EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

16 June 2016
EMA/413351/2016
Veterinary Medicines Division

Committee for Medicinal Products for Veterinary Use (CVMP)

CVMP assessment report for Sedadex (EMEA/V/C/004202/0000)

International non-proprietary name: dexmedetomidine

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

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Introduction

On 31 August 2015, the applicant Le Vet Beheer B.V. submitted an application for marketing authorisation to the European Medicines Agency (EMA) for Sedadex through the centralised procedure falling within Article 3(3) of the Annex of Regulation (EC) No 726/2004 (generic).

The eligibility to the centralised procedure was agreed upon by the CVMP on 10 April 2015 as the product would constitute a generic product of a product authorised through the centralised procedure Dexdomitor (reference product).

The applicant applied for the following indications:

- Non-invasive, mildly to moderately painful, procedures and examinations which require restraint, sedation and analgesia in dogs and cats.
- Deep sedation and analgesia in dogs in concomitant use with butorphanol for medical and minor surgical procedures.
- Premedication in dogs and cats before induction and maintenance of general anaesthesia.

The active substance of Sedadex is dexmedetomidine hydrochloride, an α2-agonist which inhibits the release of noradrenaline from noradrenergic neurons preventing sympathetic neurotransmission. The target species are dogs and cats. The product is intended for intravenous or intramuscular use in dogs and intramuscular use in cats.

Sedadex solution for injection contains either 0.1 mg/ml or 0.5 mg/ml of dexmedetomidine hydrochloride and is presented in packs containing 1 vial of solution for injection.

The applicant is registered as an SME pursuant the definition set out in Commission Recommendation 2003/361/EC.

The rapporteur appointed is Cristina Muñoz Madero and the co-rapporteur is Barbara Zemann.

The dossier has been submitted in line with the requirements for submissions under Article 13(1) of Directive 2001/82/EC – a generic application.

On 16 June 2016, the CVMP adopted an opinion and CVMP assessment report.

On 12 August 2016, the European Commission adopted a Commission Decision granting the marketing authorisation for Sedadex.

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 1 March 2015) 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

Sedadex 0.1 mg/ml solution for injection and Sedadex 0.5 mg/ml solution for injection are manufactured and packed in the EEA. The manufacturer responsible for batch release is Produlab Pharma B.V., Forellenweg 16, Raamsdonksveer 4941SJ, the Netherlands.

The manufacturing authorisation for Produlab Pharma B.V. was issued on 18 May 2015 by the Medicines Evaluation Board (the Netherlands). Appropriate GMP certification has been provided for the sites responsible for manufacture of the finished product and batch release.

A GMP declaration for the active substance manufacturing site was provided from the qualified person at the EU batch release site. The declaration is based upon an on-site audit of the active substance manufacturer carried out by a third party in July 2015.

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

Sedadex is presented as a solution for injection containing dexmedetomidine hydrochloride as active substance in two different strengths 0.1 mg/ml and 0.5 mg/ml, and methyl parahydroxybenzoate and propyl parahydroxybenzoate as preservatives. Other excipients are sodium chloride, sodium hydroxide and diluted hydrochloric acid, and water for injections. Sodium hydroxide and diluted hydrochloric acid are for pH adjustment.

Container

This veterinary medicinal product is supplied in colourless type I glass vials closed with fluorinated-polymer coated bromobutyl rubber stopper (OmniflexPlus) and sealed with aluminium caps. Initially, 5 ml, 10 ml and 20 ml vials were proposed as commercial containers. However, the 5 ml and 20 ml vials were withdrawn during the procedure. For each strength the product is presented in multidose

vials containing 10 ml of solution for injection. The particulars of the container and controls performed are considered appropriate and conform to relevant European Pharmacopoeia (Ph. Eur.) monographs. The choice of the container closure system is adequate for the intended use of the medicinal product.

Certificates of analysis have been provided for the containers which confirm compliance with the proposed specification and relevant Ph. Eur. monographs.

Development pharmaceutics

Sedadex is a generic medicinal product, and its formulation is considered pharmaceutically equivalent to the formulation of the reference products (Dexdomitor 0.1 mg/ml and 0.5 mg/ml solution for injection). Information on the composition of the medicinal product has been presented in a satisfactory manner. The efficacy of antimicrobial preservation was studied in each strength and in accordance with Ph. Eur. requirements.

A standard manufacturing process was selected and the selection of the sterilisation method was justified in accordance with the relevant guidelines.

The selection of the container and its closure system was based on that used by the reference medicinal product. Its suitability is confirmed by stability studies, closure integrity and fragmentation studies in accordance with Ph. Eur. monograph.

A photostability testing has been performed in accordance with option 1 of VICH GL5 on photostability testing and according to the results provided the medicinal product is photostable.

Method of manufacture

The manufacturing process is considered to be a standard manufacturing process, in which the components are mixed to obtain a simple solution that is clarified by filtration and terminally sterilised by autoclave at the Ph. Eur. conditions. Holding times for the bulk before filtration and for the filled vials before sterilisation are considered acceptable. The description of the process is appropriate for the proposed dosage form.

Validation of the manufacturing process has been conducted on two batches of each strength of the smallest batch size proposed for production scale. Additionally, the post-approval validation protocol for the biggest production scale batch size has been presented. The applicant is recommended to perform full validation on the first three production scale batches of the biggest size filled in the 10 ml vials.

Control of starting materials

Active substance

The active substance, dexmedetomidine hydrochloride, is the isolated single dextro enantiomer of medetomidine HCl, a chiral molecule due to one asymetric carbon. It is described in the USP pharmacopoeia.

To demonstrate the suitability of the active substance for its use in the manufacture of the medicinal product, the active substance master file (ASMF) procedure according to CVMP Guideline EMEA/CVMP/134/02-Rev.3/Corr is followed.

The manufacture of dexmedetomidine HCl consists of five synthetic steps followed by the salification and crystallisation steps. The choice of the starting materials is considered acceptable. The stereochemical properties of the molecule have been discussed. Data provided demonstrate that the route of synthesis used is able to produce the desired enantiomer with suitable quality.

This substance is known to have at least two polymorphic forms. Although polymorphism has not been discussed, this is considered acceptable by CVMP since the pharmaceutical form is a solution and therefore, potential polymorphism of the active substance is not relevant.

A comprehensive discussion and description on potential organic and inorganic impurities arising from the synthesis have been presented. Residual solvents have been appropriately discussed. Additionally, the absence of genotoxic impurities has been appropriately justified.

The 'in-house' specifications of the active substance proposed by the applicant are the same as those in the ASMF and are considered appropriate. The following parameters are tested: appearance of powder (visual) and solution (Ph. Eur.), identification dexmedetomidine (IR, HPLC), identification chloride (Ph. Eur.), pH (Ph. Eur.), optical rotation (Ph. Eur.), loss on drying (Ph. Eur.), heavy metals (Ph. Eur.), sulfated ash (Ph. Eur.), assay (titration), related substances (HPLC), enantiomeric purity (HPLC), residual solvents (GC), microbiological quality (Ph. Eur.) and endotoxins (Ph. Eur.).

The analytical methods used to control the active substance are described in the Ph. Eur. whenever possible, and for the other analytical methods an appropriate description is included. The methods are validated in accordance with the relevant VICH guidelines and are suitable for the intended use.

Appropriate batch analysis is included from three pilot batches of the active substance and the reference standards used.

The container is appropriate for the nature of the active substance and the data provided is considered sufficient.

Finally, regarding the stability study, the selection of the controlled parameters is appropriate since they are stability-indicating. Storage conditions were in accordance with the VICH guidelines. Stability data presented for 3 pilot batches of the active substance comprise 6 months at accelerated conditions and 12 months at long-term conditions. The study will continue up to 36 months at long-term conditions. Additionally, a forced degradation study was conducted with one batch of the active substance according to relevant guidelines.

The stability results presented support that dexmedetomidine HCl is a stable molecule and a re-test period of two years in the proposed packaging without any special storage conditions as proposed is acceptable.

Excipients

The remaining components of the formula are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards. There are no novel excipients used in the finished product formulation. The list of excipients is included in section 6.1 of the SPC.

Certificates of analysis from the excipients' supplier and the finished product manufacturer confirming compliance with the proposed specification have been provided.

Specific measures concerning the prevention of the transmission of animal spongiform encephalopathies

None of the starting materials used for the manufacture of the active substance or the finished product are risk materials as defined in the current version of 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). The product is therefore out of the scope of the relevant Ph. Eur. monograph and the Note for guidance.

Valid TSE declarations from the applicant and the manufacturer of the active substance have been provided.

Control tests during production

Not applicable.

Control tests on the finished product

The parameters included in the specifications to control the finished product at release are suitable for the proposed dosage form.

The following parameters are tested: appearance (visual), pH (Ph. Eur.), density (Ph. Eur.), identification and assay of active substance (HPLC), identification and assay of preservatives (HPLC), related substances (HPLC), chiral purity (HPLC) and sterility (Ph. Eur.).

Analytical methods are appropriately described and they are appropriately validated for their intended use, when applicable.

Batch analysis results are provided for two production scale batches of the smallest size proposed for each strength, confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

Stability

Stability studies on the finished product are conducted in accordance with a bracketing design. The study was performed with two production batches of the smallest size proposed for commercial production. Both strengths filled in the 5 ml and 20 ml vials initially proposed for commercialisation are tested. The vials are stored in upright and inverted position. Storage conditions were in accordance with the VICH guidelines (5 °C, 25 °C ± 2 °C/60 ± 5% RH and 40 °C ± 2 °C/75 ± 5% RH). According to the stability protocol submitted the study will continue up to 60 months at long-term conditions. Controlled parameters and analytical methods are the same as those used for the control of the finished product.

Appropriate shelf-life specifications have been established based on the data provided. However, the applicant is recommended to review the shelf-life limits for pH and total impurities at the end of shelf-life.

No significant changes have been observed following 6 months storage under refrigerated and accelerated conditions, or during the 12 months under long-term conditions. Therefore, the data presented is sufficient to justify the proposed shelf-life period of 2 years in the proposed container with no special storage conditions. Additionally, the applicant is recommended to place one additional production scale batch of each strength filled in the commercial vial (10 ml) in the stability study.

The in-use stability study is carried out with two one-month-old batches of each strength and the applicant is recommended to repeat the study close to the end of the shelf-life period (two months before the end). The 20 ml vials were initially proposed as commercial containers and were used for the in-use stability study on the basis that it is the one that poses the greatest demand on the system. Although it is not the container used for commercial batches anymore, the information provided is considered valid to support the in-use shelf life period for commercial batches which will be filled in 10 ml vials. Broached containers are stored at 25 °C/75% RH, and the analysis is performed at 28 days and 56 days after the start of the study. Data submitted show no stability problems. A repeat preservative efficacy test has been performed and the results provided confirm an in-use shelf-life of 56 days as proposed.

Overall conclusions on quality

The composition and development pharmaceutics are well presented and comprehensive. Of the three vial sizes initially proposed, only the 10 ml vial size will be commercialised.

The manufacturing process is a standard manufacturing process, in which the components are mixed to obtain a simple solution that is clarified by filtration and terminally sterilised by autoclave at the Ph. Eur. conditions. The description of the process is appropriate for the proposed dosage form. Holding times for the bulk before filtration and for the filled vials before sterilisation are supported by appropriate data.

The information regarding chemistry, development, manufacture and control of the active substance is provided in an ASMF. The active substance is the isolated single dextro enantiomer of medetomidine HCl. The information provided in the applicant's part of the ASMF is quite complete regarding the general information, container and the description of the synthesis, confirming that the proposed route of synthesis is able to produce the desired enantiomer with suitable quality. Potential impurities arising from the synthesis have been appropriately discussed. The analytical methods used to control the active substance are methods described in Ph. Eur. whenever possible, and the other analytical methods are appropriately described and validated. An appropriate stability study in accordance with VICH guidelines has been performed. Data is available for 3 pilot batches up to 6 months at accelerated conditions and 12 months at long-term conditions. The study will continue up to 36 months at long-term storage conditions. A re-test period of two years in the proposed packaging without any special storage conditions is acceptable.

The excipients of the formula are well known pharmaceutical ingredients and their quality is compliant with Ph. Eur. standards.

None of the starting materials used for the manufacture of the active substance or the finished product pose a risk of transmitting animal spongiform encephalopathy. Valid TSE declarations from the applicant and the manufacturer of the active substance have been provided.

Appropriate specifications to control the finished product at release and during shelf-life have been provided. Analytical methods are appropriately described and validated for their intended use.

The stability studies of the medicinal product are conducted in accordance with a bracketing design since initially three vial sizes were proposed. The studies have been performed in accordance with VICH guidelines and data corresponding to 6 months under refrigerated and accelerated conditions and 12 months at long-term conditions are provided. The study will continue up to 60 months at long-term storage conditions. No significant changes have been observed during the time of the study and the data presented justifies the proposed shelf-life period of 2 years in the proposed container, with no special storage conditions.

The in-use stability study is carried out with two one-month old batches of each strength and the study would be repeated close to the end of the shelf-life period (two months before the end). Data submitted show no stability problems and the results of the repeat preservative efficacy test support the in-use shelf-life of 56 days.

In conclusion, information on the development, manufacture and control of the active substance and the 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.

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

1. The manufacturing process validation should be performed on the first three full scale production batches of the biggest size filled in the 10 ml vials as stated in the post-approval validation protocol.
2. The possibility to tighten the pH limits in the shelf-life specification of the finished product should be assessed at the end of shelf-life based on the results of the stability study.
3. The possibility to tighten the total impurities limit in the shelf-life specification of the finished product to the release specification limit should be assessed at the end of shelf-life.
4. An additional commercial batch of each strength in the commercial vial (10 ml) should be placed on the stability study for 6 months under accelerated conditions and throughout the whole proposed shelf-life period under long-term conditions. Data should be provided immediately to the competent authorities if outside specifications or potentially outside specifications at the end of the shelf-life (with proposed action).
5. An in-use stability study should be conducted close to the expiry date and the relevant authorities should be immediately informed, if any out of specification results are obtained, together with the proposed actions.
6. Any out of specification result in the non-routine control of the related substances and chiral purity in the finished product at release will be notified to the competent authorities, and routine testing of those parameters would be restored in the specifications of the finished product at release.

Part 3 – Safety

Safety documentation

This is an application based on Article 13(1) of Directive 2001/82/EC and bioequivalence with the reference product has been justified. Therefore, the results of the toxicological or pharmacological tests are not required.

No in vivo bioequivalence studies have been conducted and the applicant claims an exemption for the conduct of bioequivalence studies (biowaiver) based on point 7.1.d) of the CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2). However, these formulations cannot be considered identical since two excipients identified on page 3 have been added to the generic product in order to adjust the pH. Furthermore, biowaiver based on point 7.1.d) requires that both products have identical manufacturing process.

Nevertheless, the absence of bioequivalence studies is justified according to point 7.1 a) of the above mentioned CVMP Guideline on bioequivalence studies which states that no studies on bioequivalence need to be performed when "the product is to be administered solely as an aqueous intravenous

solution containing the same active substance as the currently approved product". This point also indicates that "if any excipients interact with the active substance (e.g. complex formation), or otherwise affect the disposition of the active substance, a bioequivalence study is required unless both products contain the same excipients in very similar quantity and it can be adequately justified that any difference in quantity does not affect the pharmacokinetics of the active substance". In this case, the excipients added to the generic product for pH adjustment are not expected to affect the rate and/or extent of absorption of the active substance and, therefore, this biowaiver is considered acceptable for the intravenous administration in dogs.

According to point 7.1 b) of the above mentioned guideline, no studies on bioequivalence need to be conducted either for products intended for intramuscular, subcutaneous or systemically acting topical administration when the product is of the same type of solution, contains the same concentration of the active substance and comparable excipients in similar amounts as the reference veterinary medicinal product. This biowaiver is considered acceptable for the intramuscular administration in dogs and cats.

User safety

The applicant has presented a User Safety Assessment which has been conducted in accordance with CVMP Guideline on user safety for pharmaceutical veterinary medicinal products (EMEA/CVMP/543/03-Rev.1).

Sedadex contains 2 additional excipients compared to the reference product. Enough information has been provided to confirm that these 2 excipients do not represent an added hazard. The toxicity of these substances as well as that of the other excipients is considered low. Therefore, the review of the risk exposure is focused on the active substance.

Given the type of product and route of administration, the most probable scenario of exposure to the active substance and of major concern is the accidental self-injection. Appropriate toxicological information on the active substance has been provided to estimate the risk in case of self-injection of any of the strengths of the product. The applicant claims that the calculation has been based on the worst case scenario but, when using the highest strength the sedation of a bigger dog should have been chosen (>80 kg). In any case, the margin of exposure obtained, even taking into account that the NOAEL used for the estimation of the risk has been based on repeat dose toxicity studies, is very narrow (<100) but can be accepted, since the product will be handled only by a professional and appropriate risk mitigation measures are included in the SPC.

It can be concluded that the product to be registered does not entail a greater risk for the user than the reference product and, therefore, the same risk mitigation measures as those included in the SPC of the reference product have been proposed.

The CVMP concluded that the product does not pose an unacceptable risk to the user when used in accordance with the SPC.

Environmental risk assessment

An environmental risk assessment (ERA) was provided according to VICH GL6 and the CVMP Guideline on the Environmental Impact Assessment for Veterinary Medicinal Products in support of the VICH GL6 and GL38 (EMEA/CVMP/ERA/418282/2005-Rev.1).

Based on the data provided, the environmental risk assessment can stop in Phase I and no Phase II assessment is required because the veterinary medicinal product will only be used in non-food animals.

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

Overall conclusions on the safety documentation

This is an application based on Article 13(1) of Directive 2001/82/EC and bioequivalence with the reference product has been justified. Therefore, the results of the toxicological or pharmacological tests have not been submitted. This is considered acceptable by CVMP.

A comprehensive user risk assessment has been provided, which covers all the aspects required in the CVMP Guideline (EMA/CVMP/543/03-Rev.1). Given that Sedadex contains two additional excipients compared to the reference product, the risk assessment should confirm that the new excipients do not represent an added hazard. The applicant has submitted enough data to demonstrate that the toxicity of these substances is low. The major effects (sedation, respiratory depression, bradycardia and hypotension) would be caused, therefore, by the active substance itself and could occur in case of accidental self-injection. Although the risk assessment concluded that the margin of safety is very narrow it can be accepted since the product will be administered only by professionals who would strictly follow the instructions included in the SPC. The same risk mitigation measures as those included in the SPC of the reference product have been proposed.

An environmental risk assessment has been provided which demonstrates that the use of dexmedetomidine as recommended in the SPC does not entail any risk for the environment. The assessment ends in Phase I at Question 3 (product used only in companion animals).

The data provided are sufficient to conclude that the product is not expected to pose an unacceptable risk for the user or the environment when used as recommended.

Part 4 – Efficacy

This is a generic application submitted according to Article 13(1) of Directive 2001/82/EC and bioequivalence with the reference product has been established. Therefore, the results of pharmacological, tolerance or clinical tests are not required.

The reference product is Dexdomitor. Both products have the same active substance (dexmedetomidine hydrochloride) in the same concentration (0.1 mg/ml and 0.5 mg/ml) and the difference in excipients between the formulations is not expected to affect the rate and/or extent of absorption of the active substance. The reference product chosen by the applicant is considered acceptable.

Bioequivalence with the reference product can be accepted on the basis of compliance with the criteria for the acceptance of the absence of in vivo bioequivalence studies according to CVMP Guideline on the conduct of bioequivalence studies for veterinary medicinal products (EMA/CVMP/016/00-Rev.2) (see introduction to Part 3).

Therefore, the same efficacy profile as that of the reference product can be assumed for Sedadex.

Part 5 – Benefit-risk assessment

Introduction

Sedadex is a solution for injection, containing dexmedetomidine hydrochloride as active substance, intended for use in dogs (intravenous or intramuscular use) and cats (intramuscular use) to produce sedation and analgesia in examinations and medical and minor surgical procedures. It is also intended

for premedication before induction and maintenance of general anaesthesia.

The application has been submitted in accordance with Article 13(1) of Directive 2001/82/EC (generic application). Dexdomitor (EU/2/02/033/001-004) which was authorised in the Community in 2002 has been proposed as reference product which is considered acceptable.

Benefit assessment

Direct therapeutic benefit

The benefit of Sedadex is its efficacy on:

- Non-invasive, mildly to moderately painful, procedures and examinations which require restraint, sedation and analgesia in dogs and cats.
- Deep sedation and analgesia in dogs in concomitant use with butorphanol for medical and minor surgical procedures.
- Premedication in dogs and cats before induction and maintenance of general anaesthesia.

Since Sedadex is a generic product, its direct therapeutic benefits are expected to be the same as those for the reference product Dexdomitor. 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 absence of in vivo bioequivalence studies as the rate and/or extent of absorption is expected to be the same for Sedadex as for the reference product.

Additional benefits

Sedadex increases the range of available treatment possibilities for procedures that require restraint, sedation and analgesia, as well as for premedication before induction and maintenance of general anaesthesia in dogs and cats.

Risk assessment

Main potential risks have been identified as follows:

Quality:

Information on the development, manufacture and 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.

For the target animal:

The risks associated with the use of the product are those of the reference product.

Administration of Sedadex in accordance with SPC recommendations is generally well tolerated by dogs and cats.

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. Accidental self-injection may cause sedation, respiratory depression, bradycardia and hypotension. However, the probability of exposure is low given that the product is only

going to be handled by a professional.

The CVMP concluded that user safety for this product is acceptable when used as recommended and taking into account the safety advice in the SPC.

For the environment:

Sedadex 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, the user and the environment and to provide advice on how to prevent or reduce these risks.

Evaluation of the benefit-risk balance

The efficacy of this product has been justified for the following indications:

- Non-invasive, mildly to moderately painful, procedures and examinations which require restraint, sedation and analgesia in dogs and cats.
- Deep sedation and analgesia in dogs in concomitant use with butorphanol for medical and minor surgical procedures.
- Premedication in dogs and cats before induction and maintenance of general anaesthesia.

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

The product is well tolerated by the target animals and presents an acceptable risk for users and the environment when used as recommended.

Appropriate warnings and 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 CVMP concluded that the application for Sedadex 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.