Veterinary Medicines Directorate

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Veterinary Medicines Directorate
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NATIONAL PROCEDURE

PUBLICLY AVAILABLE ASSESSMENT REPORT FOR A VETERINARY MEDICINAL PRODUCT

RenuTend Suspension for Injection for Horses

Date Created: June 2022

MODULE 1

PRODUCT SUMMARY

Name, strength and pharmaceutical form	RenuTend Suspension for Injection for Horses, 1 ml, 2.0-3.5 X 10^6
Applicant	Boehringer Ingelheim Vetmedica GmbH Binger Strasse 173 55216 Ingelheim am Rhein Germany
Active substance	Tenogenic primed equine allogeneic peripheral blood-derived mesenchymal stem cells (tpMSCs)
ATC Vetcode	QM09AX90
Target species	Horses
Indication for use	To restore fibre alignment in horses with superficial digital flexor tendon or suspensory ligament fibre disruption.

MODULE 2

The Summary of Product Characteristics (SPC) for this product is available on the Product Information Database of the Veterinary Medicines Directorate.

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

MODULE 3

PUBLIC ASSESSMENT REPORT

Legal basis of original application	Centralised procedure application in accordance with Article 12(3) of Directive 2001/82/EC as amended.
Date of conclusion of the procedure	5/5/2022

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, any reactions observed are indicated in the SPC.[1] The product is safe for the user, the consumer of foodstuffs from treated animals and for the environment, when used as recommended. Suitable warnings and precautions are indicated in the SPC. The efficacy [2] 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.

II. QUALITATIVE AND QUANTITATIVE PARTICULARS OF THE CONSTITUENTS

II.A. Composition

The product contains tenogenic primed equine allogeneic peripheral blood derived mesenchymal stem cells (tpMSCs) and the excipients dimethyl sulphoxide and Dulbecco's Modified Eagle Medium Low Glucose.

The container/closure system consists of cyclo-olefin co-polymer (COC) vials closed with a thermoplastic elastomer (TPE) stopper and sealed with a high density polyethylene (HDPE) cap. Top and bottom rings consist of acrylonitrile butadiene styrene (ABS) which compress the stopper so it cannot be removed without damaging it and for mechanical stability respectively. The particulars of the containers and controls performed are provided and conform to regulations. The rings do not need certificates as they are not in direct contact to the product.

The choice of the formulation and the absence of preservative are justified.

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

[1] SPC – Summary of product Characteristics.
[2] Efficacy – The production of a desired or intended result.

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 manufacturing method consists of: mesenchymal stem cell production (generation of an Intermediate Cell Stock [ICS]), tpMSC production and filling vials. The cells are taken from the peripheral blood of donor horses as a source to isolate the mesenchymal stem cells as per the European Pharmacopoeia (Ph. Eur) and the cells are predifferentiated towards tenocytes. Antibiotics are added to the the culture media for sterility and are washed out at the final stage. The potential residual level of biological materials used during the production of RenuTend has been adequately calculated and assessed.

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 tenogenic primed equine allogeneic peripheral blood derived mesenchymal stem cells, a novel active substance. The active substance is manufactured in accordance with the principles of good manufacturing practice.

The active substance specifications are considered adequate to control the quality of the material. Batch analytical data demonstrating compliance with these specifications have been provided.

The nature of the product is such that it does not comply with all aspects of a pharmaceutical drug as it is of biological origin. The cells are immediately mixed with the excipients, so no specifications for the cells as such are given. Donor horses must be eligible and stated to comply with the Ph. Eur., and are selected by: satisfactory health status, freedom of infectious diseases, capability to produce functional tpMSCs, and must be quarantined before release and acceptance for donation of cells. The media components all have certificates of analysis and are either within Ph. Eur. or United States Pharmacopoiea (USP) specs or company specs. They have all been deemed free of bovine spongiform encephalopathy (BSE). The inactive materials used in the production of RenuTend also all have certificates of analysis and are also all within either Ph. Eur or company specs.

Dimethyl sulphoxide is described in the European Pharmacopoeia. Dulbecco's Modified Eagle Medium Low Glucose without phenol red is tested for sterility as described in the CoA, is manufactured within specification, and tested for fungal and bacterial contamination to Ph. Eur.

Packaging complies with the Ph. Eur. and the USP.

II.C.4. Substances of Biological Origin

Scientific data and/or certificates of suitability issued by the EDQM have been provided and compliance with the Note for Guidance on Minimising the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Human and Veterinary Medicinal Products has been satisfactorily demonstrated.

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

The tests performed during production are described and the results of 3 consecutive runs, conforming to the specifications, are provided.

II.E. Control Tests on the Finished Product

The finished product specifications control the relevant parameters for the pharmaceutical form. The tests in the specifications, 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. Control tests on the finished product are those for: cell morphology, total cell number, viability, proliferation, filling volume, appearance, packaging, identity and purity, impurity, potency, sterility and endotoxin and mycoplasma tests.

II.F. Stability

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.
As the substance is a biological cell, specific storage conditions are required and as such some stability testing is not feasible and, therefore, not provided.

G. Other Information

Shelf life of the veterinary medicinal product as packaged for sale: 2 years.
Shelf life after thawing according to directions: Use immediately.

Store and transport frozen (-90°C to -70°C) or in liquid nitrogen.

III. SAFETY AND RESIDUES DOCUMENTATION (PHARMACO-TOXICOLOGICAL)

III.A Safety Documentation

Pharmacological Studies

Bibliographical data has been provided which show that tenogenic primed equine allogeneic peripheral blood-derived mesenchymal stem cells act by promoting tissue restoring and healing mechanisms in tendons, such as improving

extracellular matrix production. The restorative effects were reflected after tpMSC administration in an experimental tendon injury model in horses through improved ultrasound echogenicity and fibre alignment scoring, higher percentages of intact and fully aligned tendon fascicles on ultrasound tissue characterization, and confirmed by a higher collagen type I content and a lower collagen type III and smooth muscle actin presence in treated tendons. The applicant has also conducted a joint safety and efficacy study (a combined TAS/proof of concept study) which shows that after injection of the product, the tpMSCs do not migrate or distribute from the treated tendon to surrounding tissues or draining lymph node.

Toxicological Studies

No toxicity data on the tpMSCs were provided. Migration of cells from the injection site to other tissues and their tumorigenic potential was considered a possible concern; however, from the combined TAS/biodistribution, no migration of cells from the injection site, or ectopic tissue formation was observed so the risk for tumorigenicity was proposed to be low. Bibliographic references were provided for dimethyl sulphoxide (DMSO). Dulbecco's Modified Eagle Medium (DMEM) is composed of ingredients that are not expected to cause any concern.

Single Dose Toxicity

tpMSCs
No single dose toxicity studies were conducted due to the biological nature of the product.

DMEM
No single dose toxicity studies were conducted due to none of the components being of any concern regarding acute toxicity.

DMSO
No single dose toxicity studies were conducted due to its long history of use in pharmaceuticals.

Repeated Dose Toxicity

tpMSCs
No repeated dose toxicity studies were conducted due to the biological nature of the product.

DMEM
No repeated dose toxicity studies were conducted due to none of the components being of any concern regarding repeated dose safety.

DMSO
Bibliographic data of repeated dose toxicity in different animal species were presented. The toxicity of DMSO is well known and is classified as a solvent with low toxic potential and is of low concern due to very low exposure.

Reproductive Toxicity, including Teratogenicity

tpMSCs
No studies on reproductive toxicity were conducted due to the biological nature of the product.

DMEM
No studies on reproductive toxicity were conducted due to none of the components being of any concern regarding reproductive safety.

DMSO
A mouse teratology NOEL of 12 g/kg/day has been established and additional teratogenicity studies in multiple species have demonstrated that DMSO is not a teratogen in mammals except at high levels. DMSO is not considered to be directly embryotoxic.

Embryotoxicity

No data has been provided so additional user warnings have been provided.

Mutagenicity

tpMSCs
No studies on genotoxicity were conducted due to the biological nature of the product.

DMEM
No studies on genotoxicity were conducted due to none of the components being of any concern regarding genotoxicity.

DMSO
DMSO is not mutagenic to *Salmonella*, *Drosophila*, and fish cultures. It is non-reactive as a mutagen. Although DMSO is bacteriostatic or bactericidal at concentrations between 5 and 50%, there is no evidence that DMSO causes chromosomal aberrations at levels that are not directly toxic to cells. An *in vivo* cytogenetics study found that there was a significant increase in aberrant femoral bone marrow stem cells in controls which likely resulted from direct toxicity injected into the animal instead of a mutagenic response. Bibliographic data shows that there no documented adverse genetic effects reported. Additionally, no adverse genetic effects have been reported from occupational exposure to DMSO in over forty years of industrial use. There is no evidence that DMSO causes chromosomal aberrations at levels that are not directly toxic to cells.

Carcinogenicity

tpMSCs
No specific study to evaluate carcinogenicity was performed. Bibliographic data showed that for adult MSCs, there is no risk for teratoma formation reported, even

when they are derived from embryonic stem cells. Additionally, it was confirmed that there was no biodistribution occurring to surrounding tissues and no ectopic tissues formed.

DMEM
No studies on carcinogenicity were conducted due to none of the components being of any concern regarding acute carcinogenicity.

DMSO
DMSO was found to be non-genotoxic and, therefore, carcinogenicity studies are not required.

Studies of Other Effects

Immunogenicity

The applicant has conducted two additional studies. The first study showed no humoral immune response in seven out of eight horses with the eighth horse having a pre-existing sarcoid. There was no evidence of serious risk or clinical evidence of real-world consequences of these antibodies in the treated horse. In the second study, the horses were treated twice, and no cellular or humoral response was observed.

Observations in Humans

No studies with the final product have been performed in humans.

User Safety

A user risk assessment was provided in compliance with the relevant guideline.

Warnings and precautions as listed on the product literature are adequate to ensure safety to users of the product. Therefore, the following applicant's user recommendations are appropriate:

When the veterinary medicinal product is stored in liquid nitrogen, direct exposure to liquid nitrogen or cold nitrogen vapours can cause extensive tissue damage or burns. When liquid nitrogen vaporises, it can expand to 700-times its volume which may create an explosion hazard in unvented cryovials. Liquid nitrogen containers should be handled by properly trained personnel only. The handling of liquid nitrogen should take place in a well-ventilated area. Before withdrawing the vials from the liquid nitrogen canister, protective equipment consisting of gloves, long sleeves and a facemask or goggles should be worn.

There is only limited data available to support the human safety of this product. In particular, women of childbearing age and people with compromised immune systems should take care to avoid contact with the product. It is recommended to wear impermeable gloves at all times whilst handling and administering the

product. Wash any spills off exposed skin, eyes, or mucous membranes immediately.

Take care not to accidentally self-administer this product. In case of accidental self-injection, this veterinary medicinal product can cause pain, local inflammatory reactions and swelling at the site of injection, which may persist for several weeks. Transient fever may also occur. Seek medical advice immediately and provide the package leaflet or label to the physician.

Environmental Safety

The Environmental Risk Assessment (ERA) was carried out in accordance with VICH and CVMP guidelines.

Phase I:
The product will be used to treat a small number of animals in a flock or herd and as such environmental exposure will be low. A Phase II ERA was not required.

III.B.2 Residues documentation

Residue Studies

No residue depletion studies were conducted for MSCs or DMSO because MSCs do not fall within the scope of MRL regulation and all components of DMSO fall within the 'no MRL required' or 'Out of Scope' lists. All but three of the components of DMEM are covered by the lists. The three that are not have been justified as to why no MRLs are required.

Withdrawal Periods

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

IV. CLINICAL DOCUMENTATION

IV.I. Laboratory Trials

Pharmacology

The applicant has provided bibliographic data and conducted studies describing the pharmacodynamics of the active substance. It is inferred that MSCs exert their activity by using paracrine signals, cell-cell contact through nanotubes, cell fusion events, or by the secretion of extracellular vesicles. These mechanisms are deemed responsible for the anti-inflammatory, angiogenic and immunomodulatory effects MSCs demonstrate and possibly the reason MSCs can stimulate local cell survival and proliferation in target tissue. The applicant proposed determination of ACTA-2 gene expression as a surrogate marker for the tenogenic priming process. The assay has been adequately validated and serves as the potency assay for final product

Dose Finding

No *in vivo* dose finding studies have been conducted in the target species. The proposed dose is based on literature review and preliminary and pilot studies performed in horses. Clinical studies used four batches which were used to examine the safety and efficacy in horses and statistical analysis of the data. The batch release criteria ensured that batches contain a minimum of 3.0×10^6 cells/ml upon release.

Target Species Safety

Classical Tolerance

The applicant has conducted one lab study in the target species to investigate the safety of the proposed product when administered at a dosage of 3.0×10^6 cells/ml intra-lesionally into the tendon, which lies within the proposed dosage of 2.5×10^6 to 3.5×10^6 cells/ml. Overdose studies were not necessary due to the nature of the product and the route of administration. The study is the combined TAS/proof of concept study which evaluated the safety and efficacy of applying tpMSCs. A placebo was used as a control. All doses were administered by intra-lesional treatment in the tendon on a single occasion. The parameters evaluated were: changes of haematological parameters, changes of serum biochemical parameters, clinical lameness assessment, ultrasound, UTC, and pathology/histology. Minimal adverse effects were seen.

Additionally, bibliographic data of intrathecal injection with 100×10^6 allogeneic MSCs in horses showed no significant alterations and no clinical abnormalities. Bibliographic data of safety studies performed in other species were also presented. No clinically or toxicologically relevant dose-associated effects were observed.

Tumorigenicity

No specific *in vivo* studies to evaluate tumorigenicity were conducted as several *in vitro* tests are performed at batch release. The tpMSCs have been shown to be genetically stable and, as described in the literature, the malignant transformation of *in vitro* cultured MSCs after *in vivo* transplantation would be extremely unlikely. Results of the combined TAS/proof of concept study confirms the safety, with the absence of ectopic tissue or malignancies and there were no indications that the cells resided long-term in the tissue.

Immunogenicity

The applicant has provided literature references which are discussed in *Studies of Other Effects* above.
The applicant has conducted two research and development studies designed to look for evidence of immunogenicity. The first study is an *in vitro* study and the second is a repeat dose study in the target animal.

In Vitro

This study was completed to supplement the pivotal target animal safety study. Three methods were used to determine if evidence of immunogenicity was present. The first was a mixed lymphocyte reaction assay (MLR) which showed that there was no significant difference between the immunogenicity samples and the negative control sample. The immunogenicity sample results were statistically significantly lower than those of the positive control samples. The MLR results indicate that tpMSCs do not elicit a cellular immune response.
The second method was a flow cytometric crossmatch assay (FCCA). For seven of the eight horses, the alloantibody responses post-treatment were consistent with pre-treatment and findings for the negative control population The single horse with the elevated response following treatment with tpMSCs exceeded the threshold for a positive result and was reported to have a sarcoid and also have elevated antibodies against cells from an epidermal and a sarcoid cell line and PBMCs.
The final method conducted was an anti-BSA antibody ELISA to investigate if anti-BSA antibodies are present in the equine sera. The same levels of anti-BSA antibodies were found in seven out of the eight horses before and after treatment. The horse with the pre-existing sarcoid displayed an increased level after the treatment. It was concluded that in the horse with the sarcoid, there was a possible cross-reactivity between the upregulation of anti-BSA titres and the other measurable antibodies after treatment. Despite the theoretical concerns raised, no clinical evidence of real-world consequences of these antibodies could be evidenced in the treated horse.
In conclusion, allogeneic tpMSCs do not induce either a cellular or a humoral response. No adverse events that would be classified as 'serious immunological reactions' occurred.

Repeated Dose

A repeat dose study was conducted as repeated administration of allogeneic cells may entail a potential immunogenic risk. The immunogenicity after the repeated dose was assessed to investigate if there was a potential adverse immunological effect. The methods used were MLR and FCCA. The MLR showed the proliferation rate in repeatedly treated samples was significantly lower than those from the negative control samples. The FCCA results showed no antibodies were detected six to eight weeks after the repeated dose. In conclusion, no cellular or humoral immune response was observed.

IV.II. Field Trials

Field Trials

Study title	A Multicenter, Randomised, Blinded and Blocked Clinical Field Study to show the Efficacy and Safety of

	RenuTend in the Treatment of Tendinopathy in Horses compared to a negative Control (Saline)
Objectives	To evaluate the efficacy and safety of RenuTend in the treatment of tendinopathy in horses compared to a negative control (saline) in horses under field conditions.
Test site(s)	Multi-centre, Belgium
Compliance with Regulatory guidelines	Good Clinical Practice (GCP)
Test Product	RenuTend (tenogenic primed equine allogeneic peripheral blood-derived mesenchymal cells), 1 ml, two batches of investigational product (IVP) and one of control product
Control product/placebo	As above. Placebo
Animals	107 horses (considering 7% drop out rate), at least 3 years old (mean 12.1 years), privately owned, sex (39% geldings, 17% stallions, 44% mares), kept in their usual housing conditions and fed normally before, during and after the study. Inclusion Criteria: • Signed owner consent • Lesion to be treated was a first-time unilateral superficial digital flexor tendon (SDFT) or suspensory ligament (SL) lesion by overstrain injury with the following findings by ultrasonograpy: o Echogenicity score of ≥2 occupying >10% of the cross-sectional area of the tendon at the maximum injury zone (MIZ) o Fibre alignment score (FAS) ≥2 at the MIZ o Increase in anterior-posterior thickness of ≥0.1 cm compared to the contralateral tendon at the MIZ • Clinical Sum Score ≥3, summarised from the following single scores: o Swelling o Pain to pressure o Heat o AAEP score Exclusion Criteria: • Bilateral lesion of the SDFT or SL • Horses intended for human consumption • Any unauthorised pre-treatment • Any severe medical condition • Any condition that would restrict successful participation

	• Previous participation in a stem cell study • Observed history of lesion in the same tendinous/ligamentous structure or previous orthopaedic problems that would preclude a return to full training and competition
Outcomes/endpoints	Primary endpoint: ultrasound assessment of Relevant improvement (RI) based on fibre alignment score on day 112±3
Randomisation	Randomised. Random Treatment Allocation Plan created using software as documented by CRO.
Blinding	Single blind; investigator/owner/
Method	Study schedule: Examining vet responsible on day 0, 1, 2, 3, 56±3, 112±3, 168±5, 336±5 Dispenser responsible for randomisation, treatment of the horse and bandaging the injection site Horses returned home on day 3 and began the prescribed exercise regime. Exercise Regime: Day 0-3: stable rest and Reduced Lameness Assessment on days 1 and 2. Day 3-84: walking for 5 minutes without a rider 3 times a day Ultrasound examination on day 56: if no improvement days 85-112 continue 5 minutes 3 times a day, if improved days 85, 86 walking with rider for 20 mins, trotting with rider for 2 mins and increase by 1 min every 2 days up to 30 mins walk and 15 mins trot at day 112 Day 113 onwards: no limitation, horses allowed to canter depending on advice from examining vet. If not allowed to canter on day 113, allowed from day 168 if FAS=0 and echogenicity=0
Statistical method	Set out *a priori* Level of significance of 5% ($p<0.05$) for two-sided tests
RESULTS	
Participant flow	100 horses in total: 66 in the IVP group (T1) and 34 horses in the control group (T2). 99 horses completed the study on day 112±3.

	One horse treated with the control product (T2) was removed after death on day 102. Death was unrelated to the study so is not regarded as treatment failure.
Duration of follow-up	Study ended on day 112 ± 3, but follow-up was performed at day 168 ± 5 and 336 ± 5.
Outcomes for endpoints	Of the 100 included animals, 99 completed the study. One animal in the control group was prematurely removed at day 102. A modified ITT population (n=99) was used as the primary population for efficacy analysis at day 112 ± 3. <u>Primary endpoint:</u> Relevant improvement (RI) - a change in fibre alignment score from 2 or 3 at day 0 to 0 on day 112 ± 3: IVP: 43/66 (65%) CP: 3/33 (9%). Difference (95% CI): 56.1 (40.9–71.2), p<0.001 Secondary endpoints: At ultrasound assessment, lesions were smaller and echogenicity scores and fibre alignment scores were lower in IVP compared to CP at day 56±3 and day 112±3 (p<0.001) indicating improved healing and restoring of anatomic structure in treated tendons. There was no significant difference in anterior-posterior thickness. Results day 112±3: lesion size (area in mm2): IVP=12.9, CP=35.2; lesion size (% of tendon): IVP=7.6, CP=19.1; normal echogenicity score: IVP=38/66 (58%), CP=4/33 (12%); normal fibre alignment score: IVP=43/66 (65%), CP=3/33 (9%); anterior-posterior thickness (mm): IVP=11.4, CP=11.6. At tendon assessment, scores for heat, pain, and swelling were lower in IVP compared to CP on day 56±3 and day 112±3 (p≤0.002). Horses with normal scores day 112±3: heat: IVP=63/66 (96%), CP=21/33 (64%); pain: IVP=53/66 (80%), CP=12/33 (36%); swelling: IVP=24/66 (36%), CP=3/33 (9%). Limb circumference, compared to baseline, decreased more in IVP group than in CP group. Lameness assessment scores were lower in IVP group compared to CP group at day 56±3 and 112±3

	(p<0.001). Horses with no lameness on day 112±3: IVP=47/66 (71%), CP=8/33 (24%). On day 112±3, 33/66 (50%) of horses in IVP group had returned to previous work level or returned to work compared to 1/33 (3%) in CP group (p<0.001). On day 112±3, owners reported no more discomfort or remarkable improvement in 52/66 (79%) of horses in IVP group compared to 4/33 (12%) in CP group (p<0.001). Observations from phone calls with owners: less pain, heat, lameness, and discomfort observed in IVP group compared to CP group at some of the time points. No difference in swelling. On day 98±3 one owner of a horse treated with CP reported re-injury. <u>Follow up results for study days 168±5 and 336±5:</u> ▪ On day 168±5 and 336±5, 57/66 (84%) and 32/66 (49%) of horses in the IVP group and 21/34 (62%) and 14/34 (41%) in the CP group were followed-up by veterinary assessment, respectively. Overall, data were in line with results observed at day 112±3, although differences were not statistically significant for all parameters. Normal fibre alignment score was observed in 48/55 (87%) and 25/32 (78%) of horses in the IVP group and in 4/21 (19%) and 2/14 (14%) of horses in the CP group on day 168±5 and day 336±5, respectively (p<0.001).
Adverse events	Data was collected by the examining vet and from the owner's observations. There were no systemic adverse events associated with treatment. o Mild injection site reactions, such as increased heat, pain at palpation, limb swelling, and increased limb circumference occurred very commonly during the first 10 days after

	administration in both treatment groups.
DISCUSSION	The FAS scores improved more significantly in the treated horses compared to control horses. Safety: Adverse events were similar in both groups (p = 0.731). Efficacy: The RI was superior in treated horses compared to the control horses (p<0.001).

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 is favourable.

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)