ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

TruScient 0.66 mg kit for implant for dogs

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial of lyophilisate contains:

Dibotermin alfa (rhBMP-2)* 0.66 mg

After reconstitution TruScient contains 0.2 mg/ml of dibotermin alfa (rhBMP-2)

*Dibotermin alfa (recombinant human Bone Morphogenetic Protein-2; rhBMP-2) is a human protein derived from a recombinant Chinese Hamster Ovary (CHO) cell line.

Two sponges made of Bovine Type I collagen.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Kit for implant

White lyophilisate and a clear colourless solvent.

4. CLINICAL PARTICULARS

4.1 Target species

Dogs

4.2 Indications for use, specifying the target species

Treatment of diaphyseal fractures as an adjunct to standard surgical care using open fracture reduction in dogs.

4.3 Contraindications

Do not use in dogs with a known hypersensitivity to the active substance or to any of the excipients.

Do not use in dogs that are skeletally immature, have an active infection at the operative site, pathological fracture, or any active malignancy.

4.4 Special warnings for each target species

None.

4.5 Special precautions for use

Special precautions for use in animals

This veterinary medicinal product should be used by an appropriately qualified veterinarian.
Failure to follow the TruScient instructions for preparation and use may compromise safety and effectiveness.

In order to avoid excessive postoperative swelling, use only the amount of prepared TruScient sponge needed to achieve coverage of accessible fracture lines and defects (less than one to up to two prepared sponges).

TruScient can cause initial resorption of surrounding trabecular bone. Therefore, in the absence of clinical data, the veterinary medicinal product should not be used for direct applications to trabecular bone when transient bone resorption may create a risk of bone fragility and, thus, increase the risk of implant failure.

TruScient does not provide mechanical stability and should not be used to fill space in the presence of compressive forces. Long-bone fracture and soft-tissue management procedures should be based on standard practice, including control of infection.

Both rhBMP-2 and bovine Type I collagen can elicit an immune response in dogs. Although no clear association with clinical outcome or undesirable effects could be observed in clinical and safety studies, the possibility of developing neutralising antibodies or hypersensitivity-type reactions cannot be excluded. The possibility of an immune response to the product should be evaluated in cases where an undesirable effect with immunological background is suspected.

The safety, including potential immune responses, and effectiveness of repeated administration have not been evaluated in dogs.

No studies have been performed in dogs with known autoimmune diseases.

No studies have been performed in dogs with metabolic bone diseases.

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

In case of accidental spillage onto skin and eyes rinse off immediately.

4.6 Adverse reactions (frequency and seriousness)

The following adverse reactions have been observed in laboratory studies in dogs:

- heterotopic ossification of the surrounding tissues

- exuberant bone formation at the site of placement and ectopic bone formation

- excessive bone and fluid filled cysts that remodel into normal bone over time

- increased swelling at the site of placement has been observed by 2-3 weeks post surgery. These swellings are the result of local proliferation of mesenchymal tissue maturing to new bone and are consistent with the pharmacologic activity of rhBMP-2

The following adverse reactions have been observed in a field study in dogs:

Very common (more than 1 in 10 animals)
Mild to moderate

- Lameness
- Firm swelling within the first 3 weeks postoperatively which recedes gradually over several months
- Soft swelling which recedes within 3 weeks

Common (more than 1 but less than 10 animals in 100 animals)
Mild to moderate

- Seroma, excessive licking of incision area, joint stiffness, local swelling, skin ulcer, incisional discharge, incisional dehiscence.
- Soft swelling generally resolved by week 6 postoperatively

Uncommon (more than 1 but less than 10 animals in 1000 animals)
Mild to moderate

- Exuberant bony callus associated with persistent (>10 weeks) moderate soft tissue swelling and excessive licking of the incision area.

Severe

- Lameness

Observed clinical signs were listed as adverse reactions for TruScient when they exceeded in intensity and/or duration of what would be considered normal for fracture healing after Standard of Care (SOC).

4.7 Use during pregnancy, lactation or lay

The safety of the veterinary medicinal product has not been established during breeding, pregnancy and lactation. BMP-2 plays a critical role during foetal development. The influence of anti-BMP-2 antibody formation on foetal development has not been assessed. The incidence of antibody titres in treated dogs under field conditions is low and the puppies will have no or very limited exposure to anti-BMP-2 antibodies due to the potential for limited transfer across the placenta in dogs.

This medicinal product should only be used in breeding, pregnant and lactating dogs following a risk/benefit assessment by the responsible veterinarian.

4.8 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. As dibotermin alfa (rhBMP-2) is a protein and has not been identified in the general circulation, it is an unlikely candidate for pharmacokinetic drug-drug interactions.

TruScient should not be mixed with other agents.

4.9 Amounts to be administered and administration route

Read the instructions for preparation and use below each time the veterinary medicinal product is used. Failure to follow the instructions may compromise the safety and effectiveness of the medicinal product.

TruScient is intended for single use only. It must not be re-sterilised.

Prepare sponges at least 15 minutes prior to use and use within 2 hours of wetting the sponges. Discard any unused veterinary medicinal product.

The recommended dose is up to two sponges (2.5 x 5 cm) per dog.

The dibotermin alfa (rhBMP-2) is reconstituted to 0.2 mg/ml solution and then distributed uniformly across both sponges.

Use care to ensure that accurate volumes are used in reconstitution and application of the dibotermin alfa (rhBMP-2) solution to the sponge.

For accurate dosing ensure there are no suspended air bubbles in the transfer volumes.

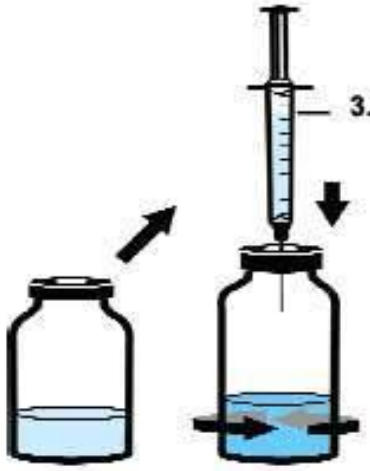
Instructions for preparation and use

Using aseptic technique, follow the directions below to reconstitute dibotermin alfa (rhBMP-2) for application to the sponges.

A. Reconstitute dibotermin alfa (rhBMP-2) in a non-sterile field:

1. Disinfect with alcohol the stoppers of the lyophilisate and the solvent vials.
2. Using the 6 ml syringe and needle withdraw **3.2 ml** of solvent (more solvent is supplied than is needed). **Do not use more than 3.2 ml.**
3. Slowly inject the 3.2 ml of solvent into the lyophilisate vial (**see Figure 1**) to achieve a 0.2 mg/ml solution of rhBMP-2.
4. Swirl the vial gently to aid reconstitution. **Do not shake**. Discard syringe and needle after use.

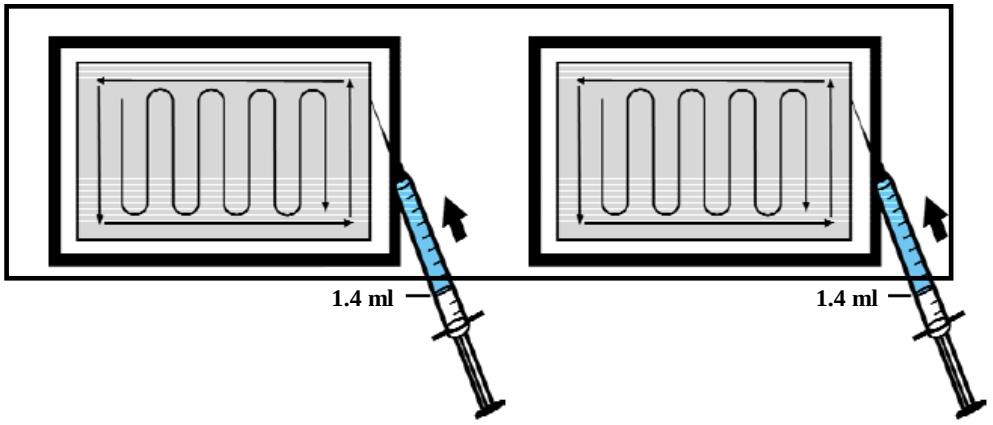
Figure 1: Reconstitution of dibotermin alfa (rhBMP-2)



B. Prepare TruScient sponges in the sterile field:

5. Using sterile technique, transfer the two 3 ml syringes with needles and the sponges inner package into the sterile field.
6. Peel open the inner package of sponges and leave them in the tray.
7. Using aseptic transfer technique and for each 3 ml syringe with needle, withdraw 1.4 ml from the reconstituted vial of dibotermin alfa (rhBMP-2) in the non-sterile field.
8. Leaving the sponges in the tray, UNIFORMLY distribute onto each sponge 1.4 ml dibotermin alfa (rhBMP-2) solution as shown in the illustration (**Figure 2**).

Figure 2: Preparation of TruScient sponges



9. Wait a MINIMUM of 15 minutes before using the prepared sponges. Use within 2 hours of wetting the sponges.
10. During handling avoid excessive fluid loss from the prepared sponges. Do not squeeze.
11. If only a portion of a prepared sponge is required, first prepare the entire package (following steps 1 – 9 above), then cut or fold the prepared sponge as needed prior to implantation.

C. Implantation

12. Achieve definitive fracture reduction, fixation, and hemostasis prior to placement of the prepared sponge. Dry the fracture site to the extent possible.
13. Cut or fold the prepared sponge as needed prior to placement. The amount of prepared sponge placed is determined by the fracture anatomy and the ability to close the wound with minimal compression of the sponge. Use only the amount of prepared sponge needed to achieve coverage of accessible fracture lines and defects (less than one up to two prepared sponges).
14. During placement, use forceps to handle the prepared sponge to avoid excessive fluid loss.
15. Place the prepared sponge so that it bridges the fracture and makes good contact with the major proximal and distal fracture fragments. The prepared sponge may be wrapped around the bone or placed up to the edges of a bone plate as the geometry of the fracture and fixation requires. Bone plates should not be covered with the prepared sponge in order to facilitate plate removal if needed following fracture healing. Area vascularity should be maintained.
16. TruScient will not provide mechanical stability and should not be used to fill spaces in the presence of compressive forces.

D. After Placement

17. Do not irrigate the wound once the prepared sponge is placed across the fracture. Irrigation will wash away the dibotermin alfa (rhBMP-2) solution.
18. If a surgical drain is required, place the drain at least one layer superficial to or remote from the prepared sponge.
19. Following placement, achieve complete soft-tissue coverage of the prepared sponges.

4.10 Overdose (symptoms, emergency procedures, antidotes), if necessary

TruScient used in concentrations or amounts greater than those recommended is associated with excessive bone formation and increased generation of fluid-filled void spaces within the induced bone. Excessive bone and fluid filled cysts remodel into normal bone over time. Biomechanical data suggest these voids had little influence on the biomechanical properties of the induced bone or its integration with the abutting cortices.

In the case of dogs receiving concentrations or amounts greater than those recommended, treatment of adverse effects, where required, should be symptomatic.

4.11 Withdrawal period(s)

Not applicable.

5. PHARMACOLOGICAL PROPERTIES

Pharmacotherapeutic group: Bone Morphogenetic Proteins
ATCvet code: QM05BC01

5.1 Pharmacodynamic properties

Dibotermin alfa (rhBMP-2) is an osteoinductive protein that results in the induction of new bone tissue

at the site of implantation. Dibotermin alfa binds to receptors on the surface of mesenchymal cells and causes cells to differentiate into cartilage- and bone-forming cells. The differentiated cells form trabecular bone as the sponge is degraded, with vascular invasion evident at the same time. The bone formation process develops from the outside of the prepared sponge towards the center until the entire prepared sponge is replaced by trabecular bone. Remodeling of the surrounding trabecular bone occurs in a manner that is consistent with the biomechanical forces placed on it. The ability of TruScient to support bone remodeling may be responsible for the biological and biomechanical integration of the new bone induced by TruScient with that of the surrounding bone. Radiographic, biomechanical, and histological evaluation of the induced bone indicates that it functions biologically and biomechanically as native bone.

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

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

The efficacy and safety of the veterinary medicinal product for the treatment of diaphyseal fractures was evaluated in a randomised, controlled, multicenter clinical field study involving dogs randomised to treatment with the veterinary medicinal product plus Standard Of Care (SOC) [n=84] or SOC [n=42] alone. Investigators were aware of treatment assignment; reviewers assessing time to radiographic fracture union for each dog were masked to treatment. Dogs were followed for 18 weeks after treatment.

The results demonstrated that TruScient was effective in reducing the time to radiographic fracture union when added to SOC compared to treatment with SOC alone regardless of fracture type (open or closed).

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

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

SOC = standard of care

While there was a treatment-related reduction in time to radiographic fracture union, there was no difference over time between the TruScient treated group and the control group for the individual clinical parameters, lameness and pain, or for an overall score based on clinical signs of fracture healing.

BMP-2 antibody response to TruScient was evaluated in 133 dogs receiving surgery for diaphyseal fractures stabilised with internal fixation. Development of BMP-2 antibodies occurred in 6.9% of dogs receiving TruScient vs. 4.3% of dogs in the control group. The antibody titers did not correlate with any adverse clinical sign including any immune mediated adverse events such as allergic reactions.

5.2 Pharmacokinetic particulars

TruScient is active at the site of implantation. In animal studies (rats) using radiolabelled dibotermin alfa on absorbable collagen sponge, the mean residence time at the site of implantation was 4-8 days. Peak levels of circulating dibotermin alfa (0.1% of the implanted dose) were observed within 6 hours following implantation. When injected intravenously, the terminal half-life of dibotermin alfa was 16 minutes in rats. It is concluded therefore that at the site of implantation dibotermin alfa is slowly released from the matrix and rapidly cleared when taken up into the systemic circulation.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Lyophilisate:
Sucrose
Glycine
Glutamic acid
Sodium chloride
Polysorbate 80
Sodium hydroxide (pH adjustment agent)
Hydrochloric acid (pH adjustment agent)

Solvent:
Water for injections

Sponge:
Bovine Type I collagen

6.2 Incompatibilities

In the absence of compatibility studies, this veterinary medicinal product must be reconstituted only with the solvent provided and should not be mixed with other solvents or other veterinary medicinal products.

6.3 Shelf life

Shelf life of the veterinary medicinal product as packaged for sale: 2 years
Shelf life in the vial after reconstitution according to directions: 3 hours
Discard any unused veterinary medicinal product.

6.4. Special precautions for storage

Do not store above 25 °C.
Do not refrigerate.
Do not freeze.
Store in the original package.

6.5 Nature and composition of immediate packaging

Each kit contains:

Lyophilisate:
- 10 ml Type I glass vial with a chlorobutyl elastomeric closure sealed with an aluminum flip-off seal and plastic cap.

Solvent:
- 10 ml Type I glass vial with a bromobutyl elastomeric closure sealed with an aluminum flip-off seal and plastic cap.

Sponge:
- Two sterile sponges 2.5 x 5 cm in a polyvinyl chloride (PVC) blister package sealed with a Tyvek lid.

The kit also includes:
- Two sterile 3 ml disposable polypropylene syringes with stainless steel needles attached.
- One sterile 6 ml disposable polypropylene syringe with stainless steel needle attached.

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

Any unused veterinary medicinal product or waste material derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Zoetis Belgium SA
Rue Laid Burniat 1
1348 Louvain-la-Neuve
Belgium

8. MARKETING AUTHORISATION NUMBER(S)

EU/2/11/136/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14/12/2011
Date of last renewal:

10 DATE OF REVISION OF THE TEXT

Detailed information on this veterinary medicinal product is available on the website of the European Medicines Agency (http://www.ema.europa.eu/).

PROHIBITION OF SALE, SUPPLY AND/OR USE

Not applicable.

ANNEX II

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. STATEMENT OF THE MRLs

A. MANUFACTURER OF THE BIOLOGICAL ACTIVE SUBSTANCE AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer of the biological active substance

Pfizer
1 Burtt Road
Andover
MA 01810
USA

Name and address of the manufacturer responsible for batch release

Zoetis Manufacturing & Research Spain, S.L.
Ctra. Camprodón s/n "la Riba"
17813 Vall de Bianya
Girona
Spain

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Veterinary medicinal product subject to prescription.

C. STATEMENT OF THE MRLs

Not applicable.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGE

KIT OUTER CARTON

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

TruScient 0.66 mg kit for implant for dogs
dibotermin alfa (rhBMP-2)

2. STATEMENT OF ACTIVE AND OTHER SUBSTANCES

One vial of lyophilisate contains 0.66 mg of dibotermin alfa (rhBMP-2)
After reconstitution, TruScient solution contains 0.2 mg/ml of dibotermin alfa (rhBMP-2).

3. PHARMACEUTICAL FORM

Kit for implant

4. PACKAGE SIZE

1 vial (lyophilisate)
1 vial (solvent)
2 absorbable collagen sponges
2 sterile 3 ml disposable syringes with needles
1 sterile 6 ml disposable syringe with needle

5. TARGET SPECIES

Dogs

6. INDICATION(S)

Treatment of diaphyseal fractures as an adjunct to standard surgical care using open fracture reduction in dogs.

7. METHOD AND ROUTE(S) OF ADMINISTRATION

For single use only.
Read the package leaflet before use.

8. WITHDRAWAL PERIOD

9. SPECIAL WARNING(S), IF NECESSARY

Read the package leaflet before use.

10. EXPIRY DATE

EXP {month/year}
Shelf life in the vial after reconstitution: 3 hours
Discard any unused veterinary medicinal product.

11. SPECIAL STORAGE CONDITIONS

Do not store above 25 °C.
Do not refrigerate.
Do not freeze.
Store in the original package.

12. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCTS OR WASTE MATERIALS, IF ANY

Disposal: read package leaflet.

13. THE WORDS "FOR ANIMAL TREATMENT ONLY" AND CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE, IF APPLICABLE

For animal treatment only. To be supplied only on veterinary prescription.

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

Keep out of the sight and reach of children.

15. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Zoetis Belgium SA
Rue Laid Burniat 1
1348 Louvain-la-Neuve
Belgium

16. MARKETING AUTHORISATION NUMBER(S)

EU/2/11/136/001

17. MANUFACTURER'S BATCH NUMBER

Lot

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

LYOPHILISATE VIAL LABEL

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

TruScient 0.66 mg kit for implant for dogs
dibotermin alfa (rhBMP-2)

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

0.66 mg

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

4. ROUTE(S) OF ADMINISTRATION

For reconstitution.

Read the package leaflet before use.

5. WITHDRAWAL PERIOD

6. BATCH NUMBER

Lot {number}

7. EXPIRY DATE

EXP {month/year}
Shelf life in the vial after reconstitution: 3 hours

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

SOLVENT VIAL LABEL

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Solvent for TruScient
Water for injections

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

10 ml
Do not use more than 3.2 ml for reconstitution

4. ROUTE(S) OF ADMINISTRATION

5. WITHDRAWAL PERIOD

6. BATCH NUMBER

Lot {number}

7. EXPIRY DATE

EXP {month/year}
Discard the remaining solvent after reconstitution.

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

ABSORBABLE COLLAGEN SPONGE LABEL

1. NAME OF THE VETERINARY MEDICINAL PRODUCT

Sponge for TruScient

2. QUANTITY OF THE ACTIVE SUBSTANCE(S)

Type I bovine collagen

3. CONTENTS BY WEIGHT, BY VOLUME OR BY NUMBER OF DOSES

2.5 x 5 cm

4. ROUTE(S) OF ADMINISTRATION

5. WITHDRAWAL PERIOD

6. BATCH NUMBER

Lot {number}

7. EXPIRY DATE

EXP {month/year}

8. THE WORDS "FOR ANIMAL TREATMENT ONLY"

For animal treatment only.

B. PACKAGE LEAFLET

PACKAGE LEAFLET FOR:
TruScient 0.66 mg kit for implant for dogs

1. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER AND OF THE MANUFACTURING AUTHORISATION HOLDER RESPONSIBLE FOR BATCH RELEASE, IF DIFFERENT

Marketing authorisation holder:
Zoetis Belgium SA
Rue Laid Burniat 1
1348 Louvain-la-Neuve
Belgium

Manufacturer responsible for batch release:
Zoetis Manufacturing & Research Spain, S.L.
Ctra. Camprodón s/n "la Riba"
17813 Vall de Bianya
Girona
Spain

2. NAME OF THE VETERINARY MEDICINAL PRODUCT

TruScient 0.66 mg kit for implant for dogs

3. STATEMENT OF THE ACTIVE SUBSTANCE(S) AND OTHER INGREDIENT(S)

One vial of lyophilisate contains 0.66 mg of dibotermin alfa (rhBMP-2)*

After reconstitution, TruScient solution contains 0.2 mg/ml of dibotermin alfa (rhBMP-2).

*Dibotermin alfa (recombinant human Bone Morphogenetic Protein-2; rhBMP-2) is a human protein derived from a recombinant Chinese Hamster Ovary (CHO) cell line.

Two sponges made of Bovine Type I collagen.

4. INDICATION(S)

Treatment of diaphyseal fractures as an adjunct to standard surgical care using open fracture reduction in dogs.

5. CONTRAINDICATIONS

Do not use in dogs with a known hypersensitivity to the active substance or to any of the excipients.
Do not use in dogs that are skeletally immature, have an active infection at the operative site, pathological fracture, or any active malignancy.

6. ADVERSE REACTIONS

The following adverse reactions have been observed in laboratory studies in dogs:
o Heterotopic ossification of the surrounding tissues
o Exuberant bone formation at the site of placement and ectopic bone formation
o Excessive bone and fluid filled cysts that remodel into normal bone over time

o Increased swelling at the site of placement has been observed by 2-3 weeks post surgery. These swellings are the result of local proliferation of mesenchymal tissue maturing to new bone and are consistent with the pharmacologic activity of rhBMP-2

The following adverse reactions have been observed in a field study in dogs:

Very common (more than 1 in 10 animals)
Mild to moderate

- Lameness
- Firm swelling within the first 3 weeks postoperatively which recedes gradually over several months
- Soft swelling which recedes within 3 weeks

Common (more than 1 but less than 10 animals in 100 animals)
Mild to moderate

- Seroma, excessive licking of incision area, joint stiffness, local swelling, skin ulcer, incisional discharge, incisional dehiscence.
- Soft swelling generally resolved by week 6 postoperatively

Uncommon (more than 1 but less than 10 animals in 1000 animals)
Mild to moderate

- Exuberant bony callus associated with persistent (>10 weeks) moderate soft tissue swelling and excessive licking of the incision area.

Severe

- Lameness

Observed clinical signs were listed as adverse reactions for TruScient when they exceeded in intensity and/or duration of what would be considered normal for fracture healing after Standard of Care (SOC).

If you notice any serious effects or other effects not mentioned in this package leaflet, please inform your veterinarian surgeon.

7. TARGET SPECIES

Dogs

8. DOSAGE FOR EACH SPECIES, ROUTE(S) AND METHOD OF ADMINISTRATION

TruScient should be used by an appropriately qualified veterinarian.

The maximum recommended dosage is the entire contents of a single TruScient kit for each dog (i.e., up to two 2.5 x 5 cm prepared TruScient sponges per dog). Prepare sponges at least 15 minutes prior to use from components contained in the kit.

Follow the instructions for preparation below. The dibotermin alfa (rhBMP-2) is reconstituted to 0.2 mg/ml solution and then distributed uniformly across both sponges.

Failure to follow the advice for correct administration for TruScient may compromise its safety and effectiveness.

9. ADVICE ON CORRECT ADMINISTRATION

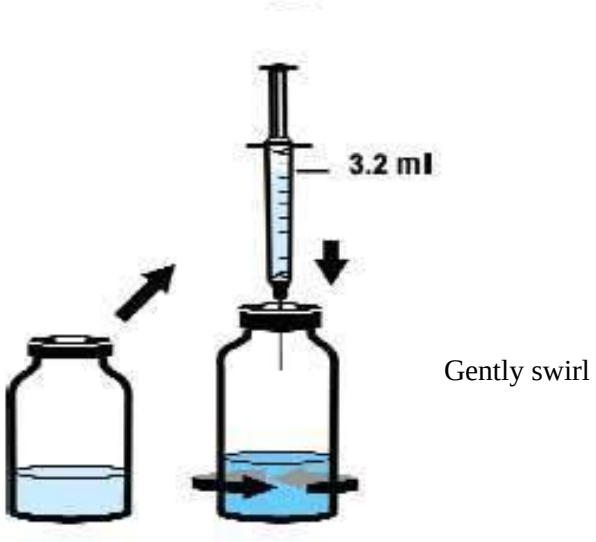
Read the instructions below each time the veterinary medicinal product is used.

Directions: Using aseptic technique, follow the directions below to reconstitute dibotermin alfa (rhBMP-2) for application to the sponges. Use care to ensure that accurate volumes are used in reconstitution and application of the dibotermin alfa (rhBMP-2) solution to the sponge. For accurate dosing ensure there are no suspended air bubbles in the transfer volumes.

A. Reconstitute dibotermin alfa (rhBMP-2) in a non-sterile field:

1. Disinfect with alcohol the stoppers of the lyophilisate and the solvent vials.
2. Using the 6 ml syringe and needle, withdraw 3.2 ml of solvent (more solvent is supplied than is needed). **Do not use more than 3.2 ml.**
3. Slowly inject the 3.2 ml of solvent into the lyophilisate vial (see **Figure 1**) to achieve a 0.2 mg/ml solution of rhBMP-2.
4. Swirl the vial gently to aid reconstitution. **Do not shake**. Discard syringe and needle after use.

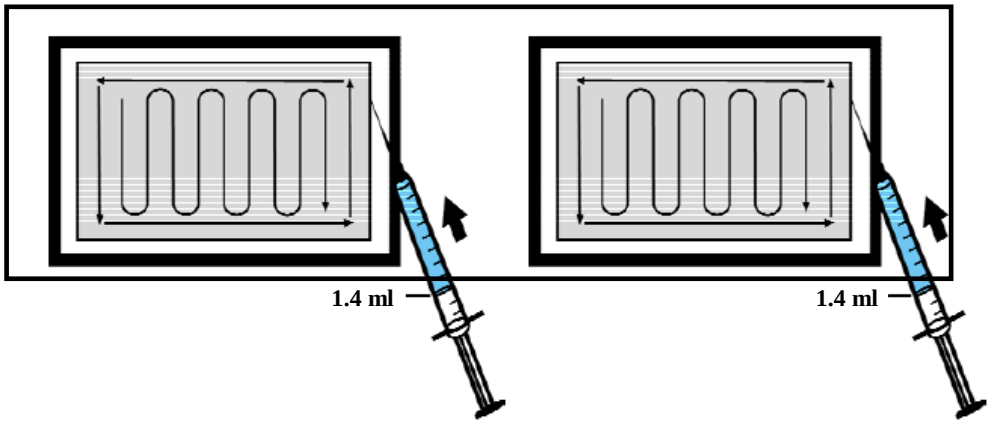
Figure 1: Reconstitution of dibotermin alfa (rhBMP-2)



B. Prepare TruScient sponges in the sterile field:

5. Using sterile technique, transfer the two 3 ml syringes with needles and the sponges inner package into the sterile field.
6. Peel open the inner package of sponges and leave them in the tray.
7. Using aseptic transfer technique and for each 3 ml syringe with needle, withdraw 1.4 ml from the reconstituted vial of dibotermin alfa (rhBMP-2) in the non-sterile field.
8. Leaving the sponges in the tray, UNIFORMLY distribute onto each sponge 1.4 ml dibotermin alfa solution as shown in the illustration (**Figure 2**).

Figure 2: Preparation of TruScient sponges



9. Wait a MINIMUM of 15 minutes before using the prepared sponges. Use within 2 hours of wetting the sponges.
10. During handling, avoid excessive fluid loss from the prepared sponges. Do not squeeze.
11. If only a portion of a prepared sponges is required, first prepare the entire package (following steps 1 – 9 above), then cut the prepared sponge as needed prior to implantation.

C. Implantation

12. Achieve definitive fracture reduction, fixation, and hemostasis prior to placement of the prepared sponge. Dry the fracture site to the extent possible.
13. Cut or fold the prepared sponge as needed prior to placement. The amount of prepared sponge placed is determined by the fracture anatomy and the ability to close the wound with minimal compression of the sponge. Use only the amount of prepared sponge needed to achieve coverage of accessible fracture lines and defects (less than one up to two prepared sponges).
14. During placement, use forceps to handle the prepared sponge to avoid excessive fluid loss.
15. Place the prepared sponge so that it bridges the fracture and makes good contact with the major proximal and distal fracture fragments. The prepared sponge may be wrapped around the bone or placed up to the edges of a bone plate as the geometry of the fracture and fixation requires. Bone plates should not be covered with the prepared sponge in order to facilitate if plate removal is needed following fracture healing. Area vascularity should be maintained.
16. TruScient will not provide mechanical stability and should not be used to fill spaces in the presence of compressive forces.

D. After Placement

17. Do not irrigate the wound once the prepared sponge is placed across the fracture. Irrigation will wash away the dibotermin alfa (rhBMP-2) solution.
18. If a surgical drain is required, place the drain at least one layer superficial to or remote from the prepared sponge.
19. Following placement, achieve complete soft-tissue coverage of the prepared sponges.

10. WITHDRAWAL PERIOD

Not applicable.

11. SPECIAL STORAGE PRECAUTIONS

Do not store above 25º C.
Do not refrigerate.
Do not freeze.
Store in the original package.
Keep out of the sight and reach of children.
Discard any unused veterinary medicinal product.

12. SPECIAL WARNING(S)

Failure to follow the product preparation instructions may compromise its safety and effectiveness.

In order to avoid excessive postoperative swelling, use only the amount of prepared TruScient sponge needed to achieve coverage of accessible fracture lines and defects (less than one to up to two prepared sponges).

TruScient can cause initial resorption of surrounding trabecular bone. Therefore, in the absence of clinical data, the veterinary medicinal product should not be used for direct applications to trabecular bone when transient bone resorption may create a risk of bone fragility and, thus, increase the risk of implant failure.

TruScient does not provide mechanical stability and should not be used to fill space in the presence of compressive forces. Long-bone fracture and soft-tissue management procedures should be based on standard practice, including control of infection.

Both rhBMP-2 and bovine Type I collagen can elicit an immune response in dogs. Although no clear association with clinical outcome or undesirable effects could be observed in clinical and safety studies, the possibility of developing neutralising antibodies or hypersensitivity-type reactions cannot be excluded. The possibility of an immune response to the product should be evaluated in cases where an undesirable effect with immunological background is suspected.

The safety, including potential immune responses and effectiveness of repeat TruScient administration have not been evaluated in dogs.

No studies have been performed in dogs with known autoimmune diseases.

No studies have been performed in dogs with metabolic bone diseases.

The safety of the veterinary medicinal product has not been established during breeding, pregnancy and lactation. BMP-2 plays a critical role during foetal development. The influence of anti-BMP-2 antibody formation on foetal development has not been assessed. The incidence of antibody titres in treated dogs under field conditions is low and the puppies will have no or very limited exposure to anti-BMP-2 antibodies due to the potential for limited transfer across the placenta in dogs.
This medicinal product should only be used in breeding, pregnant and lactating dogs following a risk/benefit assessment by the responsible veterinarian.

In case of accidental spillage onto skin and eyes rinse off immediately.

TruScient is intended for single use only. TruScient must not be re-sterilised.
Use the prepared sponge(s) within 15 minutes to 2 hours of wetting the sponges.

Discard any unused veterinary medicinal product.

TruScient should only be administered to the fracture site with utmost care.

No interaction studies have been performed. As dibotermin alfa (rhBMP-2) is a protein and has not been identified in the general circulation, it is an unlikely candidate for pharmacokinetic drug-drug interactions.

TruScient should not be mixed with other agents.

TruScient used in concentrations or amounts greater than those recommended is associated with excessive bone formation and increased generation of fluid-filled void spaces within the induced bone. Excessive bone and fluid filled cysts remodel into normal bone over time. Biomechanical data suggest these voids had little influence on the biomechanical properties of the induced bone or its integration with the abutting cortices. In the case of dogs receiving concentrations or amounts greater than those recommended, treatment of adverse effects, where required, should be symptomatic.

In the absence of compatibility studies, this veterinary medicinal product must be reconstituted only with the solvents provided and should not be mixed with other solvents or other veterinary medicinal products.

13. SPECIAL PRECAUTIONS FOR THE DISPOSAL OF UNUSED PRODUCT OR WASTE MATERIALS, IF ANY

Any unused veterinary medicinal product or waste material derived from such veterinary medicinal product should be disposed of in accordance with local requirements.

14. DATE ON WHICH THE PACKAGE LEAFLET WAS LAST APPROVED

Detailed information on this product is available on the website of the European Medicines Agency (http://www.ema.europa.eu/).

15. OTHER INFORMATION

Each kit contains:

Lyophilisate:
- 10 ml Type I glass vial with a chlorobutyl elastomeric closure sealed with an aluminum flip-off seal and plastic cap.

Solvent:
- 10 ml Type I glass vial with a bromobutyl elastomeric closure sealed with an aluminum flip-off seal and plastic cap.

Sponge:
- Two sterile sponges 2.5 x 5 cm in a polyvinyl chloride (PVC) blister package sealed with a Tyvek lid.

The kit also includes:
- Two sterile 3 ml disposable polypropylene syringes with stainless steel needles attached.
- One sterile 6 ml disposable polypropylene syringe with stainless steel needle attached.

For any information about this veterinary medicinal product, please contact the local representative of the marketing authorisation holder.

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