ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Anarthron 100mg/mL solution for injection (AT, BE, FR, NL, UK (NI))
Cartrophen Vet 100mg/mL solution for injection (PL, NO)

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ml contains:

Active substance:

Pentosan Polysulfate Sodium 100 mg

Excipients:

Qualitative composition of excipients and other constituents	**Quantitative composition if that information is essential for proper administration of the veterinary medicinal product**
Benzyl Alcohol	0.01 ml/ml
Disodium phosphate dodecahydrate	
Sodium dihydrogen phosphate dihydrate	
Sodium hydroxide	
Hydrochloric acid	
Water for injection	

Solution for injection.

A clear, colourless pale yellow solution.

3. CLINICAL INFORMATION

3.1 Target species

Dog.

3.2 Indications for use for each target species

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

3.3 Contraindications

Do not use in the treatment of septic arthritis. In this case, appropriate antimicrobial therapy should be instigated.

Do not use in dogs with advanced liver or kidney impairment, or evidence of infection.

Do not use in dogs with blood disorders, coagulation disorders, bleeding or malignancy (especially haemangiosarcoma).

Pentosan polysulfate has an anticoagulant effect. Do not use during the peri-operative period.

Do not use in the skeletally immature dog (i.e. dogs whose long bone growth plates have not closed).

3.4 Special warnings

A clinical effect may not be observed until after the second injection of the course of treatment.

3.5 Special precautions for use

Special precautions for safe use in the target species:

Use with caution in dogs with history of pulmonary lacerations.

Caution is also recommended in cases of hepatic impairment.

Do not exceed the standard dose. Increasing the recommended dose may result in exacerbation of stiffness and discomfort.

No more than 3 courses of 4 injections should be administered in a 12 month period.

Special precautions to be taken by the person administering the veterinary medicinal product to animals:

Care should be taken to avoid accidental self-injection.

Wash splashes from eyes and skin immediately with water.

Wash hands after use

Special precautions for the protection of the environment:

Not applicable.

3.6 Adverse events

Dog:

Very rare (<1 animal / 10 000 animals treated, including isolated reports)	Emesis[1,2], diarrhoea[1,2] Lethargy[1,2], anorexia[1,2] Hypersensitivity reaction[2] Prolonged activated partial thrombin time (APTT)[3], prolonged thrombin time (TT)[3] Injection site reaction, injection site swelling[4]
Undetermined frequency (cannot be estimated from the available data):	Bleeding disorder (e.g. nasal bleeding, haemorrhagic diarrhoea, haematoma)

[1] Due to a hypersensitivity reaction.
[2] May require appropriate symptomatic treatment, including antihistamine administration.
[3] 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 polysulfate 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.
[4] Transient.

Reporting adverse events is important. It allows continuous safety monitoring of a veterinary medicinal product. Reports should be sent, preferably via a veterinarian, to either the marketing authorisation holder or the national competent authority via the national reporting system. See the package leaflet for respective contact details.

3.7 Use during pregnancy, lactation or lay

Pregnancy:

Laboratory studies in rabbits showed embryotoxic effects associated with a primary effect on the parent at repeated daily doses 2.5 times the recommended dose.

The safety of the veterinary medicinal product in the pregnant bitch has not been studied, therefore use is not recommended in these circumstances.

The veterinary medicinal product should not be used at the time of parturition due to its anticoagulant effects.

3.8 Interaction with other medicinal products and other forms of interaction

NSAIDs and in particular aspirin should not be used in combination with pentosan polysulfate sodium as they may affect thrombocyte adhesion and potentiate the anticoagulant activity of the veterinary medicinal product.
Corticosteroids have been shown to be antagonistic to a number of actions of pentosan polysulfate sodium. Furthermore, use of anti-inflammatory drugs may result in a premature increase in the dog's activity, which may interfere with the therapeutic activity of the veterinary medicinal product.

Do not use concurrently with steroids or non-steroidal anti-inflammatory drugs, including aspirin and phenylbutazone.

Do not use concurrently with heparin, warfarin or other anti-coagulants.

3.9 Administration routes and dosage

Subcutaneous use

Dosage: 3 mg pentosan polysulfate sodium/kg bodyweight (equivalent to 0.3 ml/10 kg bodyweight) on four occasions, with an interval of 5-7 days between each administration.

Administration: By aseptic subcutaneous injection only of 0.3 ml/10 kg of bodyweight. An appropriately graduated syringe must be used to allow accurate administration of the required dose volume. This is particularly important when injecting small volumes.

Each case should be assessed individually by the veterinarian and an appropriate treatment program determined.

To ensure a correct dosage, body weight should be determined as accurately as possible.

3.10 Symptoms of overdose (and where applicable, emergency procedures and antidotes)

Repeated daily overdoses of five times the recommended dose or more results in anorexia and depression, which are reversible upon withdrawal of the drug.

At overdose there may be hepatocellular damage and an associated, dose-dependent, elevation in ALT. Increases in aPTT and TT are dose-dependent. At repeated doses greater than five times that recommended, these increases may persist beyond 1 week after administration in healthy dogs. Signs associated with these defects may include bleeding into the gastro-intestinal tract, body cavities and

ecchymoses. At repeated doses greater than ten times that recommended there may be fatality as a result of gastro-intestinal haemorrhage.

If overdose occurs dogs should be hospitalised and observed and supportive therapy provided as deemed necessary by the veterinarian.

3.11 Special restrictions for use and special conditions for use, including restrictions on the use of antimicrobial and antiparasitic veterinary medicinal products in order to limit the risk of development of resistance

3.12 Withdrawal periods

Not applicable.

4. PHARMACOLOGICAL INFORMATION

4.1 ATCvet code:

QM01AX90

4.2 Pharmacodynamics

The veterinary medicinal product contains Pentosan Polysulfate 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 (TIMP) increased, thereby preserving proteoglycan content and protecting cartilage matrix from degradation.

In dogs with osteoarthritis administration of NaPPS caused fibrinolysis, lipolysis 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 synthesis from fibroblasts.

4.3 Pharmacokinetics

Absorption: In the dog, a peak plasma concentration of 7.40 µg-eq pentosan polysulfate sodium/mL is achieved 15 minutes after subcutaneous administration.

Distribution: Pentosan polysulfate sodium binds many plasma proteins with a variable strength of association and dissociation resulting in a complex equilibrium between bound and unbound drug. Pentosan polysulfate sodium is concentrated in the liver and kidneys and reticuloendothelial system. Low levels occur in connective tissue and muscle. In studies carried out with rabbits, it has been shown that therapeutic concentrations of the active ingredient remain in the joint cartilage for 4-5 days after administration. The volume of distribution in dogs is 0.43L.

Biotransformation: Desulfation of pentosan polysulfate sodium occurs in the hepato-reticulo-endothelial system, the liver being the main site of activity. Depolymerisation may also occur in the kidney.

Elimination: The veterinary medicinal product is eliminated with a half life of approximately 3 hours in the dog. Forty eight hours after injection approximately 70% of the dose administered is eliminated via urine.

5. PHARMACEUTICAL PARTICULARS

5.1 Major incompatibilities

The veterinary medicinal product should not be administered in the same syringe with other substances.

5.2 Shelf life

Shelf-life of the veterinary medicinal product as packaged for sale: 3 years.

Shelf-life after first opening the immediate packaging: 3 months.

5.3 Special precautions for storage

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

5.4 Nature and composition of immediate packaging

A 10 ml Ph.Eur. Type 1 clear glass vial fitted with a 20 mm rubber stopper Ph.Eur and closed by a plastic flip off seal attached to an aluminium seal.

5.5 Special precautions for the disposal of unused veterinary medicinal products or waste materials derived from the use of such products

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any national collection systems applicable to the veterinary medicinal product concerned.

6. NAME OF THE MARKETING AUTHORISATION HOLDER

Maperath Herbal Limited.

7. MARKETING AUTHORISATION NUMBER(S)

8. DATE OF FIRST AUTHORISATION

9. DATE OF THE LAST REVISION OF THE SUMMARY OF THE PRODUCT CHARACTERISTICS

DD/MM/YYYY

10. CLASSIFICATION OF VETERINARY MEDICINAL PRODUCTS

Veterinary medicinal product subject to prescription.

Detailed information on this veterinary medicinal product is available in the Union Product Database(https://medicines.health.europa.eu/veterinary).

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

CARTON

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Anarthron 100mg/mL solution for injection (AT, BE, FR, NL, UK (NI))
Cartorphen Vet 100mg/mL solution for injection (PL, NO)

2. STATEMENT OF ACTIVE SUBSTANCES

Pentosan polysulfate sodium 100 mg/ml

3. PACKAGE SIZE

10 ml

4. TARGET SPECIES

Dog

5. INDICATIONS

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

6. ROUTES OF ADMINISTRATION

For subcutaneous use.

7. WITHDRAWAL PERIODS

Not applicable

8. EXPIRY DATE

Exp. {mm/yyyy}

Once broacheduse within 3 months.

9. SPECIAL STORAGE PRECAUTIONS

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

10. THE WORDS "READ THE PACKAGE LEAFLET BEFORE USE"

Read the package leaflet before use.

11. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

12. THE WORDS "KEEP OUT OF THE SIGHT AND REACH OF CHILDREN"

Keep out of the sight and reach of children.

13. NAME OF THE MARKETING AUTHORISATION HOLDER

Maperath Herbal Limited.

14. MARKETING AUTHORISATION NUMBERS

15. BATCH NUMBER

Lot

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGE

{VIAL LABEL}

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Anarthron 100mg/mL solution for injection for dogs (AT, BE, FR, NL, UK (NI))
Cartorphen Vet 100mg/mL solution for injection for dogs (PL, NO)

2. STATEMENT OF ACTIVE SUBSTANCES

Pentosan polysulfate sodium 100 mg/ml

3. TARGET SPECIES

Dog

4. ROUTES OF ADMINISTRATION

Subcutaneous use
Read the package leaflet before use.

5. WITHDRAWAL PERIODS

6. EXPIRY DATE

Exp.
Once broached use within 3 months.

7. SPECIAL STORAGE PRECAUTIONS

Do not store above 25 °C

Keep the vial in the outer carton in order to protect from light.

8. NAME OF THE MARKETING AUTHORISATION HOLDER

Maperath Herbal Limited.

9. BATCH NUMBER

Lot {number}

B. PACKAGE LEAFLET

PACKAGE LEAFLET

1. Name of the veterinary medicinal product

Anarthron 100mg/mL solution for injection for dogs (AT, BE, FR, NL, UK (NI))
Cartrophen Vet 100mg/mL solution for injection for dogs (PL, NO)

2. Composition

Each ml contains:

Active substance
Pentosan polysulfate sodium 100 mg

Excipient
Benzyl Alcohol 0.01 ml

A clear, colourless pale yellow solution.

3. Target species

Dog

4. Indications for use

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

5. Contraindications

Do not use in the treatment of septic arthritis. In this case, appropriate antimicrobial therapy should be instigated.

Do not use in dogs with advanced liver or kidney impairment, or evidence of infection.

Do not use in dogs with blood disorders, coagulation disorders, bleeding or malignancy (especially haemangiosarcoma).

Pentosan polysulfate has an anticoagulant effect. Do not use during the peri-operative period.

Do not use in the skeletally immature dog (i.e. dogs whose long bone growth plates have not closed).

6. Special warnings

Special precautions for safe use in the target species:

A clinical effect may not be observed until after the second injection of the course of treatment.

Dogs should be weighed prior to administration to ensure accurate dosing.

Do not exceed the standard dose. Increasing the recommended dose may result in exacerbation of stiffness and discomfort.

No more than 3 courses of 4 injections should be administered in a 12 month period.

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

Use with caution in dogs with history of pulmonary lacerations. Caution is also recommended in cases of hepatic impairment.

Pregnancy and lactation:

Laboratory studies in rabbits showed embryotoxic effects associated with a primary effect on the parent at repeated daily doses 2.5 times the recommended therapeutic dose.

The safety of the veterinary medicinal product in the pregnant bitch has not been studied, therefore use is not recommended in these circumstances.

The veterinary medicinal product should not be used at the time of parturition due to its anticoagulant effects.

Interactions with other medicinal products and other forms of interaction:

NSAIDs and in particular aspirin should not be used in combination with pentosan polysulfate sodium as they may affect thrombocyte adhesion and potentiate the anticoagulant activity of the veterinary medicinal product. Corticosteroids have been shown to be antagonistic to a number of actions of pentosan polysulfate sodium. Furthermore, use of anti-inflammatory drugs may result in a premature increase in the dog's activity, which may interfere with the therapeutic activity of the veterinary medicinal product.

Do not use concurrently with steroids or non-steroidal anti-inflammatory drugs, including aspirin and phenylbutazone.

Do not use concurrently with heparin, warfarin or other anti-coagulants. Do not use after the expiry date printed on the label and carton after EXP.

7. Adverse events

Dog:

Very rare (<1 animal / 10 000 animals treated, including isolated reports)	Emesis[1,2], diarrhoea[1,2] Lethargy[1,2], anorexia[1,2] Hypersensitivity reaction[2] Prolonged activated partial thrombin time (APTT)[3], prolonged thrombin time (TT)[3] Injection site reaction, injection site swelling[4]
Undetermined frequency (cannot be estimated from the available data):	Bleeding disorder (e.g. nasal bleeding, haemorrhagic diarrhoea, haematoma)

[1] Due to a hypersensitivity reaction.
[2] May require appropriate symptomatic treatment, including antihistamine administration.
[3] 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 polysulfate 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.
[4] Transient.

Reporting adverse events is important. It allows continuous safety monitoring of a product. If you notice any side effects, even those not already listed in this package leaflet, or you thinmk that the medicine has not worked, please contact, in the first instance, your veterinarian. You can also report any adverse events to the marketing authorisation holder <or its local representative> using the contact details at the end of this leaflet, or via your national reporting system: {national reporting system details}.

8. Dosage for each species, routes and method of administration

Dosage: 3mg pentosan polysulfate sodium/kg bodyweight (equivalent to 0.3 ml/10 kg bodyweight) on four occasions, with an interval of 5-7 days between each administration.

Administration: By aseptic subcutaneous injection only of 0.3 ml/10 kg of bodyweight. An appropriately graduated syringe must be used to allow accurate administration of the required dose volume. This is particularly important when injecting small volumes.

Each case should be assessed individually by the veterinarian and an appropriate treatment program determined.

9. Advice on correct administration

Subcutaneous use.

10. Withdrawal periods

11. Special storage precautions

Keep out of the sight and reach of children.

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

Do not use this veterinary medicinal product after the expiry date which is stated on the label.

Shelf life after first opening the immediate packaging: 3 months.

12. Special precautions for disposal

Medicines should not be disposed of via wastewater or household waste.

Use take-back schemes for the disposal of any unused veterinary medicinal product or waste materials derived thereof in accordance with local requirements and with any applicable national collection systems. These measures should help to protect the environment.

Ask your veterinary surgeon or pharmacist how to dispose of medicines no longer required.

13. Classification of veterinary medicinal products

Veterinary medicinal product subject to prescription.

14. Marketing authorisation numbers and pack sizes

10 ml vial.

15. Date on which the package leaflet was last revised

{MM/YYYY}

Detailed information on this veterinary medicinal product is available in the Union Product Database(https://medicines.health.europa.eu/veterinary).

16. Contact details

Marketing authorisation holder and contact details to report suspected adverse reactions:

To be completed nationally

Manufacturer responsible for batch release:

To be completed nationally