Divergent position on a Final CVMP opinion on an Article 33(4) referral of Directive 2001/82/EC for

Fiprex CAT 52.5 mg spot-on solution for cats, and 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 (EMEA/V/A/099)

Further to a referral notification from Ireland, on 11 December 2013 the CVMP adopted an opinion recommending refusal of the granting of the marketing authorisations and the suspension of the existing marketing authorisations for the above mentioned veterinary medicinal products.

On 20 December 2013, the marketing authorisation holder Vet-Agro Trading Sp. z o.o. submitted to the Agency a request for the re-examination of the CVMP opinion. The outcome of the discussion on the re-examination on 9 April 2014 led finally to a negative final CVMP opinion.

The undersigned agrees with the CVMP that the legal basis of the application under Art. 13a of Directive 2001/82/EC (well established use) was valid. The active substance fipronil has a low order of toxicity and no specific safety concerns exist in terms of the Fiprex spot-on formulations. It is also agreed that the clinical data from the proprietary study by Studzinska *et al*. (2007) are not reliable, and therefore do not provide data on the efficacy and safety of Fiprex spot-on solutions for the target species and indications sought. Similarly, the two other proprietary studies referred to by the MAH, Depta A, Nowicki M (2005) and Depta A, Nowicki M (2006) cannot be considered sufficiently robust to support efficacy of the product. The undersigned also shares the opinion that the quality of data on "*in vitro* testing" is rather poor and not sufficiently suited to prove the physicochemical and consequently PK properties of a product.

The CVMP concluded that the existing differences in excipients can markedly affect the duration of product efficacy. Therefore the claimed indication period (4 weeks persistent activity against fleas and 1-3 weeks persistent activity against ticks) is not considered scientifically justified by the Committee.

However, the undersigned does not support the CVMP conclusion due to the following:

- Based on this type of application the efficacy of the product may be justified by referring to the data available in the public domain related to the originator product on the market and other spot-on products containing fipronil as an active pharmaceutical ingredient. To this end, the applicant has submitted published scientific literature, including published controlled studies comparing efficacy of originator product on the market as a positive control to other formulations against tick and flea infestations in dogs and cats as well as comparison of the marketing authorisation conditions (efficacy claims provided for in the SPCs) for fipronil-containing products currently authorised in the EU. Based on the literature by J Riviere and M G. Papich (2009), efficacy of fipronil containing products is mainly influenced by the amount of fipronil applied. With this respect, it should be noted that administration of the Fiprex formulation delivers a slightly (5%) higher amount of fipronil to the animals treated as compared to originator product on the market.

- Comparability of the excipients: There is no doubt that formulation components of topically applied drugs display a significant influence on dermal absorption, persistence, transdermal delivery, distribution and other PK parameters. However, the originator product on the market and Fiprex are highly comparable with regard to total dose of the active substance, the crystallisation inhibitors, organic solvents and co-solvents. There are minor differences in terms of strength, volume of the product administered to the animals, quantitative composition (e.g. amount of butylhydrohytoluen and butylhydroxyanisol) and alcohols used (e.g. isopropyl alcohol in Fiprex vs. ethanol in the originator product on the market) as well as polysorbate 80 (in the originator product on the market only).
  There are further fipronil-containing products which indeed differ more from the originator product on the market than Fiprex, either due to the absence of the crystallisation inhibitor Povidone or due to the use of the strong dermal penetration enhancer DMSO. Therefore, regarding the chemical and physical knowledge about the characteristics of the ingredients of all the compositions used in the different medicinal products there are no relevant differences in the composition (and characteristics) of Fiprex compared to e.g. the originator product on the market. Also cited by Baynes and Riviere (2012) the variability in efficacy observed between and within breeds is mainly attributed to season, sex and skin physiology.

With respect to excipients it is further noted that:

- The reference by Baynes and Riviere (2012) cited in the final CVMP assessment report is a general reference not related specifically to fipronil but generally to the topical veterinary dosage forms. It should be recognised that fipronil due to its physico-chemical properties has a very limited potential to be systemically absorbed concentrates in the pilo-sebaceous units, stratum corneum and viable epidermis. This evidence has been published in several scientific articles and it includes radiolabelled studies in dogs and cats. As a result, the information available in the reference by Baynes and Riviere (2012) cited in the final CVMP assessment report should be interpreted in the context of the other scientifically relevant information, in particular physico-chemical properties of the active ingredient (fipronil).
- In addition, other scientific papers (cited below) show that the composition of excipients has no significant effect of the efficacy of permethrin-containing spot-on formulations.
- Published controlled studies comparing efficacy of the originator product on the market spot-on product with the other fipronil based formulation provide further scientific evidence of a limited role of excipients for the efficacy of fipronil-based spot-on products.

- Aspects on the claimed indication periods: There are around 600 publications investigating the active substance fipronil and published evidence is still growing. These published data clearly support the consistent efficacy against fleas where e.g. the originator product on the market has been used as comparator against other formulations. This is supported by the fact that no negative reports indicating lack of efficacy of different formulations when compared to the originator product on the market could be found in the scientific literature. Even different formulations of various fipronil-containing spot-on products led to comparable efficacy with regard to fleas, whereas in contrast differences in excipients have a much more profound effect on the persistence of acaricidal activity.
- Scientific considerations: Lüssenhop J. *et al*. 2011 describes that vehicles for pyrethroid active substances do not play a role in absorption and distribution. This is explained by the fact that fipronil is lipophilic (log P is ~ 4.4) and stored in the sebaceous glands and

gradually released via follicular ducts. The surface translocation (so-called spreading) of fipronil over the entire body through the sebaceous secretions explains its persistence with resistance to e.g. shampooing.

- The assessment of the bibliographic dossiers should
    - be case-specific;
    - take into account totality of the data available in the public domain,
      take into account post-marketing experience with other products with similar composition.

Conclusion by the undersigned:

- the importance of the composition of excipients for topical spot-on formulations is recognised, however, in this specific case, the data regarding efficacy published in the literature for the fipronil based spot-on products can be bridged and the efficacy for the Fiprex product can be justified based on the following major lines of evidence: amount of fipronil delivered by the Fiprex formulation is higher than for the comparable formulations without any negative consequences for the product's safety;
- physico-chemical properties of the active ingredient – fipronil – result in the concentration of this compound in the specific parts of the skin and in a slow release of this compound over a period of time;
- the role of excipients may be of limited importance as directly evidenced for permethrin containing spot-on products and also indirectly for fipronil containing spot-on products.

The totality of the data presented by the applicant and availability of published scientific literature enable the conclusion of a positive benefit-risk against fleas up to 28 days as the available evidence suggests that variation of efficacy for fleas is less dependent on the used excipients.

The data do not permit bridging the information for the efficacy against ticks as the available evidence indicates that excipients for the fipronil-based spot-on products may have a higher influence in case of this efficacy claim.

London, 9 April 2014

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