to conclude that the target animal safety was adequately supported despite the difference in formulations between the candidate product and products referenced in the published literature.

#### ***Evaluation of the benefit-risk balance***

The benefit-risk balance for Fiprex remains inconclusive in the absence of adequate data to justify the proposed indications.

#### ***Conclusion***

Whilst the CVMP accepted that Fiprex does not pose a risk in terms of target animal safety, based on the overall data presented, the CVMP concluded that the data provided for Fiprex could not adequately justify the proposed indications and that the benefit-risk balance is currently not favourable.

## **4. Re-examination procedure**

The MAH's grounds for re-examination of the CVMP opinion of 11 December 2013 focused on the factors to be taken into account to establish a "well-established veterinary medicinal use of constituents of veterinary medicinal products", largely following the headings contained under Title III of Annex I to Directive 2001/82/EC (Directive 2009/9/EC).

The MAH stated that all necessary criteria were fulfilled under Art. 13a of Directive 2001/82/EC (well-established use). Bibliographic data has been provided in order to cover all aspects of the safety and/or efficacy assessment of the product for the proposed indication in the target species using the proposed route of administration and dosage regimen.

According to the MAH, the submitted published reports provided sufficient comfort relating to the safety and efficacy of different fipronil spot-on products, such that any quantitative differences in active ingredient content or quantitative/qualitative differences in excipient content between products would not result in different safety or efficacy outcomes.

The MAH disagreed with the previous CVMP conclusion that differences in the formulation between Fiprex and other fipronil-containing products would impact on the absorption, the rate and extent of distribution, and persistence of the active substance on the target species. To this effect, the MAH provided a comparison of the differences in formulation between various fipronil-containing products and outlined the similarities in their indications. The major point put forward by the MAH was that insecticidal activity is high in both dogs and cats, irrespective of the formulation; products are effective for up to 8 weeks in dogs and up to 5 weeks in cats. In the case of ticks, the MAH asserted that the data for *Rhipicephalus* spp. allowed for the establishment of a 4-week period of acaricidal activity. The MAH further outlined studies submitted on behalf of various generic products, which showed that each product had acceptable efficacy compared to the originator product on the EU market, despite differences in excipient content.

The MAH felt that CVMP erred when refusing to assess the submitted pharmacovigilance data relating to other authorised fipronil-containing products manufactured by the same company that manufactures Fiprex (i.e. Vet-Agro). The MAH highlighted paragraph 3.5 of Title III of Directive 2009/9/EC which states that: "*Post-marketing experience with other products containing the same constituents is of particular importance and applicants shall put a special emphasis on this issue.*"

#### **CVMP conclusions after the re-examination**

The CVMP assessed the detailed grounds for re-examination presented by Vet-Agro Trading Sp. z o.o. related to the legal requirements for a well-established use application.

The Committee also confirmed that the active substance fipronil has a low order of toxicity and no specific safety concerns exist in terms of the Fiprex spot-on formulations.

In relation to clinical efficacy, the published literature demonstrates that even minor differences in formulation can significantly affect the duration of product efficacy. The duration of efficacy for currently authorised fipronil-containing spot-on products varies from 4-8 weeks for fleas and 1-4 weeks for different tick species. The CVMP had no data available to conclude upon the appropriate duration of efficacy for Fiprex. In addition, the available published literature did not allow for such a conclusion as Fiprex is qualitatively and quantitatively different from other authorised fipronil-containing products.

The pharmacovigilance data submitted by the MAH did not meet the standard of published, peer-reviewed post-marketing data, i.e. controlled studies or epidemiological studies, as required by the legislation, and therefore could not be considered in the frame of this assessment.

Having reviewed the documentation submitted by the MAH, the CVMP concluded that there were not sufficient scientific grounds to revise its conclusions of 11 December 2013, and that the overall benefit-risk balance for the range of Fiprex spot-on formulations is negative.

## **Grounds for the refusal of the granting of marketing authorisations and for suspension of the existing marketing authorisations**

Whereas

- The CVMP considered that the data submitted in support of this application are adequate to support the safety of the Fiprex spot-on formulations in the target species;
- The CVMP considered that the data submitted is insufficient to conclude on the efficacy of Fiprex, particularly in terms of duration of efficacy;
- The CVMP considered, on the basis of the data submitted in support of this application, that it is not possible to establish a positive benefit-risk balance for this product.

Therefore, the CVMP recommended the refusal of the granting of the marketing authorisation for Fiprex CAT 52.5 mg spot-on solution for cats, Fiprex S 75 mg spot-on solution for dogs, Fiprex M 150 mg spot-on solution for dogs, Fiprex L 300 mg spot-on solution for dogs, Fiprex XL 412.5 mg spot-on solution for dogs and the suspension of the existing marketing authorisations (see Annex I).

The condition for lifting the suspension of the marketing authorisations is described in Annex III.

## **Annex III**

### **Condition for lifting the suspension of the marketing authorisations**

National Competent Authorities, coordinated by the reference Member State, shall ensure that the following condition is fulfilled by the marketing authorisation holder:

- Appropriate efficacy data, in accordance with legislative requirements and with regard to the relevant CVMP guidelines, should be provided in support of the claimed indications for Fiprex CAT 52.5 mg spot-on solution for cats, Fiprex S 75 mg spot-on solution for dogs, Fiprex M 150 mg spot-on solution for dogs, Fiprex L 300 mg spot-on solution for dogs and Fiprex XL 412.5 mg spot-on solution for dogs.