EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

8 December 2011
EMA/847913/2011
Veterinary Medicines and Product Data Management

CVMP assessment report
TruScient (EMEA/V/C/2000)

International non-proprietary name: Dibotermin-alfa

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

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1. Summary of the dossier

Introduction

An application for the granting of a community marketing authorisation for TruScient 0.66mg kit for implant for dogs has been submitted to the Agency on 1 June 2010 by Pfizer Limited in accordance with Regulation (EC) No. 726/2004. The Committee agreed that the product is eligible for the centralised procedure in accordance with Article 3(1) of Regulation (EC) No 726/2004 and the Annex section I first indent as TruScient is a product developed by recombinant DNA technology.

TruScient has been developed for use in canines based on the approved use of the InductOs product in humans (EU/1/02/226/001) i.e. to induce new bone tissue at a fracture site. The active substance dibotermin alfa, acts on the bone structure. It is a copy of a protein called bone morphogenetic protein 2 (rhBMP-2), which is produced naturally by the body and helps with the formation of new bone tissue. When implanted, dibotermin alfa stimulates the bone tissue around the matrix to make new bone. The newly formed bone grows into the matrix, which then dissolves away. Dibotermin alfa is produced by recombinant DNA technology. The replacement dibotermin alfa acts in same way as BMP-2 produced naturally by the body.

TruScient 0.66 mg kit for dogs contains 0.66 mg dibotermin alfa (recombinant human Bone Morphogenetic Protein-2 (rhBMP-2)) and is presented in packs/containers of 2 vials, 2 sterile matrices, 3 syringes. It is indicated for use in the treatment of long bone fractures as an adjunct to standard surgical care using open fracture reduction in dogs. The route of administration is a kit for implantation. The target species are dogs.

The same active substance (recombinant human Bone Morphogenetic Protein-2 (rhBMP-2)) is used in both products, with the concentration in TruScient being appropriately reduced from 1.5 mg/ml in the human product to 0.2 mg/ml in the canine product. Excipient concentrations also differ between the two products.

As for InductOs, the dibotermin alfa active substance of TruScient is supplied in a lyophilised powder formulation to be reconstituted with water for injection as solvent and applied to an absorbable collagen sponge (ACS) matrix for application at the fracture site.

TruScient has been classified as a minor use minor species (MUMS) product by CVMP, in accordance with the *Policy for classification and incentives for veterinary medicinal products indicated for minor use minor species (MUMS)/limited markets* EMEA/429080/2009. Reduced data requirements therefore apply and are referenced within this assessment report for this minor use/limited market in dogs.

Part 1 - Administrative particulars

Pharmacovigilance system

The applicant has provided documents that set out a detailed description of the pharmacovigilance system (DDPS). The information presented demonstrates that the applicant has in place a pharmacovigilance system that will allow it to comply with its legal requirements in respect of pharmacovigilance.

Manufacturing Authorisations and Inspection Status

Assembly and batch release of the TruScient kit takes place at a GMP approved facility at Gerona in Spain. Valid manufacturing authorisations are in place for each site in the EU/EEA carrying out manufacture of the product, packaging and batch release.

Dibotermin alfa, which is the active substance of the lyophilised powder of TruScient, is manufactured at Pfizer's facility in USA. This site was subject to a satisfactory GMP inspection in April 2009. The US site where the absorbable collagen sponge (ACS) is manufactured was inspected in March 2011 and deemed satisfactory.

Testing

An annual sampling and testing programme for centrally authorised products is conducted in accordance with Art. 57(r) of Regulation (EC) 2004/726 in conjunction with the European Directorate for the Quality of Medicines & HealthCare (EDQM) and the Official Medicines Control Laboratories of the EU/EEA Member States. TruScient will be included in this programme for testing.

2. Quality assessment

TruScient has been classified as a minor use minor species (MUMS) product by CVMP. Section 4.3 (Existing human medicinal product for use in a minor species or minor use) of EMEA/CVMP/QWP/128710/2004 is applicable to the quality assessment of the data submitted for the dibotermin alfa drug substance.

As there are differences in the manufacturing processes used for the InductOs (the human product) and TruScient lyophilised vial formulations and the lyophilised vial formulations are manufactured at different sites, Section 4.4 (Entirely new medicine for use in a minor species or for minor use) of EMEA/CVMP/QWP/128710/2004 was taken into account for the assessment of the quality data for the lyophilised vial formulation of TruScient. Section 4.4 lists reduced requirements for process validation (i.e. for full scale batches, a process validation scheme only is required), batch analysis data and final product stability (i.e. data required for 2 pilot scale batches only).

Composition

The following components are included in each TruScient kit:

(a) 1 x 10 ml vial containing 0.66 mg of lyophilised recombinant human bone morphogenetic protein (rhBMP-2)

(b) 1 x 10 ml vial of solvent (sterile water for injection)

(c) 1 x pack of Absorbable Collagen Sponge (ACS) containing two 2.5 x 5 cm sponges

(d) 1 x 6 ml sterile syringe with 21G needle and 2 x 3 ml sterile syringes with 20G needle.

The lyophilised dibotermin alfa protein is reconstituted using 3.2 ml of the sterile water for injection solvent and then uniformly applied to the sponges before use. The sponge acts as a carrier for the dibotermin alfa protein to the fracture site.

The active substance, dibotermin alfa, is recombinant human Bone Morphogenetic Protein-2 (rhBMP-2) produced in a CHO cell culture. All excipients (sucrose, glycine, polysorbate 80, sodium chloride, L-glutamic acid, water for injections) and pH adjusters comply with the European Pharmacopoeia.

The final product volume in the reconstituted vial is 3.3 ml.

The formulation does not contain a preservative, the reconstituted vial is recommended to be used within 3 hours.

Absorbable Collagen Sponge (ACS)

This is composed of bovine tendon type I collagen cross-linked with formaldehyde. Each ACS pack includes two sponges each with dimensions of 2.5 x 5 cm.

Container

Dibotermin alfa lyophilisate

Container: 10 ml type I hydrolytic borosilicate glass vial (Ph. Eur.)

Closure: chlorobutyl rubber stopper.

Compliance of the stoppers with the requirements of Ph. Eur. 3.2.9 has been demonstrated. The vials and stoppers are sterilised in accordance with the reference conditions listed in Ph. Eur. 5.1.1 (Methods of preparation of sterile products).

Solvent - Water for injections (WFI)

The SPC refers to the solvent being supplied in a 10 ml type I hydrolytic borosilicate glass vial with a bromobutyl elastomeric closure. The SPC also refers to the fact that more WFI is provided then is needed to reconstitute the lyophilised dibotermin alfa protein.

It has been confirmed that the same WFI solvent vials are included in the TruScient and InductOs kits.

ACS pack

There are no details given in the dossier of the materials used for packaging of the sponges included in each TruScient kit. This is acceptable as it has been confirmed that the ACS packs included in TruScient are identical to those included in InductOs which is authorised for human use by EMA (EU/1/02/226/001) with the exception of the smaller size of the TruScient sponges (2.5 x 5 cm) compared to the InductOs sponges (7.5 x 10cm). The ACS sponge is packaged in trays formed from polyvinyl chloride (PVC) and sealed with Tyvek lids.

The ACS sponge is sterilised using ethylene oxide. The average and individual EO limits proposed for the Truscient sponge exceed the recommended EO limit of 1 ppm referred to in the 'Note for Guidance (NfG) on limitations to the use of ethylene oxide in the manufacture of medicinal products' and are also higher than the limits applied for the InductOs ACS. However, based on the allowable limits for 'Prolonged Exposure Devices' specified in ISO 10993-1 (Guideline for Biological Evaluation of Medical Devices: Part 7), the EO limits proposed for the Truscient sponge are not considered to represent a toxicity risk and can therefore be accepted.

Development pharmaceutics

TruScient has been developed for use in canines based on the approved use of the InductOs product in humans (EU/1/02/226/001) i.e. to induce new bone tissue at a fracture site.

The same active substance (recombinant human Bone Morphogenetic Protein-2 (rhBMP-2)) is used in both products, with the concentration in TruScient being appropriately reduced from 1.5 mg/ml in the human product to 0.2 mg/ml in the canine product.

As for InductOs, the dibotermin alfa active substance of TruScient is supplied in a lyophilised powder formulation to be reconstituted with WFI as solvent and applied to the ACS matrix for application at the fracture site.

The same excipients are present in the dibotermin alfa lyophilised powder formulations of TruScient and InductOs therefore the choice and function of the excipients are acceptable.

The vials containing the canine and human lyophilised powder formulations are the same (i.e. type I hydrolytic borosilicate glass vial (Ph. Eur.)) however, a different stopper is used. The composition of the ACS matrix supplied for use with TruScient and InductOs is the same i.e. a bovine tendon type I collagen cross-linked with formaldehyde and it has been confirmed that the ACS used for both the human and canine products are manufactured at the same site using the same process with the exception of the smaller size for the canine sponges.

The compatibility of the dibotermin alfa protein and ACS and the suitability of the combination to deliver and retain dibotermin alfa protein at the treatment site are therefore acceptable.

Method of manufacture

Active substance

The dibotermin alfa drug substance used in the manufacture of the dibotermin alfa lyophilised vial formulation of TruScient is the same as that used in the manufacture of the lyophilised vial formulation of InductOs which has been approved for use in humans (EU/1/02/226/001).

On this basis and as TruScient has been classified as MUMS, the manufacturing process of the dibotermin alfa active substance can be considered acceptable.

Dibotermin alfa lyophilised powder

A buffer solution is prepared and a certain percentage of the buffer solution is filtered into a second tank to which the thawed dibotermin alfa is added.

Based on the results of an in-process test for active substance content, the remaining quantity of buffer solution is filtered and added to obtain the required concentration of active substance.

The resulting dibotermin alfa bulk solution is then filtered through a sterilising filter before being filled in glass vials and stoppered with a stopper in the lyophiliser and then sealed with an aluminium seal.

In general, the description of the process and methods is detailed and clear. Batch analysis data from pilot scale batches are provided including the results of in-process tests conducted during manufacture of these batches. The same lyophiliser used in the manufacture of the pilot scale size batches will be used for commercial scale size batches. The lyophilisation cycle for commercial batches will be the same as that used for the pilot batches with the exception of the temperature for the secondary drying phase. As there are no changes to the critical freezing stages of the lyophilisation cycle for production batches compared to that used for the pilot batches, the lyophilisation cycle used for the pilot batches can be considered as representative of that which will be used for commercial production batches.

In addition, the process validation scheme proposed for the commercial scale size process has been provided, which is acceptable in view of the application. It is noted that a reference is included in the Note for Guidance (NfG) on Process validation (EMEA/CVMP/598/99) to the effect that the guideline is not intended to apply to products of biotechnological or biological origin as such products are stated to

be ‘very complex in nature’ and therefore generally require more extensive validation data. However, it should be noted that the NfG also states ‘the principles and practices outlined in this guideline may well also be useful in such more complex operations’.

Similarly while there is no direct reference in EMEA/CVMP/QWP/128710/2004 or EMA/CVMP/IWP/123243/2006-Rev.2 to the guidelines being applicable to biological products containing recombinant substances, such products are not excluded from the scope of either guideline. Considering the aforementioned points, aspects of Sections 4.3 (Existing human medicinal product for use in a minor species or minor use) and 4.4 (Entirely new medicine for use in a minor species or for minor use) of EMEA/CVMP/QWP/128710/2004 are considered applicable for the quality assessment of TruScient.

While Annex II to the NfG on Process validation (EMEA/CVMP/598/99) refers to aseptic processing and lyophilisation as non-standard processes, Section 4.4 of the MUMS guideline (EMEA/CVMP/QWP/128710/2004) states that a process validation scheme only is acceptable for applications for products manufactured using both standard and non-standard processes.

It is therefore considered that as the data from pilot scale batches can be considered to be predictive of the production scale process, a pre-authorisation request for submission of process validation on full scale size batches was not warranted for TruScient.

WFI solvent manufacture

It has been confirmed that the same WFI solvent is used in the TruScient and InductOs kits therefore it is not necessary to provide information in the application in relation to the manufacture of the sterile water for injection solvent.

ACS packs

Confirmation is given that the same site is used for manufacture of the TruScient and InductOs ACS. It can be accepted that the sponge material supplied for use in the canine and human products is the same and therefore it is not necessary for details of the ACS manufacturing process to be provided.

It is noted however that the size of the sponges supplied for use with TruScient is smaller (2.5 x 5 cm) than the sponges supplied for use with InductOs (7.5 x 10cm) and higher ethylene oxide (EO) residues are present after ethylene oxide sterilisation of the ACS pack comparing the human and canine products. The higher EO residues are not considered to be associated with toxicity risks as outlined above.

Control of starting materials

Active substance

The same dibotermin alfa drug substance is used as active substance in the manufacture of the canine and human dibotermin alfa lyophilised powder formulations. The drug substances used in both the human and canine products are tested using the same methods and to the same quality control release specifications, therefore the quality of the drug substance used as active substance in TruScient can be considered acceptable.

Human BMP-2 is a member of the TGF-beta superfamily of growth factors and is a glycosylated, disulfide-bonded, dimeric protein with two major subunit species of 114 and 131 amino acids. Dibotermin alfa is expressed and secreted in a Chinese hamster ovary (CHO) cell culture process. Recombinant hBMP-2 binds to receptors on the surface of mesenchymal cells and causes cells to differentiate into cartilage- and bone-forming cells.

The dibotermin alfa drug substance used in the canine and human lyophilised vial formulations is stored in identical containers and at identical conditions at the drug substance manufacturing site.

The only additional item to be considered is the potential for the active substance to introduce extraneous agents when used in dogs.

It is noted that although highlighted to the applicant during the Scientific Advice procedure, an assessment of the viral safety of the starting materials, bulk dibotermin alfa and ACS in view of the intended use of TruScient in canines, has not been addressed in the application.

On the basis of the approved use of InductOs, the biological starting materials used in the manufacture of the dibotermin alfa protein and ACS material can be considered as not presenting a risk of extraneous agent contamination in humans.

Examination of the guideline 'Table of extraneous agents to be tested for in relation to the general and species specific guidelines on production and control of mammalian veterinary vaccines' indicates that with the exception of *Brucella canis* and rabies virus, the listed canine adventitious agents can be detected by the same general test methods designed to detect cytopathic and haemadsorbent viruses relevant to humans. As both humans and canines are susceptible to rabies virus and taking into account experience from use of the InductOs product in humans for a number of years, the risk of introduction of rabies virus infection in dogs due to use of TruScient is considered negligible.

As no materials of canine origin are used as starting materials in the manufacture of the bulk dibotermin alfa or ACS material, the potential for any of the components of TruScient to be contaminated with the *Brucella canis* bacterium is extremely low.

On this basis the CVMP considers that TruScient does not present an increased risk of extraneous agent contamination in canines over that for InductOs in humans.

Excipients

Excipients used in the manufacture of the dibotermin alfa lyophilised powder formulation

All excipients used are stated to comply with the relevant Ph. Eur. monographs.

Excipients included in TruScient

ACS packs

A specification for the ACS pack to be included as a component in the TruScient kit for implant is provided. Representative certificates of analysis for the smaller 2.5 x 5 cm sponge used for TruScient are given and deemed acceptable.

Needles and Syringes
Two x 3 ml and 1 x 6 ml syringes with needles are included in the TruScient kit for use in the reconstitution process and transfer of the dibotermin alfa solution to the ACS. These are standard sterile syringes supplied for reconstitution of product and are acceptable.

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

Bovine milk and tallow derivatives are used in the manufacture of dibotermin alfa drug substance used as the active substance in the lyophilised powder. As this same dibotermin alfa drug substance is approved for use in the human product InductOs and also as the intended target species for TruScient is dogs (which are not considered to be susceptible to TSE), the risk of TSE infection is negligible.

It has been clarified that the oleic acid moiety of the polysorbate 80 is plant derived, hence the risk of TSE infection is negligible.

ACS material: A certificate of TSE suitability issued by the EDQM for this material is provided (R1-CEP 2000-372-Rev 00).

In summary, TruScient is considered to present minimal risk to TSE infection in canines.

Control tests during production

This section is referred to in the application submitted as 'not applicable'. However, an in-process test to check the dibotermin alfa concentration of the formulated bulk solution is conducted during manufacture of the TruScient lyophilised vial formulation. Details of the test used and an appropriate validation of the test are provided.

A test for bioburden is included for the filtration process to sterilise the dibotermin alfa formulated bulk solution.

Control tests on the finished product

The specifications and release criteria for dibotermin alfa should be established to assure the administration of the intended dose of dibotermin alfa. The applicant has focussed on the determination of the concentration and purity of the dibotermin alfa and in terms of product safety the bacterial endotoxin and the sterility of the final product. Tests on the finished product include appearance, pH, protein identification and protein content closure and container integrity, uniformity of dosage, particulate matter, residual moisture, sterility and bacterial endotoxin testing. Specifications have been set and methods have been validated for site transfer to the TruScient manufacturing site or are in accordance with Ph. Eur. where relevant, as described in the dossier. The proposed specifications are deemed acceptable in control of the lyophilised vial and the finished product specifications can be accepted.

The applicant has proposed not to include the potency assay as part of the release specifications however scientific advice from CVMP did require a correlation between the HPLC method for protein determination and the bioassay for potency. These data have been provided and considered acceptable therefore it is acceptable that the bioassay will only be performed as part of the stability programme and not as a release test. The good correlation between the bioassay and the HPLC method provides reassurance that the HPLC method will suffice for release testing.

Scientific advice also recommended that the dibotermin alfa identity by electrophoresis would be introduced as a release test and this is now implemented for release and stability testing.

Some of the release specifications for the canine product Truscient differ to those for the authorised human product Inductos. However, in all cases the Triscient specifications are appropriate to control the quality of the product for use in canines.

Stability

Stability results for three pilot batches have been presented in the dossier. Appearance, identity, pH, residual moisture, dibotermin alfa content, SEC-HPLC, sterility, bacterial endotoxin testing and peptide mapping were performed on all three batches. Batches were stored at different temperatures and tested at different time points. Results are presented to 24 months. The MUMS guideline lists reduced requirements where final product stability data from 2 pilot batches is required. The applicant has provided real time data for 3 pilot batches meeting MUMS requirements. The shelf life for

biotechnological/biological veterinary medicinal products (VMPs) cannot be determined from accelerated studies in line with VICH Guidelines for biotechnological/biological VMPs therefore the shelf life assigned to TruScient based on the real time data provided will be 2 years.

The proposed 3 hour in use shelf life has been addressed at 12 and 24 month time points for the three pilot batches. An in use period of 3 hours has been assigned to the reconstituted product.

Overall conclusions on quality

The medicinal product is a kit, consisting of a vial containing the active dibotermin alfa, a WFI solvent vial and matrix (Absorbable collagen sponge, ACS). The active substance, dibotermin alfa (rhBMP-2), is a dimeric glycosylated protein, produced in a CHO cell line. The cell line, working and master cell banks are adequately characterised and tested for adventitious viruses. Reference is made to the human authorised product Inductos which contains the same active with the same production method. The purification process, together with the viral testing after fermentation, assures the viral safety of the product. The product has been classified as MUMS, intended for a minor use/limited market and appropriate data in line with the published guidelines provided as outlined in the sections above.

The active substance is controlled using appropriate and validated release tests.

The ACS matrix consist of purified type I bovine collagen, cross-linked and sterilised with manufacture at the same site as for the human product. A smaller 2.5 x 5 cm sponge is supplied for this veterinary product.

The manufacturing process of the protein is validated and is controlled with appropriate and validated release tests. The protein is stable for 24 months at 2-30°C.

A shelf life of 2 years at room temperature is accepted for the kit (protein, solvent and matrix) and a 3 hour in-use shelf-life for the reconstituted product.

3. Safety assessment

Safety documentation

No reduction in data requirements as per the MUMS guidelines was applied to this section as extensive data were available from the human product.

Pharmacodynamics

Dibotermin alfa (rhBMP-2) is an osteoinductive protein that results in the induction of new bone tissue at the site of implantation. Dibotermin alfa binds to receptors on the surface of mesenchymal cells and causes cells to differentiate into cartilage- and bone-forming cells. The differentiated cells form trabecular bone as the matrix is degraded, with vascular invasion evident at the same time. The bone formation process develops from the outside of the absorbable collagen sponge (ACS) towards the centre until the entire ACS is replaced by trabecular bone. Remodelling of the surrounding trabecular bone occurs in a manner that is consistent with the biomechanical forces placed on it. The ability of ACS to support bone remodelling may be responsible for the biological and biomechanical integration of the new bone induced by dibotermin alfa with that of the surrounding bone. Radiographic, biomechanical, and histologic evaluation of the induced bone indicates that it functions biologically and biomechanically as native bone.

Preclinical studies have suggested that bone formation initiated by dibotermin alfa is a self-limiting process, forming a well-defined volume of bone. This self-limitation is likely due to the loss of dibotermin alfa from the application site, as well as the presence of BMP inhibitors in the surrounding tissues.

Clinical pharmacology studies demonstrate that the ACS alone is not osteoinductive and is completely resorbed over time.

Pharmacokinetics

The pharmacokinetic data presented in support of the present application are the same as the data presented in support of the authorised human product, InductOs. None of the studies presented were GLP compliant. However, they are considered to have been adequately conducted/reported and to be of acceptable quality for reliable interpretation.

Overall, the pharmacokinetic studies following intravenous dosing showed minimal systemic exposure of dibotermin alfa. The clearance of dibotermin alfa from the circulation is high. Although the uptake of dibotermin alfa by highly perfused tissues and organs is rapid, residence of the protein in these tissues is short. Catabolism was not investigated directly; however, the available data suggest that the protein is rapidly and extensively catabolised in the liver into small peptides or amino acids and excreted as such in the urine.

The influence of hepatic function on the pharmacokinetics of dibotermin alfa has not been studied. It is expected that the metabolic pathway of dibotermin alfa will follow the pathways of other proteins (peptide hydrolysis); therefore, impaired liver function is not expected to affect the pharmacokinetics of dibotermin alfa in a clinically significant way. In addition, the influence of renal function on the pharmacokinetics of dibotermin alfa has not been studied. This can be accepted because renal elimination of dibotermin alfa is considered to be a minor pathway for dibotermin alfa clearance.

Three studies were conducted to characterise the retention kinetics of dibotermin alfa when applied to the collagen sponge and implanted in rats. The data indicate that dibotermin alfa is slowly released from the implant site; that is, the ACS facilitates prolonged exposure at the fracture site. The relative retention of dibotermin alfa was not affected by the concentration of reconstituted solution applied to the sponge.

Because dibotermin alfa is slowly released from a site of implantation and rapidly cleared from the systemic circulation, systemic exposure to dibotermin alfa will be limited. It is argued that this limited systemic exposure predicts a favourable safety profile of dibotermin alfa/ACS following implantation.

No canine-specific pharmacokinetic data have been provided. The following selected text relating to pharmacokinetics has been taken from the EPAR for the related human product, InductOs:

> *'Altogether, the pharmacokinetic characteristics of dibotermin alfa in man are unknown. However, preclinical data suggest that any dibotermin alfa escaping the implant to circulation would be rapidly eliminated.*
>
> *In this particular case, considering the nature and intended clinical use of the product, the lack of human pharmacokinetic data is not considered an obstacle for marketing authorisation.'*

Similarly, for TruScient, it can be accepted, given the rapid clearance/short systemic residence time of dibotermin alfa, that the lack of canine specific pharmacokinetic data is not an obstacle for a marketing authorisation. It is accepted that the pharmacokinetics of dibotermin alfa have been adequately characterised.

Toxicological studies

All of the toxicology studies presented below were originally conducted as part of the development of the product for use in humans (InductOs), hence they have previously been reviewed and accepted by the EMA/CHMP. An extensive set of data were provided in the human product and no additional information was required.

Single dose toxicity

The findings of the three acute toxicity studies (two in rats, one in the dog) suggest that acute toxic potential is low when the active substance is administered by the intravenous route. In the dog study, the maximum tolerated intravenous dose was determined to be >5.33 mg dibotermin alfa/kg, whereas TruScient is administered once at a maximum of 0.56 mg dibotermin alfa/dog.

It is noted that the very rapid elimination of dibotermin alfa from blood in rats may effectively prevent the development of any toxicologically significant findings.

Repeat dose toxicity

The findings of two repeat dose toxicity studies (one in rats, one in the dog) suggest that toxic potential is low when the active substance is administered repeatedly (up to 28 days) by the intravenous route. In the dog study, the only change of toxicological significance was perivascular fibroplasia and osseous metaplasia at the site of injection. In this study, the maximum tolerated intravenous dose (except for local effects) was determined to be 0.16 mg dibotermin alfa/kg/day, whereas TruScient is administered once at a maximum of 0.56 mg dibotermin alfa/dog.

Reproductive toxicity

The available data indicate that the potential risk of dibotermin alfa in relation to maternotoxicity, embryotoxicity, embryo-foetal development would appear minimal at dosages up to 0.16 mg/kg/day. In addition, based on the findings of the rabbit developmental toxicity study designed to investigate the effect of anti-dibotermin antibodies, the potential risk of anti-dibotermin antibodies for embryo-foetal development was considered negligible. Based on field data, the incidence of antibody titres in treated dogs is low. Further, it is expected that puppies will have no or very limited exposure to anti-BMP-2 antibodies due to the potential for limited transfer across the placenta in dogs. However, given that the direct effects of dibotermin alfa, or the effects of anti-dibotermin antibodies, on breeding/pregnancy have not been studied in the target species, the following recommendation will be included in section 4.7 of the SPC: 'This medicinal product should only be used in breeding, pregnant and lactating dogs following a risk/benefit assessment by the responsible veterinarian.' This is considered appropriate.

Mutagenicity / genotoxicity

Dibotermin alfa was considered non-mutagenic in the Ames *in vitro* study. No further data are required.

Carcinogenicity

In vitro studies to assess the potential effects of dibotermin alfa on tumour cell growth using various tumour cell lines and primary tumour isolates, including studies of osteosarcoma cell lines, have shown minimal evidence of growth potentiation. Additionally, studies in mice to assess whether surgical implantation of dibotermin alfa/ACS augmented the growth of subcutaneously injected human tumour cell lines (xenografts) suggest minimal potential for dibotermin alfa to stimulate tumour cell growth. Based on these data, carcinogenic potential is considered low.

A classical carcinogenicity study was not presented with this application. The absence of such a study can be accepted given that the Note for Guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals (CPMP/ICH/302/95) states that standard carcinogenicity studies are generally inappropriate for biotechnology derived pharmaceuticals. In addition, it should be noted that the product is intended for single dose administration and biologically active dibotermin alfa is expected to be present locally for a limited period of time. Dibotermin alfa released into blood circulation is rapidly eliminated in all studied animal species.

Studies of other effects

The following selected text relating to pharmacodynamics has been taken from the EPAR for InductOs:

General and safety pharmacology programme

A series of conventional safety pharmacology studies were conducted in accordance with GLP regulations to examine the potential extraneous pharmacological effects of dibotermin alfa. These experiments showed that dibotermin alfa had no effects on locomotion, the central nervous system, locomotor activity, respiration and cardiovascular systems, gastrointestinal systems, urinary system and blood coagulation at the doses tested. Therefore, it is concluded that the potential of dibotermin alfa exerting extraneous pharmacological effects, if there were to be inadvertent systemic exposure, is minimal.

Conclusions of other effect studies that have been performed with dibotermin alfa/ACS include:

There was no evidence of significant irritation or toxicity.

No significant evidence of delayed type sensitisation was observed.

No evidence of cytotoxicity was observed with the test article extract.

No evidence of cell lysis or toxicity was observed.

Other effect studies that have been performed with dibotermin alfa/ACS include:

- Modified USP Intracutaneous Toxicity Study in the Rabbit
- Delayed Contact Sensitisation Study in the Guinea Pig (maximisation method)
- Cytotoxicity test of a Sample Extract Using the MEM Elution method in the WI-38 Human Embryonic Lung Cell Line
- In Vitro Cytotoxicity Study (Agarose Overlay Method) in the L-929 Mouse Fibroblast Cell Line

Based on the findings of this series of studies, it can be concluded that the test article (dibotermin alfa/ACS) does not appear to be a dermal irritant, does not have dermal sensitisation potential and is not cytotoxic. Ocular irritancy has not been investigated. However, the absence of an ocular irritancy study has been scientifically justified.

Dibotermin alfa is approved for human use as InductOs. A summary of studies conducted in humans is provided in the European Public Assessment Report (EPAR) for that product.

User safety

The user safety assessment provided in support of this application is presented in accordance with the relevant CVMP guideline, EMEA/CVMP/543/03-FINAL.

Available data suggest that the toxicological potential of the active substance is low.

The different excipients present in the product can be considered non toxic and at the quantities present in the reconstituted final dibotermin alfa formulation pose no hazard to the user of the product.

The test article (dibotermin alfa/ACS) does not appear to be a dermal irritant, does not have dermal sensitisation potential and is not cytotoxic. Ocular irritancy has not been investigated. However, the absence of an ocular irritancy study has been scientifically justified.

The nature of the product is such that it must be used in a sterile setting: therefore, users must be appropriately attired (sterile gloves, gowns, etc). Consequently, when used in accordance with label recommendations, there is minimal risk of exposure.

The product, when used as recommended should not present an unacceptable risk to the user.

Environmental risk assessment

TruScient 0.66 mg Kit for implant for dogs is intended for single use in specialised orthopaedic surgery in dogs, which are classified as companion animals, and the potential for residues to enter the environment is extremely low. Under this use pattern, TruScient does not present a risk to the environment, and as such, in accordance with VICH Phase I, no further assessment is required.

Overall conclusions on the safety documentation

The available data suggest that the toxicological potential is low and that the product, when used as recommended should not present an unacceptable risk to the user.

The findings of the toxicological studies submitted in support of the application can be summarised as follows:

- Single dose toxicity (dibotermin alfa alone): in both rats and dogs the single-dose intravenous no-toxic effect level was 5.33 mg/kg, the highest dose tested.
- Repeated dose toxicity (dibotermin alfa alone): in rats and dogs receiving i.v. injections of dibotermin alfa daily for 28 days, there were no effects on haematology, clinical chemistry, urinalysis, or organ weights.
- Reproduction studies (dibotermin alfa alone): the potential risk of dibotermin alfa treatment in relation to maternotoxicty, embryotoxicty, embryo-foetal development would appear minimal at dosages up to 0.16 mg/kg/day.
- Carcinogenicity (dibotermin alfa alone): dibotermin alfa was considered non-mutagenic in the Ames *in vitro* study. *In vitro* studies to assess the potential effects of dibotermin alfa on tumour cell growth have shown minimal evidence of growth potentiation. Additionally, studies in mice to assess whether surgical implantation of dibotermin alfa/ACS augmented the growth of subcutaneously injected human tumour cell lines (xenografts) suggest minimal potential for dibotermin alfa to stimulate tumor cell growth. Based on these data, carcinogenic potential is considered low.

Safety for the Target Animal is discussed under Part 4.

The product, when used as recommended does not pose an unacceptable risk to the user. No evidence of dermal toxicity or dermal sensitation was seen. The SPC includes a statement that in case of accidental spillage onto skin and eyes the product should be rinsed off immediately.

The product, when used as recommended does not pose an unacceptable risk to the environment.

4. Efficacy assessment

No reduction in data requirements as per the MUMS guidelines was applied to this section as full studies were provided.

Development of resistance

Not applicable.

Dose determination / justification

The technique of infusing commercially available absorbable collagen sponge (ACS) with specific concentrations of dibotermin alfa in solution and applying it directly to surgically repaired fracture sites was first developed for human use. The EU human dibotermin alfa/ACS product approved as InductOs is a combination of 1.5 mg/ml solution of dibotermin alfa applied at a volume of 8 ml to a 7.62 x 10.16 cm Helistat ACS sponge, which is placed in apposition to the fracture line. A number of preliminary studies were done in dogs and other laboratory species using this dibotermin alfa formulation. The dog data developed as part of the pre-clinical data package for the human product indicate dibotermin alfa induces bone production in dogs at lower concentrations than are required to produce similar responses in humans. These studies also showed that the matrix (ACS) was also suitable in the dog.

The clinical development for canine use was done by developing a lyophilised product specifically for use in dogs containing the same active and excipients as used in the human product but at a different concentrations in order to allow the delivery of a smaller dose, and selecting the size of the ACS sponge that would be most suitable for canine use. Characterisation of the dose (that is, the concentration of active substance in mg/ml added to the ACS for application at the fracture site) was done in six canine studies using two different models (radius segmental defect and tibial osteotomy). Based on the findings of those studies, the following can be concluded:

Efficacy

- Dibotermin alfa induces bone growth in models of long bone fracture in the dog. In one series of studies, dibotermin alfa was capable of inducing sufficient bone growth to bridge a 2.5 cm segmental defect.
- At all concentrations evaluated (0.05, 0.2, 0.4 and 0.8 mg/ml), the substance was effective compared to negative controls based on various radiographic, biomechanical and/or histological parameters.
- The bone induced by dibotermin alfa shows characteristics of normal host bone based on radiographic, histological and biomechanical criteria.
- Efficacy at both 0.05 and 0.2 mg/ml dibotermin alfa was considered comparable to fracture healing induced by autologous bone graft Depending on the study, 0.2 mg/ml dibotermin alfa was shown to be as effective or more effective than 0.05 mg/ml dibotermin alfa
- In terms of efficacy, there is no apparent benefit in increasing the dose concentration above 0.2 mg/ml dibotermin alfa.

Safety

- While evaluation of target animal safety was not a specific objective of these studies, it would appear that dibotermin alfa at the quantities administered was well tolerated: in all studies, no

systemic adverse effects that could be attributed to the dibotermin alfa /ACS implant were noted.

- In a segmental defect study, the highest concentration tested, 0.8 mg/ml, was associated with formation of voids in the bone, heterotopic bone formation and potentially inferior biomechanical strength and radiographic density of the defect area. In that study, 0.2 mg/ml dibotermin alfa was also associated with void formation. However, in a subsequent study, the void effect noted with the dosage of 0.2 mg/ml appears temporary: radiographic and histological evaluation suggested the void spaces within dibotermin alfa/ACS induced bone remodelled with time following load bearing, although long-term data are limited. Void formation was observed in the radius segmental defect studies and not the tibia osteotomy studies and the intended use of dibotermin alfa/ACS as an onlay implant for clinical fracture repair (rather than as a volume filler for large segmental defects) may decrease the potential for such voids to occur in the clinical setting. It is suggested that the formation of voids may be due to angiogenic activity associated with dibotermin alfa induced bone formation and pooling of accumulated extra-cellular fluids.
- While heterotopic bone formation was a feature in the segmental defect studies, particularly at doses >0.2 mg/ml, bone induced by dibotermin alfa is typically self-limiting. Heterotopic bone formation was not a concern at the dosage of 0.2 mg/ml. There was no evidence of bone formation at sites distant from the implant. Indeed, this is to be expected given the slow release of dibotermin alfa from the implant site and the rapid systemic clearance.

Based on the above, it would appear that 0.2 mg/ml is the optimal dose concentration for investigating in a field study. Further elaboration on the dose, i.e. the size and number of sponges used on different size of dogs, is discussed under the clinical field trial.

Target animal tolerance

A large body of data have been presented in support of the safety of the product.

The recombinant human protein, dibotermin alfa, has been evaluated following parenteral administration to the target species for potential acute, and subchronic effects. The dibotermin alfa protein has been studied in single- and multiple-dose general toxicology studies in the beagle dog with up to 28 days of daily dosing, developmental toxicity studies in the rat and rabbit, and a fertility study in the rat. dibotermin alfa was administered intravenously and doses were selected to constitute a range of doses that varied from slightly lower to substantially higher than the total doses (weight based) of dibotermin alfa that have been used in the canine clinical study. The product appeared to be well tolerated in these studies (see Part 3).

The potential toxicity of dibotermin alfa/ACS was evaluated in a chronic 6-month mandibular/maxillofacial inlay study in the beagle dog. This study examined both the potential systemic effects as well as the local response at the site of implantation. Doses (concentrations) utilized in these studies represented 2x optimal concentration and markedly supra-pharmacologic multiples (8x and 20x). These studies have shown dose-related osteoinductive activity of dibotermin alfa/ACS at the site of implantation but have not shown adverse systemic or local effects other than swelling indicative of clinical effect. One obvious deficiency with the study is that it was not conducted in dogs when administered for the proposed indication (long bone fracture repair). The mandibular/maxillofacial model was selected because it was of interest from point of view of potential human use, the site contains both endochondral and membranous bone which allows extrapolation of safety data to other implant sites and, this model tested the device at a site which undergoes stresses

during mastication. While use of this model is acceptable for the investigation of systemic tolerance, the local effects evident in this study may not reflect the local effects that are likely to occur when the product is used for the treatment of diaphyseal fractures. However, local effects of dibotermin alfa treatment, when administered for the proposed indication, have been evaluated in a number of efficacy studies (see below).

Antibody responses to dibotermin alfa and type I bovine collagen have been evaluated in two studies in dogs.

Based on the information presented, there were no measurable antibody responses to bovine type I collagen. However, dibotermin alfa was clearly immunogenic. Typically, the antibody response was of low titre and transient. While it is not possible to be definitive about the relevance of this response, no clinical signs or allergic reactions were observed in any of the test dogs that developed antibodies to dibotermin alfa. In addition, the presence of antibodies to dibotermin alfa did not appear to impact the efficacy of dibotermin alfa/ACS. It is noted that both dibotermin alfa and bovine Type I collagen have been found to elicit immune responses in human patients. However the clinical relevance of such responses in man, as in the dog, is not clear.

The safety and effectiveness of repeat administration or more than one kit per dog has not been investigated. While it is accepted that repeat administration is likely to be an uncommon event there is the potential for adverse effects relating to immunogenic potential (allergic reaction, lack of efficacy by neutralising activity of the test material). The SPC includes a clear statement that the safety and effectiveness of repeat TruScient administration have not been evaluated in dogs. This is considered to be appropriate.

In the laboratory efficacy studies, the product was well tolerated. No systemic effects attributable to treatment were observed. Where local effects occurred, these were characterised by swelling. It is noted that the incidence of infection or heterotopic ossification did not appear to increase with dibotermin alfa use. Similarly, in the field study, there were no systemic effects attributable to treatment. However, the following local adverse effects (AE) associated with use of the product were observed:

- Swelling: an increase in swelling at the fracture site is observed in treated animals. Dogs treated with dibotermin alfa/ACS had slightly more swellings and slightly greater severity of swelling at the region under study than dogs in the untreated group. Based on the dibotermin alfa mechanism of action this observation is not unexpected. By week 3, the occurrence of firm swelling increased in both groups, with greater frequency in the dibotermin alfa/ACS treated group. Exuberant callus: In one dog, exuberant bone growth, considered to have a “probable” relationship to the treatment, was detected. This case had a complex fracture which may have contributed to the amount of callus/bone formed. This was addressed by removal of some of the bone callus.
- Seroma: seroma was reported as an AE for 5.7% (5/87) of treated dogs and 0% (0/46) of control dogs. Relationship to treatment was considered by the investigator to be unlikely in 80% (4/5) and “possible” in 20% (1/5). Overall, the relationship of these effects with treatment is unclear. None of the five seromas was reported as a serious AE.
- Incisional dehiscence/incisional drainage: Six treated dogs had an AE that was recorded as “Skin Disorder”: these consisted of four with incisional discharge and two with incisional dehiscence.
- Lameness: lameness was the most common AE and was reported in 12.6% (11/87) of treated and 6.5% (3/46) of control dogs; this difference was not statistically significant

For all potential local adverse effects, it is accepted that the majority will be transient and will regress over time, with or without treatment. Where necessary, treatment of local effects for individual dogs will be symptomatic.

Overall, the data presented indicate that the product is well tolerated systemically, but with the potential for local effects. The potential adverse effects are appropriately detailed in the SPC.

Field trials

The efficacy and safety of TruScient for the treatment of diaphyseal fractures was evaluated in a randomised, controlled, multicentre clinical field study. Test animals were randomised to one of two treatment groups: TruScient (dibotermin alfa/ACS) plus standard of care (SOC) or SOC alone. Reviewers assessing time to radiographic healing for each dog were masked to treatment. Dogs were followed for 18 weeks after treatment.

Based on the primary analysis in the present study, dibotermin alfa/ACS +SOC was effective in reducing the time to radiographic fracture union (P = 0.0001). At each time point, a larger percentage of dogs in the dibotermin alfa/ACS group achieved radiographic union compared with those treated solely with SOC.

Summary of the cumulative percent of radiographic fracture unions by week and treatment

	Weeks					
Treatment	**3**	**6**	**9**	**12**	**15**	**18**
TruScient + SOC (n=84)	9.5	83.3	92.9	97.6	98.8	100.0
SOC (n=42)	0	50.0	83.3	88.1	90.5	95.2

SOC = standard of care

Notwithstanding the faster time to fracture union (based on radiography) for the dibotermin alfa/ACS +SOC group, there was no difference between treatment groups with respect to overall clinical assessment score. The clinical condition assessment score was based on clinical signs of healing, including degree of lameness, pain, swelling, infection at the region under study, secondary intervention, hardware complications and other adverse events. When individual clinical parameters are considered, scores for lameness and pain were highest at week 3 (indicating more severe lameness and pain). Scores for both parameters decreased (improved) similarly in both groups throughout the study.

In conclusion, while a significant effect on clinical parameters (clinical signs of healing) has not been detected, the primary objective in terms of efficacy was achieved: that is, there was a statistically significant difference between groups with respect to time to radiographic fracture healing. The findings of this study support the indication as currently proposed.

In the field study, the dose of product used and the method of application is in line with the recommendations in the proposed SPC. The number of dibotermin alfa/ACS implants applied per fracture ranged from <25% of one implant to 100% of two implants (mean =1.33 sponges used), with an estimated total of <0.035 mg to 0.56 mg dibotermin alfa applied (mean =0.37 mg applied). It is noted that there were no reports of difficulties in applying the treatment to the fractured bone.

The applicant conducted a review of the field study data to investigate if the quantity of ACS/active substance administered to individual dogs varies with the size of the dog and/or the nature of the fracture and the occurrence/seriousness of local adverse effects. Analysis of the data reveals there is no apparent correlation between the size/volume of the sponge implanted relative to the dog's size and nature of fracture. Similarly, there is no apparent correlation between the size/volume of the sponge

implanted relative to the occurrence/seriousness of local adverse effects. Based on feedback from investigators participating in the clinical study, only the amount of prepared ACS needed to cover the accessible fracture lines and defects should be used in order to avoid excessive post-operative swelling. In conclusion, it is accepted that selection of the appropriate amount of prepared sponges is straightforward and the advice as presented in the SPC is appropriate:

> '*The amount of prepared sponge placed is determined by the fracture anatomy and the ability to close the wound with minimal compression of the sponge. Use only the amount of prepared sponge needed to achieve coverage of accessible fracture lines and defects (less than one up to two prepared sponges).*
>
> *……..*
>
> *Place the prepared sponge(s) so that it bridges the fracture and makes good contact with the major proximal and distal fracture fragments. The prepared sponge may be wrapped around the bone or placed up to the edges of a bone plate as the geometry of the fracture and fixation requires. …….. Area vascularity should be maintained.'*

Dibotermin alfa antibody response to TruScient was evaluated in the field study. Development of antibodies occurred in 6.9% of dogs receiving TruScient vs. 4.3% of dogs in the control group. The antibody titers did not correlate with any adverse clinical sign including any immune mediated adverse events such as allergic reactions.

Other studies

Based on the pre-clinical documentation presented in support of the proposed dose, the following conclusions can be made with regard to efficacy:

- dibotermin alfa induces bone growth in models of long bone fracture in the dog. In one series of studies, dibotermin alfa was capable of inducing sufficient bone growth to bridge a 2.5 cm segmental defect.
- At all concentrations evaluated (0.05, 0.2, 0.4 and 0.8 mg/ml), the substance was effective compared to negative controls based on various radiographic, biomechanical and/or histological parameters.
- The bone induced by dibotermin alfa shows characteristics of normal host bone based on radiographic, histological and biomechanical criteria.
- Efficacy at both 0.05 and 0.2 mg/ml dibotermin alfa was considered comparable to fracture healing induced by autologus bone graft (studies BBA94025-11, BBA96030-11, BBA95002-11)
- Depending on the study, 0.2 mg/ml dibotermin alfa was shown to be as effective (study BBA94025-11) or more effective (study 0981-C-US-01-03) than 0.05 mg/ml dibotermin alfa.
- There is no apparent benefit in increasing the dose concentration above 0.2 mg/ml dibotermin alfa.

Based on the data provided, it is accepted that a dose of 0.2 mg dibotermin alfa/ml is an appropriate dose concentration for investigating efficacy in a field study.

In addition to the dose determination/confirmation studies, the applicant presented reports of a number of other studies conducted in dogs to evaluate the osteoinductive ability of dibotermin alfa/ACS. The studies are considered supportive only because they were pilot studies and/or used doses different to the RTD and/or investigated effect at sites other than long bones (e.g. maxillofacial

and dental applications). Notwithstanding the limitations of these data, the following conclusions can be made:

- 0.2 mg/ml dibotermin alfa appears to be effective at inducing bone growth in a variety of models of bone defect in the dog.
- While evaluation of target animal safety was not a specific objective of these studies, it would appear that dibotermin alfa at the quantities administered was well tolerated. In all studies, no systemic adverse effects that could be attributed to the dibotermin alfa/ACS implant were noted. Some local effects (swelling), the incidence and severity of which were dose dependent, were observed. In some studies, newly formed bone included radiolucent voids that appeared to regress over time.

Overall conclusion on efficacy

Based on the pre-clinical data provided, it is accepted that a dose of 0.2 mg dibotermin alfa/ml is the optimal dose concentration.

Based on the findings of the field study, while a significant effect on clinical parameters (clinical signs of healing) was not detected, the primary objective in terms of efficacy was achieved: that is, there was a statistically significant difference between groups with respect to time to radiographic fracture healing.

The CVMP discussed the need to request specific training material be provided to veterinary surgeons on the use of this product as part of the marketing authorisation application and concluded that this was not necessary.

The available efficacy data support the indication as included in the SPC.

5. Benefit/risk balance

Benefit risk assessment

Introduction

TruScient 0.66 mg kit for dogs is presented in packs/containers consisting of a vial of lyophilised powder which contains 0.66 mg of the active substance dibotermin alfa (recombinant human bone morphogenetic protein (rhBMP-2)); a vial of solvent (sterile water for injection); a pack containing two sterile Absorbable Collagen Sponges (ACS) and sterile syringes and needles. The indication is 'Treatment of diaphyseal fractures as an adjunct to standard surgical care using open fracture reduction in dogs.' TruScient has been classified as a MUMS product and the data requirements as per the MUMS guidelines have been applied where appropriate.

Dibotermin alfa has been approved for use in humans as part of the InductOs kit (EU/1/02/226/001).

Benefit assessment

TruScient 0.66mg kit for dogs is a new treatment principle.

The principal intended action of dibotermin alfa is to promote new bone growth and enhance the natural healing of fractured bone. Specifically, the dibotermin alfa binds to receptors on the surface of mesenchymal cells and causes cells to differentiate into cartilage- and bone-forming cells. These differentiated cells form trabecular bone. When used as directed, while a significant effect on clinical

parameters (clinical signs of healing) was not detected, it is claimed that the product will significantly accelerate a reduction in time to radiographic bone union.

Based on laboratory studies in dogs, it has been demonstrated that a concentration of 0.2 mg dibotermin alfa/ml, when used as directed, induces bone growth in canine models of long-bone fracture and results in accelerated fracture healing as evidenced by a reduction in time to radiographic bone union, faster return of bone strength and normal bone morphology.

Based on the analysis in the field study, dibotermin alfa/ACS was effective in reducing the time to fracture union (P = 0.0001). At each time point where measurement of efficacy was conducted, a larger percentage of dogs in the dibotermin alfa/ACS group achieved radiographic union compared with those treated solely with 'standard of care'. These data support the indication as currently proposed.

Risk assessment

Because dibotermin alfa is slowly released from a site of dibotermin alfa/ACS implantation and rapidly cleared from the systemic circulation, systemic exposure to dibotermin alfa will be limited. It is argued that this limited systemic exposure predicts a favourable safety profile of dibotermin alfa/ACS following implantation of dibotermin alfa/ACS.

A large body of data has been presented in support of the safety of the product in the target species. Overall, the data presented indicate that the product is well tolerated systemically, with the potential for local effects. The potential local effects are appropriately detailed in the SPC

The available data suggest that the toxicological potential is low and that the product, when used as recommended should not present an unacceptable risk to the user.

The product, when used as recommended does not pose an unacceptable risk to the environment.

Evaluation of the benefit risk balance

The available efficacy data support the indication as currently proposed. The active substance has a satisfactory safety profile.

The product has been shown to have a positive benefit risk balance overall.

Conclusion on benefit risk balance

Given that the available data adequately support the claimed indication, the benefits of the product are proven. No unacceptable risks are identified. Consequently, the benefit risk balance is positive.

Based on the original and complementary data presented, the Committee for Medicinal Products for Veterinary Use concluded that the quality, safety and efficacy of the product were considered to be in accordance with the requirements of Directive 2001/82/EC as amended.