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Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use

CVMP assessment report for Prevomax (EMEA/V/C/004331/0000)

International non-proprietary name: maropitant

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

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Introduction

The applicant Le Vet Beheer B.V. submitted on 15 April 2016 an application for a marketing authorisation to the European Medicines Agency (The Agency) for Prevomax 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 6 November 2015 as the product would constitute a generic product of a product authorised through the centralised procedure Cerenia (reference product). The applicant is registered as an SME pursuant to the definition set out in Commission Recommendation 2003/361/EC. The rapporteur appointed is Sylvie Louet and the co-rapporteur is Cristina Muñoz Madero.

The applicant applied for the following indications:

Dogs

- For the treatment and prevention of nausea induced by chemotherapy.
- For the prevention of vomiting except that induced by motion sickness.
- For the treatment of vomiting, in combination with other supportive measures.
- For the prevention of perioperative nausea and vomiting and improvement in recovery from general anaesthesia after use of the μ-opiate receptor agonist morphine.

Cats

- For the prevention of vomiting and the reduction of nausea, except that induced by motion sickness.
- For the treatment of vomiting, in combination with other supportive measures.

The active substance of Prevomax is maropitant, a neurokinin 1 (NK1) receptor antagonist, which acts as an antiemetic by inhibiting the binding of substance P, a neuropeptide of the tachykinin family. The target species are dogs and cats. Prevomax is presented as a solution for injection (for intravenous or subcutaneous use) containing 10 mg/ml maropitant. The primary packs are amber multidose glass vials containing 10 ml, 20 ml, 25 ml or 50 ml solution for injection. The secondary (outer) pack is a cardboard carton containing 1 vial.

The dossier has been submitted in line with the requirements for submissions under Article 13(1) of Directive 2001/82/EC – a generic application. The reference product is Cerenia 10 mg/ml solution for injection for dogs and cats (EU/2/06/062/005), which was first authorised by the European Commission on 29 September 2006.

The CVMP adopted an opinion and CVMP assessment report on 12 April 2017.

The European Commission adopted a Commission Decision granting the marketing authorisation for Prevomax on 19 June 2017.

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 (dated 2015/01) 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

The manufacture of the dosage form takes place at a duly authorised site in the EEA. Manufacturing for batch release takes place in the Netherlands, at Produlab Pharma B.V. A GMP certificate issued by the Ministry of Economic Affairs of the Netherlands on 18 May 2015 has been provided. This confirms that the proposed site is authorised for manufacturing for batch release of parenteral solutions. The last inspection took place in March 2015.

The manufacturer of the active substance maropitant is in the EEA. A GMP declaration for the active substance manufacturing site was provided from the Qualified Person (QP) at the EU batch release site. The declaration was based on an on-site audit by the manufacturing site responsible for batch release.

Overall conclusions on administrative particulars

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

The GMP status of both the active substance and finished product manufacturing sites has been satisfactorily established and are in line with legal requirements.

Part 2 - Quality

Composition

The product is an aqueous solution for injection containing 10 mg/ml maropitant.

The other ingredients present in the formulation are: benzyl alcohol, betadex sulfobutyl ether sodium, citric acid anhydrous and sodium hydroxide, and water for injections. The list of excipients is included in section 6.1 of the SPC.

Containers

The product is presented in amber type I multidose glass vials containing 10 ml, 20 ml, 25 ml or 50 ml. The vials are closed with coated bromobutyl rubber stoppers and aluminium caps. Each vial is then placed in an outer cardboard box (containing a package leaflet). The pack sizes are consistent with the dosage regimen and duration of use.

The primary packaging materials (glass vials and bromobutyl stoppers) 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.

Development pharmaceutics

The objective of the pharmaceutical development program was to develop a generic solution for injection of maropitant, based on the reference product Cerenia.

Information on the choice of excipients in the formulation, the preservative concentration and the sterilization method of the product has been presented in a satisfactory manner. Clarification on the structure of the complexing agent has been provided. The efficacy of the preservative in the formulation at its lower concentration limit has been satisfactorily demonstrated, in accordance with the Ph. Eur. chapter 5.1.3. Additionally, comparative physicochemical data and information on the impurity profiles of both this and the reference product have been provided and show similarity.

The use of amber glass for the primary packaging for the finished product has been justified based on the results of a photostability study performed in accordance with option 1 of the relevant VICH Guideline.

Method of manufacture

The manufacturing process is considered a standard one. All the components are successively dissolved in water for injections under stirring. The bulk solution is then filtered and terminally sterilised in the final container by autoclaving, according to standard Ph. Eur. conditions.

The manufacturing process has been satisfactorily described, and the proposed in process controls are considered adequate. Holding times before filtration and for filled vials before autoclaving have been validated and are therefore justified.

Validation data on two production scale batches has been provided, and the results comply with the proposed release specification.

The process is capable of producing the finished product of intended quality in a reproducible manner. A larger production scale batch will be validated post authorisation to ensure the consistency of the manufacturing process.

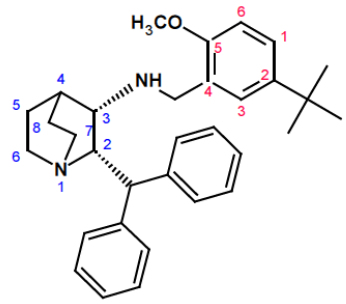
Nitrogen (low oxygen) is used during the production process of the finished product but only because it is standard practise at the manufacturing site. Confirmation has been provided that its quality complies with the relevant Ph. Eur. requirements.

Control of starting materials

Active substance

The chemical name of maropitant is [*(2S,3S)*-2-Benzhydryl-1-aza-bicyclo[2.2.2]oct-3-yl]

-(5-tert-butyl-2-methoxybenzyl)-amine and it has the following structure:



The active substance is a white to off-white powder, soluble in alcohol and practically insoluble in water.

Maropitant exhibits stereoisomerism due to the presence of 2 chiral centres. Enantiomeric purity is controlled routinely by chiral HPLC. The absence in the specifications of a test for optical rotation has been justified.

Polymorphism has been observed for maropitant, but only one polymorph is produced.

The information on the active substance is provided according to the Active Substance Master File (ASMF) procedure. The characterisation of the active substance and its impurities are in accordance with the guideline on the Chemistry of new active substances (CPMP/QWP/130/96-Rev.1). Potential and actual impurities were well discussed with regards to their origin and were characterised.

Adequate in-process controls are applied during the synthesis. The specifications and control methods for intermediate products, starting materials and reagents have been presented.

Maropitant is synthesised using well defined starting materials with acceptable specifications.

Detailed information on the manufacturing of the active substance has been provided in the restricted part of the ASMF and was considered satisfactory.

The active substance specification includes tests for: appearance, appearance of solution, identity (IR, HPLC), assay (HPLC), pH, impurities (HPLC), residual solvents (GC), loss on drying (Ph. Eur.), metal residues, sulphated ash (Ph. Eur.), enantiomeric purity (HPLC), microbial contamination (Ph. Eur.) and bacterial endotoxins (Ph. Eur.).

The analytical methods used have been adequately described and appropriately validated in accordance with VICH guidelines GL1 and GL2.

Satisfactory information regarding the reference standards used for the assay and impurities tests has been presented.

Batch analysis data from 3 production batches of the active substance have been provided. The results are within specification and consistent from batch to batch.

The proposed container offers an adequate protection of the active substance, and the data provided confirm its suitability.

Stability data on 3 batches have been initiated under long term (25 °C/65% RH), intermediate (30 °C/65% RH) and accelerated conditions (40 °C/75% RH). Results from up to 12 months storage are available. Although some tests in the specification were not conducted at certain time points during the stability study, justification was provided and considered acceptable.

Results from testing under stress conditions were also provided.

The parameters tested during stability testing are the same as in the active substance specification. The

analytical methods used were the same as for the active substance specification and were stability indicating.

All tested parameters were within the specification. The stability results indicate that the active substance manufactured by the proposed supplier is sufficiently stable. The stability results also justify the proposed retest period of 2 years with no storage precaution in the proposed container (double LDPE bags).

Excipients

Betadex sulfobutyl ether sodium is not described in the European Pharmacopeia, or in the pharmacopeia of an EU member state. It is however described in the USNF and reference to this monograph is made by the applicant. The specification and associated methods are considered acceptable.

All other excipients are well known pharmaceutical ingredients and their quality is compliant with their respective Ph. Eur. monographs.

No novel excipient is used in the finished product formulation.

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

The product does not contain any materials derived from human or animal origin. The product is therefore out of scope of the relevant Ph. Eur. monograph and 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).

Control tests on the finished product

The proposed specifications contain tests suitable for this type of dosage form: appearance, pH, density, identification and content of the active substance, related substances content, enantiomeric purity, identification and content of the preservative, fill volume and sterility. The specifications and limits proposed are considered appropriate to control the quality of the finished product. The total impurity content is supported by the batch data provided, and skip testing for related substances content and enantiomeric purity will be considered justified once satisfactory data on 5 additional production batches have been collected. Confirmation has been provided that those parameters will be tested at least once a year thereafter.

The analytical methods used have been adequately described and appropriately validated in accordance with the relevant VICH guidelines.

Satisfactory information regarding the reference standards used for assay and impurities testing has been presented.

Batch analysis results are provided for 2 production scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

The proposed shelf life specification includes tests suitable for this type of dosage form, and is considered acceptable.

Stability data were provided from samples of 2 production scale batches of the finished product stored under refrigerated (5 °C) conditions for 6 months, long term conditions for 12 months at 25 °C/60% RH, and for up to 6 months under accelerated conditions at 40 °C/75% RH, in accordance with VICH guideline GL3. The bracketing principle was followed (the stability study was performed on the smallest and largest proposed pack sizes, that is, the 10 ml and 50 ml presentations). The product was packaged in the same primary packaging as proposed for marketing. The study will be continued for up to 60 months.

Control parameters and analytical methods used are the same as those used for the control of the finished product at release. The analytical procedures used are stability indicating. No significant changes were observed.

Photostability was evaluated as recommended in VICH guideline GL5. The proposed primary packaging (amber glass vials) has been demonstrated to offer sufficient light protection to the product.

Based on the available stability data, a shelf life of 2 years with no special storage conditions, as stated in the SPC, was considered justified.

An in-use stability study was performed up to 56 days (after first opening) on 2 newly manufactured batches (1 month old) of the product, and will be repeated when the batches are close to the end of their shelf lives. The study was performed on the 50 ml vial presentation, and samples of the solution were regularly removed from the vial to mimic use of the product. The broached vials were stored at 25 ºC/75% RH, and analysis of the remaining solution was performed after 28 days and 56 days. A repeat preservative efficacy test was performed after 28 days. All the results after 56 days complied with the shelf life specification, so an in-use shelf life of 56 days was considered justified.

Overall conclusions on quality

Prevomax is an aqueous solution for injection containing 10 mg maropitant per ml. The composition has been justified. The product is presented in amber glass multidose vials sealed with a rubber stopper. The use of amber glass vials has been justified. A range of sizes of vials from 10 ml to 50 ml were proposed and have been satisfactorily justified.

The development pharmaceutics of the formulation has been suitably explained.

The manufacturing process of the finished product has been sufficiently described and validated using production scale batches.

Suitable data have been provided (via the ASMF procedure) on the manufacture and control of the active substance.

Betadex sulfobutyl ether sodium is not described in the Ph. Eur. or any pharmacopoeia of an EU member state; however, it is described in the USNF, and its specifications comply with those requirements. All the other excipients meet their respective current Ph. Eur. requirements.

The proposed finished product specifications, both at release and end of shelf life, are acceptable.

Certificates of analysis have been provided for 2 production scale batches manufactured at the site proposed for commercial manufacture, and include results for each vial size.

Stability data on the finished product have been produced under VICH conditions. To date data have been provided from up to 12 months storage under long term conditions and from up to 6 months storage under accelerated conditions. The results currently support a proposed shelf life of 2 years without any special storage precautions.

Results from an in-use stability study have been provided which support the in-use shelf life of 56 days after first opening.

Based on the review of the data on quality, the manufacture and control of Prevomax are considered acceptable.

In addition, the applicant is recommended to provide the following information post-authorisation:

1. A production scale batch will be validated post authorisation to ensure the consistency of the manufacturing process. The relevant authorities should be informed immediately if any results are outside specification.
2. The impurity content of the 5 first production batches of the finished product should be tested and shown to be within the specification limits before skip testing can be performed. Impurity content testing should then be performed at least once a year thereafter. The relevant authorities informed immediately if any results are outside specification.
3. The enantiomeric purity content of the 5 first production batches of the finished product should be tested and shown to be within the specification limits before skip testing can be performed. Enantiomeric purity content testing should then be performed at least once a year thereafter. The relevant authorities informed immediately if any results are outside specification.
4. The in-use stability study should be repeated when the 2 batches of the finished product (in the in-use stability study) are close to the end of their shelf lives. The relevant authorities informed immediately if any results are outside specification.

Part 3 – Safety

Since this is an application based on Article 13(1) of Directive 2001/82/EC (generic application) and bioequivalence with the reference product has been established (see part 4, bioequivalence), the results of the toxicological or pharmacological tests are not required.

The applicant has provided a new user safety assessment and a phase I environmental impact assessment according to the relevant guidelines.

To ensure comprehensive adverse event surveillance and to benefit from the possibility to align periodic safety update report (PSUR) submission for generic products as foreseen in the legislation, it is recommended that the applicant synchronises the PSUR submissions for Prevomax according to the reference product Cerenia, which is currently on a three-yearly cycle. The next data lock point (DLP) for the Prevomax PSUR should therefore be 31 December 2017.

Tolerance in the target species of animal

See Part 4.

The pharmaceutical product is not identical to the reference product since new excipients are used. These excipients are well-known and widely used in pharmaceutical products intended for human and veterinary use, and not expected to be of concern for the target species.

User safety

A user safety assessment has been performed according to the Guideline on user safety for pharmaceutical veterinary medicinal products (EMA/CVMP/543/03-Rev.1).

Information has been provided on the acute toxicity on laboratory animals, the repeated dose toxicity, the reproduction toxicity, the mutagenicity and the eye and dermal irritation. The new excipients (as compared to the reference product) used in the product are well-known and widely used in other pharmaceutical products. These excipients do not represent a particular risk for the user.

For exposure scenario, dermal, ocular and accidental self-injection exposure are identified. The levels of the different exposures allow calculating a quantitative risk which results in no changes to the risk management sentences that are already present in the SPC of the reference product.

Based on this assessment, the fact that this is an application based on Article 13(1) of Directive 2001/82/EC and considering that bioequivalence with the reference product has been established, it is considered acceptable to keep the same mitigation measures as those present of the SPC of the reference product.

Environmental risk assessment

The Environmental Risk Assessment (ERA) of the pharmaceutical product was performed according to the relevant guidelines (VICH guidelines GL6 and GL38 and CVMP Guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH guidelines GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1).

The conclusion is that the ERA can stop at phase I and no phase II is required because the veterinary medicinal product will only be used in non-food animals.

The product is not expected to pose a risk for the environment when used according to the SPC.

Overall conclusions on the safety documentation

As this is a generic application submitted according to Article 13(1) of Directive 2001/82/EC as amended, and bioequivalence with the reference product has been established (pharmaceutical equivalent composition), results of toxicological or pharmacology tests are not required. The excipients used in the formulation are well-known and widely used in pharmaceutical products intended for human and veterinary use, and not considered to be of concern.

A user risk assessment and an environmental risk assessment have been provided as required for this type of applications.

Based on the user safety assessment and the type of application it is acceptable to keep the same mitigation measures as those present in the SPC of the reference product.

The environmental risk assessment can stop at phase I. The product is not expected to pose a risk for the environment when used according to the SPC.

To ensure comprehensive adverse event surveillance and to benefit from the possibility to align periodic safety update report (PSUR) submission for generic products as foreseen in the legislation, it is recommended that the applicant synchronises the PSUR submissions for Prevomax according to the reference product Cerenia, which is currently on a three-yearly cycle. The next DLP for the Prevomax PSUR should therefore be 31 December 2017.

Part 4 – Efficacy

This is a generic application according to Article 13(1) of Directive 2001/82/EC. The reference product is the centrally authorised product Cerenia 10 mg/ml solution for injection for dogs and cats. Both products

have the same active substance (maropitant) in the same concentrations and the same pharmaceutical form; however they contain slightly different excipients.

Bioequivalence

No *in vivo* bioequivalence (BE) study with the reference product has been provided. However, the product will be administered intravenously or subcutaneously, and a waiver for such studies can be accepted, according to the current bioequivalence guideline (EMA/CVMP/016/00-Rev.2):

For the intravenous route, a waiver of a bioequivalence study in dogs and in cats can be accepted according to the current bioequivalence guideline (EMA/CVMP/016/00-Rev.2, exemption 7.1.a), given that the new product is an aqueous intravenous solution containing the same concentration of the active substance as the reference product.

For the subcutaneous route, the waiver of a bioequivalence study is considered acceptable according to the current bioequivalence guideline (EMA/CVMP/016/00-Rev.2, exemption 7.1.b), given that:

- The tested and the reference products are both aqueous solution, containing the same concentration of active substance and although Prevomax and its reference product Cerenia differ in excipients (see part II), these excipients are considered to be comparable excipients in similar amounts;
- Both products have similar to identical physicochemical properties (pH, density, refractive index, viscosity, surface tension and osmolality);
- The qualitative difference in excipients between the two formulations is not expected to have any influence on the rate and/or extent of absorption of the active substance.

It was noted that the active ingredient of the reference product is maropitant citrate, but the active ingredient of Prevomax is maropitant base. However, an appropriate compensatory adjustment of the excipient quantitative composition was made, therefore this difference in the formulation is not expected to affect the bioequivalence of the product

As Prevomax is considered bioequivalent with the reference product, results of toxicological, pharmacological or clinical tests are not required.

Dose determination / finding / confirmation

Not applicable for this type of application, considering that bioequivalence has been established with the reference product.

Target animal tolerance

As this is a generic application submitted according to Article 13(1) of Directive 2001/82/EC as amended and bioequivalence with the reference product has been established (pharmaceutical equivalent composition) result of tolerance tests are not required. Moreover, the excipients used in the product are well-known and widely used in other pharmaceutical products. One of the excipients is benzyl alcohol. Considering the potential toxicity of benzyl alcohol in cats, literature indicates that signs of toxicity do appear at doses of benzyl alcohol significantly higher than those produced by the use of the product. Therefore, this excipient is not expected to be of concern for the target species.

Clinical field trials

No clinical efficacy studies were provided. Given the nature of the application (generic application according to Article 13(1) of Directive 2001/82/EC as amended) and the fact that bioequivalence has been established with an authorised reference product, this is considered acceptable.

Overall conclusion on efficacy

Prevomax is a generic application submitted according to Article 13(1) of Directive 2001/82/EC as amended.

Prevomax and its reference product, Cerenia are both aqueous solutions containing the same concentration of active substance and comparable excipients in similar amounts. *In vivo* bioequivalence studies have been exempted as it could be adequately justified that the differences in the excipients have no influence on the rate and/or extent of absorption of the active substance in line with the CVMP Guideline on the conduct of bioequivalence studies for veterinary products (EMA/CVMP/016/00-Rev.2 exemption 7.1.b). Therefore both generic and reference products are expected to have similar safety and efficacy profiles and the same indications and posology.

Part 5 – Benefit-risk assessment

Introduction

Prevomax is an aqueous solution for injection for use in dogs and cats, containing 10 mg/ml maropitant as the active substance. The product is intended for use in cats and dogs for following indications:

Dogs

- For the treatment and prevention of nausea induced by chemotherapy.
- For the prevention of vomiting except that induced by motion sickness.
- For the treatment of vomiting, in combination with other supportive measures.
- For the prevention of perioperative nausea and vomiting and improvement in recovery from general anaesthesia after use of the μ-opiate receptor agonist morphine.

Cats

- For the prevention of vomiting and the reduction of nausea, except that induced by motion sickness.
- For the treatment of vomiting, in combination with other supportive measures.

The effective dose of 1 mg/kg bodyweight (1 ml/10 kg bodyweight) injected subcutaneously or intravenously, once daily for up to 5 consecutive days will be the same as for the reference product on the basis of bioequivalence. Prevomax is available in four pack sizes, vials containing 10, 20, 25 or 50 ml.

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

Benefit assessment

Direct therapeutic benefit

Prevomax is a generic product, containing maropitant as active substance. Maropitant is a neurokinin 1 (NK1) receptor antagonist, which acts as an antiemetic by inhibiting the binding of substance P, a neuropeptide of the tachykinin family.

The benefit of Prevomax is its efficacy in prevention and treatment of vomiting in dogs and cats, in combination with other supportive measures and for the prevention of nausea and vomiting, except that induced by motion sickness.

Since Prevomax is a generic product, its direct therapeutic benefits are expected to be the same as those for the reference product Cerenia. The evidence for the direct therapeutic benefit is considered established on the basis of bioequivalence to the reference product. Taking into account the acceptance of the exemption of *in vivo* bioequivalence studies, the rate and/or extent of absorption is expected to be the same as for the reference product, Cerenia when administered at the same recommended dose regimen.

Additional benefits

None identified.

Risk assessment

Quality:

Information on development, manufacture, control of the active substance and 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.

Safety:

Risks for the target animal:

Given that the bioequivalence with the reference product has been established (pharmaceutical equivalent composition) and that the excipients of the tested product are well-known and widely used in other pharmaceutical products, the risks associated with the use of the product in the target species are the same as for the reference product.

Pain at injection site may occur when injected subcutaneously. In cats, moderate to severe response to injection is very commonly observed (in approximately one third of cats). In very rare cases, anaphylactic type reactions (allergic oedema, urticaria, erythema, collapse, dyspnoea, pale mucous membranes) may occur.

Risk for the user:

A user risk assessment has confirmed that the use of the product does not entail a greater risk for the user than the reference product. The CVMP concluded that user safety for this product is acceptable when used according to the SPC recommendations.

Risk for the environment:

Prevomax is not expected to pose a risk for the environment when used according to the SPC.

Risk management or mitigation measures

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

To ensure comprehensive adverse event surveillance, submissions of the PSURs for Prevomax should be synchronised with those for the reference product, as foreseen in the legislation.

Evaluation of the benefit-risk balance

The overall benefit-risk evaluation for the product is positive.

The direct therapeutic benefits of the product are the same as those for the reference product Cerenia, i.e. antiemetic effects in dogs and cats.

Information on development, manufacture and control of the active substance and finished product has been presented and lead to the conclusion that the product will have a satisfactory and uniform performance in clinical use.

The product is overall 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.

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 Prevomax 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.