ANNEX I

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

Member State	Applicant or Marketing Authorisation Holder	Product invented name	Pharmaceutical form	Strength	Animal species	Frequency and route of administration	Recommended dose
Netherlands, Austria, Belgium, Denmark, Finland, France, Germany, Greece, Hungary, Ireland, Italy, Luxembourg, Norway, Poland, Portugal and Spain.	Le Vet B.V. Williskop 212 3421 GW Oudewater The Netherlands	Equimectin	Oral gel	12mg/g	Horses	Oral use. A single administration of 0.2 mg ivermectin per kg of odyweight. Retreatment should be done according to the epidemiological situation, but not at less than 30 days interval	A single administration of 0.2 mg ivermectin per kg of bodyweight.

ANNEX II

SCIENTIFIC CONCLUSIONS

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The current application cannot be considered satisfactory as there is no scientific basis on which to grant an authorisation with the proposed SPC.

No data were provided concerning the efficacy against ectoparasites.

The wording of the proposal for Section 4.2 of the SPC is not supported. The statement 'The treatment of gastrointestinal endoparasite infections in horses' implies that **all** gastrointestinal endoparasite infections in horses are treated with this product; 'particularly' implies that the product has a specific action against those species listed. It is not practical for an SPC for an equine wormer to only indicate use of the product against 5 specific parasites that do not include the important Strongylus genus in horses, but to imply that the product has efficacy against a wider population of parasites. Therefore, this product would not be considered interchangable with other ivermectin containing products already on the market.

The indication proposed cannot be accepted. The effect against e.g. the large strongyles that are important parasites in the horse is not supported by the presented data and moreover, as the effect on the L4 stage of the small strongyles is not substantiated, the period between necessary prophylactic deworming will be significantly shortened. Ivermectin containing pastes/oral gels for horses are well established on the market and the prescriber/animal owner would expect Equimectin to be interchangeable with other available products of the avermectin class. This has not been shown, and in fact the indication is so restricted that the product could not be used for routine deworming in the horse. Thus the proposal from the MAH, although scientifically justified, remains practically very questionable.

Based on the following, interchangeability with other ivermectin containing products cannot be accepted:

The documentation submitted with this application consists of literature referring to the use of the originator product Eqvalan, a comparative pharmacokinetic study using Equimectin and Eqvalan, and a supplementary clinical field study.

During the referral procedure, it has been established that the submitted bioequivalence study was inadequate to demonstrate bioequivalence (as defined in current guidance EMEA/CVMP/016/00-corr-FINAL), however from the comparative pharmacokinetic data it is possible that the test product is systemically less bioavailable than the reference product. Therefore the relevance of the bibliographical data regarding Eqvalan to the test product cannot be confirmed. The residue data provided was inadequate and the withdrawal period is therefore inadequately supported.

A single field study was submitted in support of the efficacy of the product. There is no reference in the Marketing Authorisation Holder's responses to the study that generated the results tables. If it is assumed that the tables submitted in the response dossier refer to the results from the field study submitted in the original dossier, then these data are inadequate and therefore irrelevant due to the following reasons:

- The principle criteria used for a comparison of effect is egg count reduction/larval identification or parasite counts in dose confirmation studies. The test procedure did not follow the methods for a controlled or critical test. This does not comply with the recommendations of the current guidance document (CVMP/VICH/832/99), 'where pharmacokinetic parameters cannot demonstrate a relationship with effectiveness, two dose confirmation studies using the dose limiting parasite for therapeutic claims ….. will be needed.' For dose confirmation studies, 'at least two controlled or, where appropriate, critical dose confirmation studies ….. are recommended.' Efficacy could be claimed if effectiveness against each parasite declared on the labelling was at 90% or above based on calculation of geometric means and there was a statistically significant difference in parasite numbers between control and treated horses.

- The tables included in the response dossier do not indicate which parasites are referred to, and there is no break down of species of parasite.

- The dose-limiting parasite had not been specified or selected. It is known that there is a potential resistance build up to ivermectin in *Parascaris equorum*, however the highest number of *P. equorum* may be found in grazing horses 3-18 months old. The youngest horse included in the field trial was 16 months old. *Parascaris equorum* should have been selected as the dose limiting parasite.

- Based on the type of study conducted, the background exposure of the ponies included in the trial was not stated therefore the adequacy of the infections cannot be documented. The number of horses with an adequate infection pretreatment is impossible to determine as no negative control group was included.

- The number of horses recruited was too low to produce meaningful results. The WAAVP guidelines state that, for a field trial, data from at least 100 horses should be obtained in each of 3 different areas.

- This was not a multicentric trial.

- The mean dose of test product administered was consistently and significantly more (40%, 0.278mg/kg) than the recommended treatment dose. Efficacy should have been investigated at the lowest dose recommended. The dose of Eqvalan was found to be 10% higher in the field trial than indicated.

- The test product demonstrated lower bioavailability compared to Eqvalan, the cited reference product, during the bioequivalence study, and the test product was administered at greater than the recommended treatment dose in the field study. Therefore, if the product is administered at the recommended dose rate, there is the possibility of lack of efficacy and the potential for anthelmintic resistance.

- Although non-inferiority was demonstrated to Eqvalan, this is not a recognised measure of efficacy of a new product. Relative reductions for the number of eggs per gram of faeces for the test product were calculated as 88.2% against Strongylus type eggs on day 3, and 88.2% at day 8. For Parascaris type eggs, the results were 50% by day 3 and 65.2% by day 8. The results for efficacy of Eqvalan measured this way were also below 90%. The results were not divided for each parasite species. These results were below the accepted 90% or higher and, as there was no control group to compare the differences in parasite counts statistically, which should be significant at $p<0.05$, it is not possible to determine the efficacy of Equimectin from this study. The Marketing Authorisation Holder re-examined the data from this study and stated that on day 6 after treatment no small nor large strongyle larvae were detected in a minimum amount of 25 gram faeces indicating 100% efficacy for all animals, and the recalculated effectiveness against Strongylides is >> 90% on 2 and 7 days after treatment. Based on the critical test performed, the efficacy against Parascaris was 100%. The relative egg reductions calculations do not reflect these findings, particularly regarding *P. equorum*. Without necropsy or a large sample size, it is impossible to draw any meaningful conclusions from this study regarding the efficacy of Equimectin.

The Committee, having considered the matter, concluded that on the basis of the available data for Equimectin bioequivalence with the reference product has not been shown. The efficacy of the product for the treatment of endo- and ectoparasitic infections has not been demonstrated. Even the amended indication for the treatment of gastrointestinal endoparasitic infections in horses has not been demonstrated by the data provided.

The CVMP recommended the refusal of the granting of the Marketing Authorisation and the suspension of the Marketing Authorisation for Equimectin where appropriate.

ANNEX III

CONDITION FOR THE LIFTING OF THE SUSPENSION

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The bioequivalence with the originator product should be demonstrated by appropriate bioavailability study or adequate data should be provided with regard to residues and efficacy for this kind of application and the results of such study or such data should be submitted to the relevant national authority for further assessment.