ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

Opgenra 3.3 mg powder for implantation suspension.

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

One vial contains 1g powder with 3.3 mg of eptotermin alfa*.

After reconstitution, Opgenra contains 1 mg/ml eptotermin alfa.

*Eptotermin alfa is human recombinant osteogenic protein 1 (OP-1) produced in Chinese hamster ovary (CHO) cell line.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for implantation suspension.
The powder containing the active substance is granular and white to off-white.
The powder containing the excipient carmellose (carboxymethylcellulose) is yellowish white.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Opgenra is indicated for posterolateral lumbar spinal fusion in adult patients with spondylolisthesis where autograft has failed or is contra-indicated.

4.2 Posology and method of administration

This medicinal product should be used by an appropriately qualified surgeon.

Posology

Opgenra is intended only for single use in each patient. Treatment requires a single surgery. To fuse a single level of the lumbar region of the spine, one unit of medicinal product is used on each side of the spine. The maximum human dose should not exceed 2 units since efficacy and safety for spinal fusion requiring higher doses has not been established.

Paediatric population

Opgenra is contraindicated in children (<12 years old), adolescents (12-18 years old) and the skeletally immature (see section 4.3).

Renal/hepatic impairment

Care should be used when Opgenra is used in patients with renal or hepatic impairment (see section 4.4).

Method of administration

For intraosseous use.

The reconstituted product is administered by direct surgical placement into the lumber region of the spine following surgical preparation of the site. The surrounding soft tissues are then closed around the implanted material.

For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

Opgenra must not be used in patients who:

- have a hypersensitivity to the active substance or to any of the excipients listed in section 6.1;
- have an autoimmune disease, including Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, Sjögren's syndrome and dermatomyositis/polymyositis;
- have an active infection at the site of spinal fusion or history of recurring infections;
- have inadequate skin coverage and vascularity at the site of spinal fusion;
- have prior history of exposure to any bone morphogenetic protein (BMP) product;
- have an active malignancy or are undergoing treatment for a malignancy;
- require arthrodesis as a result of metabolic bone disease or tumour.

Opgenra is contraindicated in children aged 0 to 12 years old, adolescents aged 12 to 18 years and the skeletally immature.

4.4 Special warnings and precautions for use

Use of Opgenra does not guarantee fusion; additional surgeries may be required.

Containment

Any material dislodged from the fusion site can cause ectopic ossification in the surrounding tissues with potential complications. Therefore, Opgenra may only be administered to the fusion site under adequate vision and with utmost care. Special care must be taken to prevent any leakage of Opgenra due to irrigation, defective closure of surrounding tissue or inadequate haemostasis. CT examination has suggested that significant medial displacement of Opgenra can occur post-operatively and this can result in bone forming medially. This should be considered in follow-up of patients with CT or X-ray.

Immune response

In a clinical study of the medicinal product, antibodies to the protein eptotermin alfa were detected in 194 out of 207 (94%) patients treated with it and 18 out of 86 (21%) treated with autograft bone (control group). Within the test group, 26% of patients produced antibodies with neutralizing capacity versus 1% in the control group. The peak antibody response was seen 3 months following treatment. There were no patients with neutralizing antibodies 2 years following treatment. The clinical significance of these antibodies is not known. The clinical study results suggest that there does not appear to be any association between neutralizing antibodies and the development of adverse events related to the immune system. However, an immune response to eptotermin alfa should be considered and appropriate validated tests for the presence of antibodies in serum should be performed in cases where an immune-mediated undesirable effect is suspected, including cases where the medicinal product is ineffective.

Opgenra is intended only for single use in each patient. Repeated use of the medicinal product cannot be recommended. Studies with anti-OP-1 antibodies demonstrated some cross-reactivity with closely related bone morphogenetic proteins BMP-5 and BMP-6. Anti-OP-1 antibodies have the ability to

neutralise the in vitro biological activity of at least BMP-6. Therefore, upon re-administration of Opgenra, a risk of developing autoimmunity towards the endogenous BMP proteins may exist.

Renal and hepatic impairment

There is limited experience on the use of the medicinal product in patients with renal or hepatic impairment therefore caution with its use in such patients is advised.

Use in cervical spine

Clinical studies to investigate the efficacy and safety of this medicinal product in cervical spine surgery have not been performed; consequently its use outside the region of the lumbar spine cannot be recommended.

Use with bone void fillers

The concomitant use of Opgenra with a synthetic bone void filler is not recommended (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed.

Post-marketing surveillance data includes reports that the use of the medicinal product in combination with a synthetic bone void filler, may lead to an increase in local inflammation, infection and occasionally migration of the implanted materials (see section 4.4).

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be advised to use effective contraception for a period of at least 2 years after treatment. Women of child-bearing potential should inform their surgeon of the possibility of pregnancy prior to treatment with Opgenra.

Pregnancy

Animal studies that have been conducted cannot rule out possible effects of anti-OP-1 antibodies on embryofoetal development (see section 5.3). Due to the unknown risks to the foetus associated with the potential development of neutralizing antibodies to OP-1 protein, the medicinal product should not be used during pregnancy unless the potential benefit justifies the potential risks to the foetus (see section 5.3).

Breast-feeding

In animal studies, excretion of IgG class anti-OP-1 antibodies into milk was shown. As human IgG is secreted into human milk, and the potential for harm to the infant is unknown, women should not breast-feed during Opgenra therapy (see section 5.3). The medicinal product should be used in breast-feeding women only when the attending physician decides that the benefits outweigh the risks. It is recommended that breast-feeding be discontinued following treatment.

4.7 Effects on ability to drive and use machines

Opgenra has no known pharmacological effect on neuro-motor coordination or performance consequently it is unlikely to alter any pre-existing skills used for driving vehicles or operating machines.

4.8 Undesirable effects

Summary of the safety profile

Opgenra is implanted during an invasive surgical procedure performed under general anaesthesia. Adverse events recorded during the clinical studies following such surgery and not specifically causally related to the implanted materials included superficial wound infection, wound dehiscence, osteomyelitis, complications of mechanical support, haematoma formation, nausea, vomiting, fever and pain. The frequency and severity of post-operative adverse events was similar in both test and control groups. The pattern of unrelated post-operative adverse events varied with the extent of surgical trauma, procedural complications and the pre-operative health of the patient.

Tabulated list of adverse reactions

The following adverse reactions were reported with Opgenra. The frequency of adverse reactions listed in the table below is based on the following convention:

Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤1/1,000); very rare (≤1/10,000), not known (cannot be estimated from the available data).

Infections and infestations	Common: post-operative infection
General disorders and administration site conditions	Uncommon: localised swelling, Not known: implant site complications (e.g. abscess, implant site induration, pain, oedema, pyrexia)
Immune system disorders	Not known: hypersensitivity, urticaria
Injury, poisoning and procedural complications	Common: wound dehiscence, secretion, pseudarthrosis Uncommon: product migration when mixed with synthetic bone void filler, seroma Not known: Post-procedural complications (e.g. post procedural discharge, swelling, other wound complications)
Musculoskeletal and connective tissue disorders	Common: bone formation increased (heterotopic bone formation) Not known: osteolysis
Skin and subcutaneous tissue disorders	Common: erythema

Pre-existing co-morbidities

In the study populations, some patients with common pre-existing co-morbidities (e.g. cardiovascular, respiratory, genitourinary disorders, neoplasms) experienced exacerbations of their prior disease during the long term (three year) follow up period. Patients with a known history of heart disease or frequent infections should be identified and observed more closely following surgery.

Interaction with bone void fillers

Post-marketing surveillance data includes reports that the use of the medicinal product in combination with a synthetic bone void filler, may lead to an increase in local inflammation, infection and occasionally migration of the implanted materials.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Drugs for the treatment of bone diseases, bone morphogenetic proteins, ATC code: M05BC02

Opgenra is an osteoinductive and osteoconductive medicinal product.

Eptotermin alfa, the active substance, initiates bone formation through the induction of cellular differentiation in mesenchymal cells, which are recruited to the implant site from bone marrow, periosteum and muscle. Once bound at the cell surface, the active substance induces a cascade of cellular events leading to the formation of chondroblasts and osteoblasts, which play a key role in the bone formation process. The collagen matrix is insoluble and consists of particles with a size range of 75-425µm. This provides an appropriate bioresorbable scaffold for the anchorage dependent cell proliferation and differentiation processes induced by the active substance. The carmellose imparts a putty-like consistency to the medicinal product for ease of molding and placement on each side of the spine. The cellular events induced by the active substance take place within the product matrix. The matrix is also osteoconductive and it allows bone in-growth into the defect area from the adjacent healthy bone.

The pivotal study with 295 patients involved un-instrumented postero-lateral lumbar spine fusion in 208 patients treated with Opgenra.

5.2 Pharmacokinetic properties

There are no data on the pharmacokinetics of the active substance in man. However, results from implantation studies in animals demonstrate that the active substance eptotermin alfa is released from the implant site over several weeks and never reaches a level higher than 3% of the total amount implanted in the peripheral blood.

5.3 Preclinical safety data

Single dose and repeat dose studies in a range of animal models (rats and primates) were performed. The results of these showed no unanticipated or systemic effects of toxicity during the observation period and after administration.

In a 2 year subcutaneous implantation study in rats, heterotopic bone formation was observed, as expected. Sarcoma was associated with the long-term presence of the heterotopic bone. This effect, termed solid state carcinogenicity, has been frequently observed in rats in which solid materials (plastics or metals) were implanted subcutaneously.

Heterotopic ossification commonly occurs in humans following accidental or surgical trauma to the skeleton. It has been observed following use (see section 4.8). However, there is no evidence to suggest that heterotopic ossification is linked to sarcoma development in humans.

The effect of anti-OP-1 antibodies on the bone healing process was studied in dogs with two long bone defects treated with repeat implantations. The results of radiological and histological examinations in this study showed bone healing following the initial and repeat exposure in the same animal. Antibodies to OP-1 and bovine bone collagen type 1 were found after both exposures. Not surprisingly, the antibody peak concentration was higher after the second exposure. The antibody levels declined towards baseline during the follow-up period.

Controlled studies of the effects of exposure to eptotermin alfa on pre and postnatal development were performed in rabbit models. Eptotermin alfa in Freund's adjuvant was first administered subcutaneously with booster doses given after 14 and 28 days. Blood and milk samples were collected at regular intervals and analysed using a solid phase enzyme-linked immunoassay (ELISA) test. Detectable levels of IgG and IgM antibodies to eptotermin alfa had developed and were found in the serum of all exposed adult animals. Antibodies to eptotermin alfa were also found in sera from pooled foetal and umbilical cord blood, at levels that correlated to that of the maternal blood. Antibodies were detectable in adults and offspring during the gestation and lactation periods. Significantly high titers of IgG class anti-OP-1 antibodies were detected in milk throughout the whole post-natal phase study until the lactation day 28 (see section 4.6).

A statistically significant increase in foetal malformations (misaligned sternabrae) was seen in litters of the OP-1 immunized group. However the rate of malformations was similar to those from historical controls. In another study a difference in body weight gain was seen in the immunized adult females between lactation days 14 to 21 when compared to the control animals. The weight of the offspring in the treated group was noted to be less than that of the control group during the observation period. The clinical implications of these observations for human use of the finished medicinal product remain uncertain (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Bovine collagen
Carmellose

6.2 Incompatibilities

Potential interaction with Calstrux, a bone void filler has been reported (see section 4.5). This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

3 years.

The reconstituted medicinal product should be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

Keep the blisters in the outer carton.

For storage conditions after reconstitution, see section 6.3.

6.5 Nature and contents of container

One unit of Opgenra is supplied in two Type I glass vials, sealed with a butyl rubber stopper and aluminium crimp cap.

The vials are maintained sterile within individual blisters and packaged together in an outer tray and box.

One vial containing 1g of powder (3.3 mg eptotermin alfa); one vial containing 230 mg carmellose powder.

Pack sizes:

- a single unit pack with 1 vial containing 1g of powder (3.3 mg eptotermin alfa) and 1 vial containing 230 mg carmellose powder

- a pack of two units with 2 x 1 vial containing 1g of powder (3.3 mg eptotermin alfa) and 2 x 1 vial containing 230 mg carmellose powder.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Each unit of Opgenra consists of two vials of powder, which are first combined and then reconstituted with 2.5 ml of sodium chloride 9 mg/ml (0.9%) solution for injection prior to use. Once Opgenra is prepared it should be used immediately.

1. Using sterile technique, remove the vials from the packaging.

2. Lift the plastic flip-tops and remove the crimp caps from the vials.
   Handle the crimp caps with care. The edges of the crimp caps are sharp and may cut or damage gloves.

3. Using your thumb pry up the edges of the stoppers. Once the vacuums are broken, remove the vial stoppers while holding the vials upright to prevent loss of contents.

   Do not insert a needle through the stoppers. Puncture of the stoppers with a needle may result in particles of stopper material contaminating the medicinal product.

4. Place the contents of the eptotermin alfa vial and carmellose vial in a sterile bowl. To avoid breakage, do not tap the bottom of the vial when transferring contents.

5. Using a sterile syringe, add 2.5 ml of sterile 9 mg/ml sodium chloride solution for injection (0.9% w/v) to the sterile bowl slowly and carefully.

6. Gently stir the contents of the bowl with a sterile spatula to aid mixing.

7. The same procedure should be used to prepare the medicinal product for the contralateral side of the spine. Use the product promptly following reconstitution.

8. Debride and decorticate bone so that the reconstituted medicinal product will directly contact viable tissue.

9. Provide adequate haemostasis to ensure that the material stays at the surgical site. Irrigate the surgical site as necessary prior to the implantation of the medicinal product. Where practical, surgical manipulations to the site should be completed prior to product implantation.

10. Remove the reconstituted product from the sterile bowl with a sterile instrument such as a spatula or curette. The product should have a malleable, coherent putty-like consistency.

11. Carefully apply the product to the prepared site on each side of the spine, bridging the dorsal surfaces of the adjacent transverse processes.

12. Close soft tissues around the site containing the product using suture material of choice. Closure is critical for containment and maintenance of the product in the area of intended fusion.

13. Do not place a drain directly in the implant or fusion site. Place it subcutaneously if possible.

14. After closure of the soft tissues around the implant, irrigate the field if necessary to remove any stray particles of the medicinal product which may have been dislodged during soft tissue closure.

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

7. MARKETING AUTHORISATION HOLDER

Olympus Biotech International Limited
Block 2, International Science Centre
National Technology Park
Castletroy
Limerick
Ireland

Tel +353 61 585100
Fax +353 61 585151
medicalinfo@olympusbiotech.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/489/001
EU/1/08/489/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 February 2009
Date of renewal: 19 February 2014

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

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

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

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

Name and address of the manufacturer of the biological active substance

Olympus Biotech Corporation
9 Technology Drive
West Lebanon NH 03784
USA

Name and address of the manufacturer responsible for batch release

Olympus Biotech International Limited
Raheen Business Park
Raheen, Limerick
Ireland

Olympus Biotech International Limited
Block 2, International Science Centre, National Technology Park
Castletroy, Limerick
Ireland

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2. of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

- **Additional risk minimisation measures**

The MAH shall agree the details of an education programme for surgeons with the National Competent Authorities and must implement such programme nationally to ensure that:

Prior to use of the product, surgeons should be provided with educational material containing:
- a copy of the SPC
- a detailed description of:
  - the recommended methods for reconstitution of the product prior to implantation
  - the preparation of the selected paraspinal site where the intended implantation will occur
  - the recommended manner of placement of the material together with some comments on the importance of local haemostasis
  - the methods for soft tissue closure around the implant. These descriptive texts are included in the product information.
- information about:
  - hypersensitivity and antibody formation
  - embryo-foetotoxicity and the need for women with childbearing potential to use effective contraception for 2 years following implant
  - the risks of ectopic bone formation
  - interaction with bone void fillers
  - that the product should only be used once
- details of the post marketing surveillance studies including information on how to enroll patients

In addition, prior to use, surgeons intending to use Opgenra should receive a Training DVD containing animated images of an operation on a patient and including the following information:
- Product description
- Placement in sterile field
- Wound opening (soft and hard tissues)
- Reconstitution of product
- Implant field preparation (haemostasis)
- Administration (implantation)
- Containment of implanted materials (soft tissues)
- Instrumentation
- Wound closure (drainage)
- Follow-up measures

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	Due date
The MAH shall submit the results of a study or studies to investigate the long term safety and efficacy of patients treated with Opgenra and also actual drug utilisation in real life.	December 2018

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Opgenra 3.3 mg powder for implantation suspension
eptotermin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

One vial containing 3.3 mg of eptotermin alfa.
After reconstitution, Opgenra contains 1 mg/ml eptotermin alfa.

3. LIST OF EXCIPIENTS

Excipients : Bovine collagen, carmellose.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for implantation suspension.
1 vial containing 1 g of powder (3.3 mg eptotermin alfa).
1 vial containing 230 mg carmellose.

4 vials:
2 x 1 vial containing 1 g of powder (3.3 mg eptotermin alfa).
2 x 1 vial containing 230 mg carmellose.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intraosseous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
The reconstituted medicinal product should be used immediately.
Keep the blisters in the outer carton.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Olympus Biotech International Limited
Block 2, International Science Centre
National Technology Park
Castletroy
Limerick
Ireland

Tel +353 61 585100
Fax +353 61 585151
medicalinfo@olympusbiotech.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/08/489/001
EU/1/08/489/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BLISTER FOIL ACTIVE SUBSTANCE POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT

Opgenra 3.3 mg powder for implantation suspension
eptotermin alfa

2. STATEMENT OF THE ACTIVE SUBSTANCE(S)

One vial containing 3.3 mg of eptotermin alfa

3. LIST OF EXCIPIENTS

Excipients : Bovine collagen

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for implantation suspension.
1 vial containing 1 g of powder (3.3 mg eptotermin alfa).

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Intraosseous use
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator (2°C – 8°C).
The reconstituted medicinal product should be used immediately.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Any unused product or waste material should be disposed of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

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Tel +353 61 585100
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medicalinfo@olympusbiotech.com

12. MARKETING AUTHORISATION NUMBER(S)

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL OF ACTIVE SUBSTANCE POWDER

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Opgenra 3.3 mg

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

1 g (3.3 mg eptotermin alfa)

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

BLISTER FOR THE CARMELLOSE POWDER VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Carmellose powder for implantation suspension for Opgenra
Intraosseous use

2. METHOD OF ADMINISTRATION

Read the package leaflet before use.

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

230 mg

6. OTHER

Do not open before use.
The reconstituted medicinal product should be used immediately.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

CARMELLOSE VIAL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Carmellose (Opgenra)

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

230 mg

6. OTHER

HEALTHCARE PROFESSIONAL EDUCATIONAL STICKER

To be attached to the patient's medical record.

"{Patient Name} was implanted with a medicinal product containing eptotermin alfa on {dd/mm/yyy}. Repeat use of this bone morphogenetic protein (BMP) is not recommended."

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Opgenra 3.3 mg powder for implantation suspension
eptotermin alfa

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See end of section 4 for how to report side effects.

Read all of this leaflet carefully before you are administered this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor.
- If you get any side effects talk to your doctor. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet:

1. What Opgenra is and what it is used for.
2. What you need to know before you are administered Opgenra.
3. How to use Opgenra.
4. Possible side effects.
5 How to store Opgenra.
6. Contents of the pack and other information.

1. What Opgenra is and what it is used for

Opgenra contains the active substance eptotermin alfa.

Opgenra is a type of medicine known as a bone morphogenetic protein (BMP). This group of medicines cause new bone to grow at the location where the surgeon has placed (implanted) it.

Opgenra is implanted in adult patients with slippage of the spine (spondylolisthesis) in cases where treatment with autograft (transplanted bone from your hip) has failed or must not be used.

2. What you need to know before you are administered Opgenra

Do not use Opgenra
- if you are allergic to eptotermin alfa or to any of the ingredients of this medicine (see section 6).
- if you have an autoimmune disease (disease arising from or directed against your own tissues), including Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus, scleroderma, Sjögren's syndrome and dermatomyositis/ polymyositis.
- if you have an active infection in your spine or have been told that you have an active internal (systemic) infection.
- if you have inadequate skin coverage and inadequate blood supply at the site of surgery (your doctor should have told you if this is the case).
- have had this medicine, eptotermin alfa or any similar medicine before.
- have any tumours in the area intended for surgery.
- if you require a spinal fusion because of a metabolic bone disease or tumours.
- if you are receiving chemotherapy, radiation treatment or immunosuppression**.**
- if you are a child (less than 12 years old).
- if you are an adolescent (12-18 years old) or your skeleton is not yet be fully formed (you are still growing).

Warnings and precautions

Talk to your doctor before you are administered this medicine.

- Use of this medicine does not guarantee fusion. Additional surgeries may be needed.
- There is a possibility that new antibodies can form in your body when this medicine is used. It is possible they may impair the effectiveness of this medicine or cause an immune system response.
- Inform your doctor or surgeon if you have been administered this medicine in the past. Repeated use of this medicine cannot be recommended. Laboratory studies have demonstrated that there is a theoretical risk of developing autoimmunity towards the natural (endogenous) BMP proteins in your body following repeat exposure to this medicine.
- Inform your doctor if you have a history of liver or kidney disease.
- Inform your doctor or surgeon if you have a history of heart problems or are prone to frequent infections so that they can closely monitor you.
- Opgenra has not been studied for use in cervical spine surgery. Use of this medicine in the cervical spine cannot be recommended.
- Use of this medicine with synthetic bone substitutes is not recommended.

Talk to your doctor or surgeon about these precautions before you are administered this medicine.

Other medicines and Opgenra
Tell your doctor if you are taking or have recently taken any other medicines.

Use of this medicine with synthetic bone substitutes is not recommended. There have been reports of swelling and infection following the use of this medicine with synthetic bone substitutes.

Pregnancy and breast-feeding
Opgenra should not be administered during pregnancy unless the benefits to the mother outweigh the risks to the unborn child. Women of child-bearing potential should inform their surgeon of the possibility of pregnancy before they are administered this medicine. Women of childbearing potential are advised to use effective contraception for a period of 2 years after their treatment.

Do not breast-feed your baby during treatment with this medicine. As the potential for harm to the breast fed infant is unknown, women should not breast-feed during the period immediately following treatment with this medicine. If you are nursing, you should receive this medicine only if your treating physician or surgeon considers the benefits to you outweigh the risks to your child.

Driving and using machines
It is unlikely that Opgenra will affect the ability to drive and use machines

3. How to use Opgenra

Opgenra is only used by an appropriately qualified surgeon during the course of spinal fusion surgery. This is normally done under a full general anaesthetic so you will not be awake during the surgery.

A small quantity (one unit) of this medicine is reconstituted and placed directly on each side of the spine at the site requiring fusion. The surrounding muscle tissue is then closed around the implanted medicine as is the skin on top of the muscle. This specialised medicine is used instead of autograft bone (some of a patient's own bone taken from the hip) to fuse the spine.

The maximum dose of this medicine should not exceed 2 units (6.6 mg eptotermin alfa) since its effectiveness and safety in higher doses has not been studied.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Talk to your doctor if you have any of the following:

- Common (may affect up to 1 in 10 people):
  - redness of the skin (erythema) ,
  - increased bone formation or bone formation outside of the fusion area (heterotopic bone formation),
  - failure of the spine to fuse (pseudarthrosis),
  - wound problems including infection, discharge and rupture.

- Uncommon (may affect up to 1 in 100 people):
  - localised swelling, swelling over the implant site,
  - collection of fluid in the tissues (seroma),
  - product migration (this has been observed when the product was mixed with a synthetic product used to fill the bone void)

- Not known (cannot be estimated from available data)
  - problems at the implant site (for example abscess, hardening, pain, swelling, or fever)
  - allergic reactions (for example rash or hives)
  - post-surgery problems (for example discharge, swelling or other wound complications)
  - resorption of bone (osteolysis).

Some patients that had a history of heart problems or were prone to frequent infections became worse after being administered this medicine. Inform your doctor or surgeon if you have a history of heart problems or are prone to frequent infections so that they can closely monitor you.

Reporting of side effects
If you get any side effects, talk to your doctor or surgeon. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Opgenra

Keep out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the carton and blisters. The expiry date refers to the last day of the month. Opgenra should be used immediately after reconstitution.

Store in a refrigerator (2°C - 8˚C).

Keep the blisters in the outer carton.

The hospital pharmacist or surgeon is responsible for the correct storage of this medicine both before and during its use, as well as for its correct disposal.

6. Contents of the pack and other information

What Opgenra contains

The active substance is eptotermin alfa (a recombinant human osteogenic protein 1 produced in a Chinese hamster ovary (CHO) cell line).

The other ingredients are bovine collagen and carmellose.

One vial of this medicine contains 1 g of powder including 3.3 mg of eptotermin alfa and the excipient bovine collagen. The other vial contains the excipient carmellose.

What Opgenra looks like and contents of the pack

One unit of Opgenra powder for implantation suspension comes as two separate powders. The powder containing the active substance and the excipient bovine collagen has the appearance of a white to off-white granular powder; the carmellose powder is a yellowish white powder.

The powders come in glass vials. Each vial is secured in a sterile blister. Each outer carton contains one 3.3 mg eptotermin alfa vial containing 1 g of powder and one carmellose powder vial containing 230 mg powder.

Pack sizes:
- a single unit pack with 1 vial containing 1g of powder (3.3 mg eptotermin alfa) and 1 vial containing 230 mg carmellose powder

- a pack of two units with 2 x 1 vial containing 1g of powder (3.3 mg eptotermin alfa) and 2 x 1 vial containing 230 mg carmellose powder.

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

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This leaflet was last revised in <Month YYYY>.

Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu.

Annex IV

Grounds for one additional renewal

Grounds for one additional renewal

The CHMP recommend an additional five-year renewal based on the following pharmacovigilance grounds: the clinical experience with the product in the designated indication has been very limited in the EU during the first 5-year period of marketing authorisation. Indeed, there has been a limited exposure due to a recent and limited marketing of the product (launched in the EU only in August 2011 and marketed in only few Member States). In addition, results of the post-authorisation studies to investigate the long term safety and efficacy of Opgenra and also investigate the actual drug utilisation in 'real life' are needed to further characterise the safety and efficacy profile.