ASSURING THE SAFETY, QUALITY AND EFFICACY OF VETERINARY MEDICINES

United Kingdom
Veterinary Medicines Directorate
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DECENTRALISED PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

Anarthron 100 mg/ml Solution for Injection

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0223/001/DC
Name, strength and pharmaceutical form	Anarthron 100 mg/ml Solution for Injection
Applicant	Arthropharm (Europe) Ltd 50 Bedford Street Belfast BT2 7FW Northern Ireland
Active substance	Pentosan polysulphate sodium
ATC Vetcode	QM01AX90
Target species	Dogs
Indication for use	For the treatment of lameness and pain of degenerative joint disease/osteoarthrosis (non-infectious arthrosis) in the skeletally mature dog.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Heads of Medicines Agencies (veterinary) (HMA(v)) website (www.hma.eu).

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Decentralised application in accordance with Article 12 of Directive 2001/82/EC as amended.
Date of completion of the original decentralised procedure	01 May 2007
Date product first authorised in the Reference Member State (MRP only)	Not applicable
Concerned Member States for original procedure	Austria Belgium France The Netherlands
Concerned Member States for Repeat Use procedure	Austria Belgium France Iceland The Netherlands Norway Poland

I. SCIENTIFIC OVERVIEW

The product is produced and controlled using validated methods and tests which ensure the consistency of the product released on the market. It has been shown that the product can be safely used in the target species; the slight reactions observed are indicated in the SPC. The product is safe for the user, and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy of the product was demonstrated according to the claims made in the SPC. The overall risk/benefit analysis is in favour of granting a marketing authorisation.

II. QUALITY ASPECTS

A. Composition

The product contains pentosan polysulphate sodium as the active substance and excipients, benzyl alcohol, disodium phosphate dodecahydrate, sodium dihydrogen phosphate dihydrate, sodium hydroxide, hydrochloric acid, nitrogen and water for injections

The product is a solution for injection supplied in 10 ml clear glass type I vials fitted with a 20 mm rubber stopper, and closed by a plastic flip off seal attached to an aluminium seal. The particulars of the containers and controls performed are provided and conform to the regulation.

The choice of the formulation is justified.

The product is an established pharmaceutical form and its development is adequately described in accordance with the relevant European guidelines.

B. Method of Preparation of the Product

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site.

Process validation data on the product have been presented in accordance with the relevant European guidelines.

C. Control of Starting Materials

The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Supporting data have been provided in the form of a European Drug Master File (EDMF). It is considered that the manufacturing process is adequately controlled and the active substance specification has been suitably justified

D. Specific Measures concerning the Prevention of the Transmission of Animal Spongiform Encephalopathies

There are no substances within the scope of the TSE Guideline present or used in the manufacture of this product.

E. Control on intermediate products

There are no intermediate products

F. Control Tests on the Finished Product

The finished product specification controls the relevant parameters for the pharmaceutical form. The tests in the specification, and their limits, have been

justified and are considered appropriate to adequately control the quality of the product.

Satisfactory validation data for the analytical methods have been provided.

Batch analytical data from the proposed production sites have been provided demonstrating compliance with the specification.

G. Stability

Stability data on the active substance have been provided in the form of a drug master file, demonstrating the stability of the active substance when stored under the approved conditions.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating the stability of the product throughout its shelf life when stored under the approved conditions.

- Do not store above 25°C.
- Keep container in the outer carton in order to protect from light.

H. Genetically Modified Organisms

Not applicable

J. Other Information

Shelf life: 3 years.
Following withdrawal of the first dose, use the product within 3 month. Discard unused material.

III. SAFETY AND RESIDUES ASSESSMENT (PHARMACO-TOXICOLOGICAL)

III.A Safety Testing

Pharmacological Studies

The applicant has submitted an extensive dossier in support of the pharmacodynamics of sodium pentosan polysulphate and its effect on osteoarthritic diseases. Pentosan polysulphate has a positive impact on arthritic diseases through a complex interaction with a number of metabolic pathways. The references provided also address the normal function of joints and the components of mammalian joints.

The main pharmacodynamic features are incorporated in the SPC:

The product contains Pentosan Polysulphate Sodium (NaPPS), a semi-synthetic polymer with a mean molecular weight of 4000 Daltons.

In a model of osteoarthritis in dogs, when NaPPS was administered at similar to therapeutic doses, levels of metalloproteinases in cartilage were reduced and levels of tissue inhibitor of metalloproteinase[1] (TIMP) increased, thereby preserving proteoglycan content and protecting cartilage matrix from degradation.

In dogs with osteoarthritis administration of NaPPS caused fibrinolysis[2], lipolysis[3] and decreased platelet aggregability."

In *in vitro* studies and *in vivo* studies in laboratory species using doses above those proposed for therapeutic use, NaPPS suppressed levels of anti-inflammatory mediators and stimulated hyaluron[4] synthesis from fibroblasts.

The pharmacokinetics of pentosan polysulphate are also well described in the references provided. Pharmacokinetics are described in a number of species, including rat, rabbit and man and there is a good correlation between the species. The similarity of pentosan polysulphate with naturally occurring sulphated polymeric sugars defines the pharmacokinetics of the compound. The pharmacology of pentosan polysulphate has been adequately addressed.

Toxicological Studies

- Single Dose Toxicity

The applicant has provided limited data on the acute toxicity of pentosan polysulphate. However, the LD_{50}[5] values indicate that the compound is of extremely low acute toxicity and is considered sufficient to demonstrate that acute exposure is unlikely to present an undue hazard to the operator.

- Repeated Dose Toxicity

The applicant has provided a number of repeat dose studies of varying treatment length and in different species. Repeat toxicity of pentosan polysulphate derived NOELs ranging from 2 - 50mg/kg/day in different species and via different routes of administration. However, in all species, the signs of toxicity were reversible on discontinuation of treatment and consistent between species. The organs and tissues mostly affected by treatment with pentosan polysulphate were liver and kidney. There were also adverse effects on coagulation times. Repeated dose toxicity of pentosan polysulphate has been adequately addressed and it is considered unlikely that exposure of the operator to the compound would result in undue hazard.

- Reproductive Toxicity, including Teratogenicity:

The potential of pentosan polysulphate to elicit adverse effects on reproductive potential, maternotoxicity, embryotoxicity and teratogenicity has been examined

[1] These constitute a family of enzymes
[2] Fibrinolysis is the process where a fibrin (protein involved in blood clotting) clot, the product of coagulation, is broken down
[3] Lipolysis is the breakdown of fat stored in fat cells
[4] hyaluron polysaccharide
[5] This is the dose at which 50% of subjects will die

in a number of studies. Pentosan polysulphate has been shown not to possess activity in any of the parameters examined, except for maternal toxicity in one study in rabbits at repeated daily doses 2.5 times the recommended dose. Although a number of the studies are very old and do not comply with modern standards, the results are sufficiently consistent to provide confidence that pentosan polysulphate will not adversely impact on reproductive parameters or directly on foetal development.

- Mutagenicity

Pentosan polysulphate has been investigated in a number of *in vitro* and *in vivo* mutagenicity studies. The compound was negative in all assays. The absence of carcinogenicity studies has been satisfactorily justified.

Other Studies

- Skin sensitisation:

The applicant has provided the final report of a study investigating the sensitisation potential of sodium pentosan polysulphate. The study involved application of 500 mg of compound for the first exposure and 50 mg for subsequent exposures to guinea pigs. The concentrations evaluated were significantly in excess of those likely to be encountered when exposed to the product. This was considered satisfactory and concluded that sodium pentosan polysulphate did not induce sensitization and can be considered a non-sensitizer.

- Eye and skin irritation:

Primary irritancy of the active ingredient, pentosan polysulphate sodium, to the skin and eye has been studied. Local tolerance was tested by the application of an ointment containing 0.5% pentosan polysulphate sodium into rabbits' eyes and it was found that it did not provoke irritation of conjunctiva or cornea. The administration for 24 hours to the hairless part of the external ear of rabbits was tolerated without local reaction. A repeat dose dermal toxicity study, using hairless rats, did not lead to macroscopical or histological skin irritation and did not affect other toxicological parameters. Neither local incompatibilities nor systemic reactions were observed. These results are in agreement with the skin sensitisation study.

As the active ingredient in Anarthron has been proven safe to the skin and eye and the excipients in Anarthron, benzyl alcohol, disodium phosphate dodecahydrate and sodium dihydrogen phosphate dihydrate are pharmacologically well known and used widely in pharmaceuticals, local tolerance studies of the final formulation of Anarthron were not undertaken.

- Immunotoxicity:

The applicant has provided a number of references relating to immunotoxic reactions to pentosan polysulphate in humans. Although twenty-five cases of immunoallergic thrombocytopenia have been reported in the literature to be associated with the systemic use of pentosan polysulphate, it is also noted that pentosan polysulphate has been used in millions of patients in several countries for more than 25 years without major concerns relating to immunotoxicity.

Observations in Humans

The applicant has submitted a number of references relating to the use of pentosan polysulphate in humans. Pentosan polysulphate has been widely used in Europe for post-operative thromboprophylaxis in humans for more than 25 years. Parenteral doses up to 4mg/kg/day in patients and healthy human volunteers have had little or no impact on primary haemostasis or bleeding time and platelet numbers in circulating (peripheral) blood.

User Safety

The applicant has provided a satisfactory user risk assessment, identifying all potential routes of exposure of the operator to the product. The proposed user safety warnings are fully justified by the user risk assessment. The applicant has included the following user warnings in the SPC and product literature:

"Normal precautions should be observed. Care should be taken to avoid accidental self-injection. Wash splashes from eyes and skin immediately with water. Wash hands after use."

Ecotoxicity

The applicant provided a first phase environmental risk assessment in compliance with the relevant guideline which showed that no further assessment is required. The assessment concluded that exposure of the environment to the active ingredient is not considered to be extensive.

Warnings and precautions as listed on the product literature are adequate to ensure safety to the environment when the product is used as directed.

IV CLINICAL ASSESSMENT (EFFICACY)

IV.A Pre-Clinical Studies

Pharmacology

The applicant has provided a number of references to studies which indicate hypothetical modes of action for sodium pentosan polysulphate in osteoarthrosis in dogs of varying treatment length and in different species. These are reflected in the SPC as shown in section IIIA of this discussion.

The applicant has also provided reference to a number of pharmacokinetic studies in different species. The studies conducted in the dog support rapid absorption and elimination of sodium pentosan polysulphate from the plasma. The half-life for elimination from the main compartment was approximately 3 hours. One study showed that even at a dose of 30 mg/kg, clearance was rapid. A study also found that 70% of administered radioactivity was excreted in the urine within 48 hours.

Tolerance in the Target Species of Animals

Extensive toxicity studies in various species have been conducted over many years. Various summaries of the methods used and findings have been presented . The SPC clearly represents these findings.

Pentosan polysulphate sodium is contra-indicated for the treatment of septic arthritis.

Emesis, diarrhoea, lethargy and anorexia have been reported following the use of pentosan polysulfate. These signs may be the result of a hypersensitivity reaction and may require appropriate symptomatic treatment including antihistamine administration.

Administration of the product at recommended dose rates results in increases of activated partial thromboplastin time (aPTT) and thrombin time (TT) which may persist for up to 24 hours after administration in healthy dogs. This very rarely results in clinical effects, but because of the fibrinolytic action of pentosan polysulphate sodium, the possibility of internal bleeding from a tumour or vascular abnormality should be considered if signs develop. It is recommended that the animal should be monitored for signs of blood loss and treated appropriately

Bleeding disorders such as nasal bleeding, haemorrhagic diarrhoea and haematomas have been reported.

Local reactions such as a transient swelling have been observed post injection.

IV.B Clinical Studies

A double-blind pivotal clinical study showed that when this product was administered in accordance with the proposed dosing regime, it had a similar efficacy to the comparator formulation in the alleviation of the pain and lameness associated with osteoarthritis in dogs. This product was, however, slower in onset of action and did not appear to be equivalent with the comparator formulation until after the second injection. However, this product maintained some efficacy at 4 weeks after the final injection. These findings are supported by those of the dose determination study, which was conducted under field conditions but where a placebo control group was used.

The applicant evaluated the product in terms of its efficacy in treating the clinical signs of osteoarthritis, and the parameters of “lameness” and “pain” were chosen as the primary outcome variables for the clinical efficacy studies. These variables establish the indications for the product.

From the data available, this product delivered an optimal response when administered at 3 mg/kg, subcutaneously, weekly on 4 occasions, in the treatment of lameness and pain associated with osteoarthritis in the dog. The full effect was not apparent until after the second injection, but was maintained up to

4 weeks after the final injection.

A number of supportive studies which contribute to the overall clinical efficacy and safety data were also provided. Overall, vomiting was the most common adverse reaction. Several studies involved dogs that were > 9 years old and the product was demonstrated to have good tolerability in this age group. One dog with pre-existing renal disease had further deterioration of its condition. There was no evidence of hepatic problems or haemorrhagic syndromes as may have been predicted from the tolerance studies.

Taking into account the data provided, the indication of this product is justified and included on the SPC and product literature as follows:

For the treatment of lameness and pain of degenerative joint disease/osteoarthrosis (non-infectious arthrosis) in the skeletally mature dog.

V OVERALL CONCLUSION AND BENEFIT– RISK ASSESSMENT

The data submitted in the dossier demonstrate that when the product is used in accordance with the Summary of Product Characteristics, the risk benefit profile for the target species is favourable and the quality and safety of the product for humans and the environment is acceptable.

MODULE 4

POST-AUTHORISATION ASSESSMENTS

The SPC and package leaflet may be updated to include new information on the quality, safety and efficacy of the veterinary medicinal product. The current SPC is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)

The post-authorisation assessment (PAA) contains information on significant changes which have been made after the original procedure which are important for the quality, safety or efficacy of the product.

The PAA for this product is available on the Product Information Database of the Veterinary Medicines Directorate website.

(www.gov.uk/check-animal-medicine-licensed)