European Medicines Agency
Veterinary Medicines and Inspections

ANNEX I

NAME, PHARMACEUTICAL FORM, STRENGTH OF THE MEDICINAL PRODUCT, ANIMAL SPECIES, ROUTES OF ADMINISTRATION, AND MARKETING AUTHORISATION HOLDER

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Member State	Applicant or Marketing Authorisation Holder	Product invented name	Pharmaceutical form	Strength	Animal species	Frequency and route of administration	Recommended dose
The Netherlands, Belgium, Germany, France, Italy, Spain and the United Kingdom.	ACE Pharmaceuticals BV Schepenveld 41 3891 ZK Zeewolde The Netherlands + 31 36 522 7201 + 31 36 522 9096 fs@ace-pharm.nl	Enurace 50	Tablets	50 mg	Female dogs	For oral administration only, to be administered with food	A starting dose of 2 mg Ephedrine HCl per kg of bodyweight per day, divided in two oral doses is recommended.

ANNEX II

SCIENTIFIC CONCLUSIONS

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1. Introduction and background

Enurace 50 was first authorised in The Netherlands on 15 September 2000. A Mutual Recognition Procedure started on 29 June 2006 with The Netherlands as Reference Member State and Belgium, Germany, Spain, France, Italy and the United Kingdom as Concerned Member States. The application was made in accordance with Article 12.3 of Directive 2001/82/EC as a stand alone application.

At Day 90 of the MRP, 27 September 2006, France and Italy could not agree to the granting of a marketing authorization as they consider there are potentially serious risks for animal health. The matter was referred to the Co-ordination Group for Mutual Recognition and Decentralised Procedures CMD(v) for a 60 day procedure in accordance with Article 33(1) of Directive 2001/82/EC, as amended. This procedure ended on 28 November 2006. CMD(v) could not reach an agreement by day 60 of this procedure, as France and Italy maintained their concerns. Consequently the matter was referred to the CVMP.

France considers the risk/benefit analysis unfavourable for the animal when the adverse effects (in very rare cases atrium fibrillation and tachycardia) are weighed against the potential benefits of effective treatment of incontinence.

Italy could accept the application with revised wording in the SPC .

The CVMP during its meeting of December 2006 started a referral procedure under Article 33(4) of Directive 2001/82/EC as amended for Enurace 50. The Marketing Authorisation Holder should provide all supporting data (preclinical and clinical documentation, including the expert reports, efficacy and tolerance studies conducted), to justify a positive benefit-risk ratio for the treated animal.

2. Discussion

For the reason of very limited treatment options, high risk of euthanasia if treatment fails or is not affordable, ephedrine is a substance of other eventual choice - Propalin instead Enurace and *vice versa*, considering that sympathicomimetic treatment of urinary incontinence is far better than hormonal treatment (an alternative is surgical therapies as colposuspension, urethropexy and the endoscopic injection of collagen in refractory cases). Proposed dose of 1 – 3 mg Ephedrine HCl /kg/day, divided in two oral doses is effective and safe, but some animals may need a higher dose, which is associated with individual variation in the response to ephedrine. Indeed, treatment is not successful in all animals, but the level of efficacy is such that there is an advantage in treatment.

Taking the benefit of the treatment into account and the relatively low level of adverse effects, as it appears from PMS studies, the risk/benefit balance is considered favourable.

Enurace has been officially authorised since 2000 (since 1995 available in the Netherlands). Since 1998 post-marketing studies have been performed as well as regular monitoring of adverse effects by FAQ system.

There is no doubt that treatment of the dog with Enurace may involve an occurrence of adverse reactions due to peculiar activity of ephedrine. The use of human labelled preparations or dosage forms obtained from a compounding pharmacy which contain ephedrine constitute a much more dangerous alternative for treatment of urinary incontinence in dogs if the product with a marketing authorisation and a proved efficacious use in the RMS for many years is not available.

The data provided by the applicant show that Enurace 50 is an effective medicinal product for treatment of urinary incontinence in ovariohysterectomised bitches.

Considering safety, the product seems not to create a considerable risk to young and healthy animals. However, in Europe ovariohysterectomy is most frequently performed in middle aged and old bitches. Taking into account that urinary incontinence may occur even several years after the operation it can be suspected that Enurace would be used mostly in older animals, more frequently suffering form cardiovascular, liver, renal and other diseases. Although the influence of age was not reflected in the tolerance studies, it was taken into account in the efficacy and post- marketing studies. Regarding cardiac dysfunction, this was one of the exclusion criteria so the studies give no information on use of the product in animals with such a condition but there is also no data suggesting that the cardiac patients must not be treated with the substance. Possible risk connected with the use of ephedrine in this group of animals can be reduced by appropriate management measures.

3 Conclusion and Recommendation

In response to the questions related to toxicity, the applicant argues that due to the pharmacologic effect of ephedrine and the individual variation in receptor density no safety margin can be determined and increasing doses will be associated to increased intensity and frequency of well known adverse effects. This conclusion is accepted. Although toxicity data for the target animal may be scarce, the adverse effects connected to ephedrine treatment are well known from human use, and the applicant has provided some post-marketing information regarding the use in dogs. At the recommended dose level, which according to the suggested SPC should be individually adjusted, safety is ensured to a reasonable level.

With regard to the related to cardiovascular diseases, the SPC is to be modified under section 4.5 to include the sentence “the dog’s cardiovascular functionality should be carefully assessed before the start of the treatment with Enurace 50 and it should be periodically monitored during the treatment”.

Efficacy data are connected to several shortcomings and the amount of data available is sparse. However, the study where Enurace 50 is compared to Propaline (ACE129802) is convincing although a non-inferiority analysis has not been performed. The raw outcome shows good effect in both test and control groups (87% vs 85.5%), an effect that might be somewhat higher in treatment naïve animals (93.7% vs 88.9%). These figures seem highly convincing when compared to the 20 % placebo treated animals that became continent in study ACE129801.

The CVMP has concluded that the risk/benefit for this product is favourable.

The valid Summary of Product Characteristics, labelling and package leaflet are the final versions achieved during the Coordination Group procedure with the following amendment:

Section 4.5 of the SPC and Section 12 of the Package Leaflet:

ANNEX III

SUMMARY OF PRODUCT CHARACTERISTICS, LABELLING AND PACKAGE INSERT

4.5. Special precautions for use

The dog’s cardiovascular functionality should be carefully assessed before the start of the treatment with Enurace 50 and it should be periodically monitored during the treatment.

12. SPECIAL WARNING(S)

The dog’s cardiovascular functionality should be carefully assessed before the start of the treatment with Enurace 50 and it should be periodically monitored during the treatment.