Veterinary Medicines Directorate

United Kingdom
Veterinary Medicines Directorate
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MUTUAL RECOGNITION PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

SynVet-50; 50 mg Solution for Injection for Horses

Date Created: 19th September 2014

PuAR correct as of 15/01/2019 when RMS was transferred to IE.
Please contact the RMS for future updates.

MODULE 1

PRODUCT SUMMARY

EU Procedure number	UK/V/0505/001/MR
Name, strength and pharmaceutical form	SynVet-50; 50 mg/ml Solution for Injection
Applicant	Equimed Ltd Jeffcott 2 Hillards Court Chester Business Park Chester CH4 9PX UK
Active substance(s)	Sodium hyaluronate
ATC Vetcode	QM09AX01
Target species	Horses
Indication for use	For adjunctive intra-articular treatment of joint disease associated with non-infectious synovitis in horses.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Veterinary Medicines Directorate website (www.vmd.defra.gov.uk)

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Well established veterinary use application in accordance with Article 13a of Directive 2001/82/EC as amended.
Date of completion of the original mutual recognition procedure	9th May 2014
Date product first authorised in the Reference Member State (MRP only)	9th September 2010
Concerned Member States for original procedure	Austria, Belgium, Denmark, Finland, France, Germany, Ireland, Italy, The Netherlands, Norway, Spain and Sweden.

I. SCIENTIFIC OVERVIEW

SynVet-50; 50 mg solution for injection for horses is authorised for adjunctive intra-articular treatment of joint disease associated with non-infectious synovitis in horses. The application was submitted in accordance with Article 13a of Directive 2001/82/EC, a 'well established veterinary use' application. The product was first authorised in the UK on 9th September 2010.

SynVet-50; 50 mg solution for intra-articular injection should be administered intra-articularly into medium sized and large joints in horses using a pre-filled syringe of 2.5 ml. Each 2.5 ml syringe of the product contains the 50 mg active substance sodium hyaluronate, which is equivalent to 47 mg of hyaluronic acid. The injection should be administered under strict aseptic conditions and excess synovial fluid should be removed when possible prior to injection. Treated horses should be box-rested for 2 days before gradually resuming a normal exercise pattern.

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 used safely in the target species; the slight reactions observed are indicated in the SPC[1].

The product is safe for the user, the consumer, and the environment when used as recommended. Suitable warnings are indicated in the SPC. The efficacy of the product was demonstrated according to the claims made in the SPC. The overall benefit/risk analysis is in favour of granting a marketing authorisation.

[1] Summary of Product Characteristics

II. QUALITATIVE AND QUANTITIATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains 20 mg / ml sodium hyaluronate as the active substance and the excipients sodium chloride, disodium phosphate dodecahydrate, citric acid monohydrate and water for injections.

The container/closure system consists of a single-dose glass syringe barrel with a luer tip and rigid tip cap. The syringe is Type 1 glass which is lubricated with dimethicone, a styrene-butadiene rubber cap and a bromobutyl rubber plunger. The product is available in single cartons or packs of 6 single cartons overwrapped with plastic film. Not all pack sizes may be marketed. 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.

II.B. Description of the Manufacturing Method

The product is manufactured fully in accordance with the principles of good manufacturing practice from a licensed manufacturing site. The product is manufactured by mixing the active substance with salts, followed by stirring. Following dissolution of the active the solution is filtered under pressure and the solution is held under vacuum and subsequently filled into the syringe. Filled syringes are then packed into blisters. Process validation data on the product have been presented in accordance with the relevant European guidelines.

II.C. Control of Starting Materials

The active substance is sodium hyaluronate which is the sodium salt of hyaluronic acid. Sodium hyaluronate is described in the European Pharmacopoeia and Ph. Eur. Certificate of Suitability has been supplied for the manufacturer of the active substance. The active substance is manufactured in accordance with the principals of good manufacturing practice.

The active substance specification is considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with this specification have been provided.

The excipients are described in the European Pharmacopoeia are manufactured in accordance with the relevant Ph. Eur. monographs.

II.C.4. Substances of Biological Origin

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

II.D. Control Tests Carried Out at Intermediate Stages of the Manufacturing Process

Not applicable.

II.E. 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. These tests include appearance, polydispersity, identification and content of the active, average molecular weight, osmolality, pH, dynamic viscosity, sterility and uniformity of dosage units.

Satisfactory validation data for the analytical methods have been provided. Batch analytical data from the proposed production site have been provided demonstrating compliance with the specification.

II.F. Stability

Stability data on the active substance have been provided in accordance with applicable European guidelines, demonstrating the stability of the active substance when stored under the approved conditions. Sodium hyaluronate is manufactured in accordance with the Ph. Eur. Certificate of Suitability and the retest period for the manufacturer is 36 months.

Stability data on the finished product have been provided in accordance with applicable European guidelines, demonstrating stability of the product throughout its shelf life when stored under the approved conditions. Data were provided for batches stored at 25°C/60% RH for 36 months and batches stored at 40°C/60% RH for 6 months. The data support a shelf life of 3 years for the finished product.

G. Other Information

Shelf-life of the veterinary medicinal product as package for sale: 3 years
Any solution remaining in the syringe following withdrawal of the required dose should be discarded.
Do not store above 25°C.
Store in the original container.
Store in a dry place.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Pharmacodynamics

Sodium hyaluronate is a natural physiological component of connective tissue in all mammals and its chemical structure is the same in all mammals. Sodium hyaluronate is the sodium salt of hyaluronic acid, a non-sulphated, high viscosity mucopolysaccaride or glycosaminoglycan of high molecular weight. It competes with other polysaccharides for receptor binding and thus for update in the specific tissue. The therapeutic effects of sodium hyaluronate are attributed to anti-inflammatory, analgesic, lubricant or anti-oxidant effects. Intra-articularly administered sodium hyaluronate alleviates aseptic joint inflammation and enhances joint lubrication. The mechanism of action of the active substance is not fully understood.

Pharmacokinetics

The pharmacokinetics of hyaluronic acid is well-established in various species including humans. Studies with radio-labelled hyaluronic acid in rabbit and sheep indicate that hyaluronic acid is cleared from the joint within 4 to 5 days of intra-articular injection. Elimination half-life from synovial fluid after intra-articular injection of any joint was highly variable, however the mean $T_{1/2}$[2] determined in only a few horses, was approximately 24 hours. Intra-articularly administered hyaluronic acid moved into and disappeared from the circulation at a first- order rate. Uptake is primarily via the lymphatics and metabolised in liver epithelial cells. The main metabolites are water, carbon dioxide, lactate, D-glucosamine-N-acetyl-D-glucosamine, low weight hyaluronic acid and monosaccharides.

Toxicological Studies

Single dose toxicity

A 1% solution of sodium hyaluronate (NaHA) was administered subcutaneously to male dogs. Dogs received various doses of NaHA orally. Skin protuberance was observed in a dose dependant manner at the injections site. Dogs receiving the highest dose showed hair loss at the injection site and decreased food consumption. No significant drug related changes were noted in the body weight or in clinical examination. In another study rats were administered a 1% solution of sodium hyaluronate via the oral, subcutaneous or intra-peritoneal routes. Doses given to the rats were based on the highest technical achievable dose. No death occurred in any group. Oral administration had no effect on general appearance, bodyweight or necropsy findings and no toxic signs were observed in the animals. The oral, subcutaneous and intra-peritoneal LD_{50}[3] of sodium hyaluronate was estimated to exceed 500 mg/kg, 200 mg/kg and 2000 mg/kg respectively.

[2] $T_{1/2}$ – elimination half-life
[3] LD_{50} – The dose that kills half the population

Repeated dose toxicity
A chronic toxicity test on sodium hyaluronate was carried out in 7 male and female dogs. Animals were administered the active substance intra-articularly twice weekly for 6 months at various doses. No toxic changes were detected in relation to sodium hyaluronate with respect to general symptoms, bodyweight, and clinical examination. The only change observed was the slight limping of some animals following injection, which was likely due to the route of administration rather than to the test material. The NOAEL[4] was estimated to be at least 12 mg/kg.

Reproductive toxicity, including teratogenicity
A fertility study was carried out in male and female rats receiving various doses of sodium hyaluronate subcutaneously prior to and during the early stages of pregnancy. No effects on bodyweight or food consumption were noted during the treatment period. Swelling occurred at the injection sites and was dose-dependent. No influence on fertility, mortality, inhibition of development and teratogenicity was observed.

A second fertility study was performed using 1% hyaluronate in phosphate-buffered saline, which was injected subcutaneously into rats at various doses. Doses were administered to male rats prior to and through the mating period and to females during early stages of pregnancy. Sodium hyaluronate has no effect on the oestrus cycle, copulation, conception or ovulation. At the higher doses, parts of the compound remained at the injection site. No effects on the development of the embryos or foetuses, nor teratogenic toxicity were noted. A NOAEL of 40 mg/kg per bodyweight was calculated.

A teratogenicity study in rats was performed. Rats were injected subcutaneously with sodium hyaluronate at various doses from days 7 to 17 of gestation. During treatment swellings were observed at the injections sites which correlated to the dosage administered, this was observed as subcutaneous deposits of viscous solution at necropsy. High absolute and relative weights of the ovaries were observed in the 20 mg/kg and 50 mg/kg groups compared to the control group. The fertility index was low in the 50 mg/kg group. In foetuses there was no toxic effect on viability or developments and no teratogenic effects. No adverse effects were noted. The NOAEL was established at 50 mg/kg per day from dams, foetuses and live pups.

Mutagenicity
The mutagenicity potential of sodium hyaluronate was evaluated *in vitro* in the reverse mutation test using *Salmonella typhimurium* and *Escherichia coli* in a chromosomal aberration test. Sodium hyaluronate caused no increase of revertants nor did it increase the number of aberrant cells in comparison to the negative control. Sodium hyaluronate is not classified as mutagenic.

Mutagenicity of sodium hyaluronate was investigated *in vivo* by micronucleus test with male mice. Mice were administered intra-peritoneally twice daily at

[4] NOAEL – No observed adverse effect limit.

various doses and bone marrow was collected at regular intervals. The results showed that sodium hyaluronate is not mutagenic.

Carcinogenicity
No data was submitted. As sodium hyaluronate has no mutagenic potential as demonstrated both *in vitro* and *in vivo*, it is not considered a potential carcinogen.

Studies of Other Effects

The results of a cytotoxicity test were performed and were negative for a 2% solution of hyaluronic acid. No studies were submitted on the final formulation. Given the pharmacokinetics and pharmacodynamics of the active substance and excipients, this was acceptable.

Observations in Humans

Intra-articular hyaluronate therapy has been used for the treatment of knee osteoarthritis and osteoarthritis pain in humans for more than 30 years. It is predicated that over 100 million injections of commercially available sodium hyaluronate preparations are given worldwide.

Microbiological Studies

No data were provided for the microbiological activity of sodium hyaluronate.

User Safety

A user risk assessment was provided in compliance with the relevant guideline which shows that the most likely routes of exposure are through accidental injection and dermal spillage post-administration. Exposure though inhalation is unlikely due to the physical form of the product. As the product should only be used by veterinarians the probability of exposure is reduced. A quantitative risk assessment highlighted that in the worst case scenario, (an entire dose injected into the user), the dose is considerably lower than the LOAEL found in rats, in which toxic signs were pain at the injection site. Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product.

- In case of accidental contact with skin, wash with soap and water.
- In case of accidental contact with eyes, blurred vision may occur because of the viscous nature of the product. Rinse immediately with plenty of clean water.
- In the event of accidental self-injection seek medical advice.

Environmental Safety

Phase I:
The applicant has provided a Phase 1 environmental risk assessment in compliance with the relevant guideline. A PBT[5] analysis has been submitted based on published literature. This indicates that sodium hyaluronate does not have the potential to be a PBT substance. A $PEC_{soil\ initial}$[6] has been provided using the values in the CVMP[7] guidance document and a calculated value of 5.18µg/kg was determined. This product did not require a Phase II assessment and is not expected to pose a risk to the environment when used as recommended.

III.B.2 Residues documentation

Residue Studies
Hyaluronic acid is currently included in Table 1 of Regulation 37/2010 with a 'no MRL required' entry; therefore it is not necessary to establish a maximum residue limit for hyaluronic acid. All excipients are substances registered for use in food or medicinal products and are also found in Table 1 of Regulation 37/2010 with a 'no MRL require' entry. The applicant submitted numerous references in support of the pharmacological requirements, detailing that sodium hyaluronate is a natural constituent of both extracellular matrix and synovial fluid, and presents a low toxicity risk. No significant concentrations of the active substance and any metabolites are to be expected in meat when animals are treated with local intra-articular injections at a single dose of 50 mg and it is considered that the target organs for treatment (joints) are unlikely to be consumed. It is considered unlikely that animals treated therapeutically with the product will be slaughtered immediately after treatment as there will be a period of time to gauge the success of this product improving lameness. No depletion studies or any other studies have been provided, and a withdrawal period of zero days was accepted.

Withdrawal Periods

Based on the data provided, a withdrawal period of zero days for meat in horses and zero days for milk is justified.

IV CLINICAL DOCUMENTATION

The active substance in SynVet-50, sodium hyaluronate, has been used for many years for the treatment of degenerative joint disease in horses and humans. Joint diseases are common in athletic horses and may constitute to one third of all cases of lameness in racehorses. Mechanical stress during racing is the main causative factor in producing joint lesions in racehorses. One of the treatments of joint disorders was previously intra-articular administration of

[5] PBT – persistence, bioaccumulation and toxicity
[6] $PEC_{soil\ initial}$ - initial predicted environmental concentration (PEC) in soil
[7] CVMP – The Committee for Medicinal Product for Veterinary Use.

corticosteroids, however use of corticosteroids have been found to have various side effects on arthritic joints, including detrimental effects on articular cartilage and synovial soft tissue structures. A bacterial fermentation process produces the sodium hyaluronate used in SynVet-50. Sodium hyaluronate is extracted from the capsule of *Streptococcus spp*. and purified, resulting in a form which is free of protein, pyrogen and nucleic acids. Sodium hyaluronate is the sodium salt of hyaluronic acid, a non-sulphated acid mucopolysaccaride, or glycosaminoglycan, of high molecular weight composed of equimolar amounts of D-glucosamine and N-acetyl-D-glucosamine, linked by glycosidic bonds. The applicant has submitted a number of published references to support the defined action of hyaluronic acid.

IV.I. Pre-Clinical Studies

Pharmacology

Pharmacodynamics
The applicant has submitted a number of published references to support the action of hyaluronic acid (HA). Sodium hyaluronate is a natural physiological substance of connective tissue in all mammals, and its chemical structure is the same in all mammals. Sodium hyaluronate is the sodium salt of hyaluronic acid, a non-sulphated, high viscosity mucopolysaccaride or glycosaminoglycan of high molecular weight. It competes with other polysaccharides for receptor binding and thus for update in the specific tissue. The therapeutic effects of sodium hyaluronate are attributed to the anti-inflammatory, analgesic, lubricant or anti-oxidant effects. Intra-articularly administered sodium hyaluronate alleviates aseptic joint inflammation and enhances joint lubrication. The mechanism of action of the active substance is not fully understood.

Pharmacokinetics
The pharmacokinetics of hyaluronic acid is well established in various species including humans. No studies using the test product were submitted.

Published references were provided by the applicant. A study with radio-labelled hyaluronic acid in rabbit and sheep indicates that hyaluronic acid is cleared from the joint within 4 to 5 days of intra-articular injection. Elimination half-life from synovial fluid after intra-articular injection of any joint was highly variable, however the mean $T_{1/2}$ determined in only a few horses, was approximately 24 hours. Intra-articularly administered hyaluronic acid moved into and disappeared from the circulation at a first-order rate. Uptake is primarily via the lymphatics and metabolised in liver epithelial cells. The main metabolites are water, carbon dioxide, lactate, D-glucosamine-N-acetyl-D-glucosamine, low weight hyaluronic acid and monosaccharides.

Tolerance in the Target Species

No specific target species tolerance studies were performed with SynVet-50, as the pharmacology of the substance is well described in the literature. The safety aspects of the product are limited to its use in the target species. SynVet-50 is

administered intra-articularly. Target species studies have been conducted with two other products containing sodium hyaluronate and administered intra-articularly to horses, Synacid and Equron, which have been accepted by the Food and Drug Administration (FDA).

The dose of Equron into the small and medium size joints of horses is 2 ml (10 mg) injected intra-articularly, in larger joints the dose is 4 ml (20 mg). Depending on the clinical response the treatment may be repeated weekly for a total of 4 weeks treatment. An acute toxicity was conducted to evaluate the safety of Equron injected intra-articularly four times using 100 mg/dose per horse. Injections were given at two week intervals for eight weeks. Each horse was given 20 mg and 30 mg in both carpal and tibiotarsal joints at each injection period. Physical examination occurred at regular periods throughout the study. The injection site was monitored for 24 hours after each injection for signs of local inflammation. No significant adverse effects, systemic or local were observed. Post-injection joint effusions were noted in some animals. A number of post-injection swellings were noted and in all cases were transient and resolved in 24-48 hours. Due to the randomness of the effusions noted, they were considered not to be the direct result of injection of the product. The level of synovial protein showed a slight rise after the first injection and remained slightly high throughout the study. Relative viscosity showed a minor decrease after the first injection, but remained unchanged for the remainder of the study. No significant trends were observed which suggest any toxic effect of acute Equron administration.

Another reference provided evaluated the safety of Synacid in four healthy horses using intra-articular injections at 1.5x and 3x the recommended dose. The recommended dose is 5 ml (50 mg) of Synacid given intra-articularly into the carpal and fetlock joints. Two injections of Synacid (10 mg/ml) were administered at various time points. 75 mg was injected into the left radiocarpal and left intercarpal joints, and 150 mg was injected into the left femoropatellar joint. The total dose administered was 300 mg Synacid. The right limbs of the animals served to provide control tissue. Synovial fluid was drawn weekly from ‘treated’ and ‘control’ carpal joints. Clinical analysis was performed at various time points throughout the study. No changes were observed in the post-treatment radiographs. The high doses of the active substance did not produce systemic drug-related side effects, or untoward local effects.

An acute toxicity study was conducted to evaluate the systemic safety of 200 mg Synacid injected intra-articularly, weekly, for three weeks at 4x, 12x and 20x the recommended dose. Each treatment was divided between any combination of carpal, fetlock and stifle joints to accommodate the total designated dose. Clinical observations occurred at various time points throughout the study. There were no clinically significant abnormal haematology or biochemistry levels compared to pre-injection levels. No significant differences in either carpal or fetlock joints were found during the observation period and no lameness or significant joint reactions were observed in any joint. Histopathology revealed no lesions that were related to Synacid treatment. Synacid was safe at doses as high as 60x the recommended dose and 3x the recommended treatment frequency.

Sub-acute systemic toxicity was evaluated in a study where 2x recommended doses of Synacid was administered for six intra-articular injections in horses. The dose was divided between the radio- and intercarpal joints to accommodate the volume. The right radio- and intercarpals served as controls. Clinical observations occurred at various time points throughout the study. Physical examination showed no abnormality and no indications of systemic toxicity on haematology and biochemistry. Treatment did not cause any adverse local reactions or signs of toxicity. There were no long term effects on the joint size as a result of multiple injections of Synacid.

Synacid contains sodium hyaluronate (NaHA) plus preservatives, Equron contain NaHA plus sodium chloride. SynVet-50 contains NaHA, sodium chloride and well-known buffers, therefore the target species tolerance studies submitted can be considered relevant to SynVet-50.

Resistance

Resistance is not considered an issue for this type of product, therefore no data were submitted.

IV.II. Clinical Documentation

A number of references were submitted to support the efficacy of SynVet-50. As the application was a bibliographic application, no studies were submitted using SynVet-50. Both experimental and clinical field studies have been conducted using a range of other sodium hyaluronate products. They demonstrate that sodium hyaluronate leads to a substantial improvement of the signs of traumatic arthritis and these are not significantly different from results achieved with reference products.

Four dose-determination trials/clinical trials were submitted, studying sodium hyaluronate concentration in doses from 5 - 75mg in horses with artificially induced arthritis. These studies demonstrated the significant superiority of sodium hyaluronate treatment in reducing lameness, improving joint function and longer-term soundness and reducing pain, joint heat and effusion. In earlier experimental studies, the use of up to 40 mg sodium hyaluronate was studied; however a second intra-articular injection was necessary 1-2 weeks after the first to allow full clinical improvement. Later studies showed an improved efficacy using a concentration of 50 mg per joint in only one injection, with no significant improvement in efficacy in injecting more than 50 mg. A positive-controlled study with Synacid, a negative-controlled study with Synacid, a comparative study including Synacid, and two clinical field trials using Synacid all demonstrated the efficacy of 50 mg sodium hyaluronate per injection. One study stated that a second injection of 50 mg was required in horses with radiographic evidence of severe degeneration.

One study demonstrated a significant improvement in lameness for both a sodium hyaluronate-treated group and a placebo-treated group, which were injected with saline. The reduction in lameness and time until soundness was

shown to be significantly improved in the sodium hyaluronate-treated group. Synovial fluid protein levels were also reduced in the sodium hyaluronate-treated group. The references submitted demonstrated that synovial fluid protein levels were reduced in all sodium hyaluronate-treated joints.

Another study using an induced equine carpitis model, the high molecular weight preparation of the product, 3 x 10^6 Da restored the mean synovial fluid molecular weight to pre-model normal levels, showed an improved efficacy in resolution of lameness and associated parameters with a longer duration of efficacy compared to the low molecular weight preparation, 0.3 x 10^6 Da. This study used only a small number of horses per study group, but the horses were examined up to 16 weeks post-treatment. In another study observing naturally occurring carpitis in a suitable number of horses, no clinically significant differences were found between a high molecular weight product, 3.8 x 10^6 Da and a low molecular weight product, 1.5 x 10^5 Da. The evaluation period was only 2 weeks. However, the results were slightly better in the low molecular weight group, which were injected with a higher concentration of the product.

A further clinical field trial comparing a number of sodium hyaluronate products in a suitable number of horses per study group, demonstrated that there was little difference in duration of soundness in horses treated with lower molecular weight products, but the duration of soundness for all joints treated was longest for high molecular weight products. These horses were evaluated for up to 6 months post-treatment. This same study showed that the duration of soundness was longest in the hock joint for all treatments, as a double dose was injected due to the size of the joint. Concentration was also shown to be a factor in efficacy. The product with twice the concentration, but less molecular weight of another produced a longer duration of soundness. The results suggested that the therapeutic benefit of duration of soundness is dependent on the combination of molecular weight, dosage and concentration of the preparation of sodium hyaluronate. The horses studied in the references submitted were evaluated post-treatment over a range of 2 weeks to 6 months. Horses evaluated for 4-6 months post-treatment demonstrated a significant difference between injections of high molecular weight and low molecular weight sodium hyaluronate products. Horses injected with a high molecular weight product, evaluated over a longer period of time, demonstrated an increased return to function including return to normal exercise. Only one study demonstrated the efficacy of low molecular weight product in older horses. The product was still efficacious; however, in horses with radiographic signs of severe joint degeneration, a second injection was required 2 - 3 weeks after the first injection.

The majority of pharmacodynamic effects of sodium hyaluronate were demonstrated *in vitro* with sodium hyaluronate of molecular weight greater than 1.0 x 10^6 Da. The effects of sodium hyaluronate treatment were related to the concentration or viscosity of the preparations in only a few clinical studies. The duration of soundness after a single intra-articular injection depends on the concentration, dosage and the molecular weight of the sodium hyaluronate. The duration of soundness with a low molecular weight product used at a high

dosage should be comparable to those achieved with higher molecular weight products in lower dosages.

A small number of local adverse reactions were observed throughout the clinical trials. These are generally transient joint inflammation and heat, which may be associated with a slight increase in lameness. These signs resolved without therapy within 24-96 hours. These signs may be attributed to arthrocentesis, as in several references, adverse reactions were shown to be equally attributable to sodium hyaluronate, treated joints, and placebo injected joints. A suitable statement is included in the SPC at section 4.4, regarding box resting treated horses for approximately 2 days before resuming exercise.

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 benefit/risk profile of the product(s) is favourable

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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)