ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Osigraft 3.3 mg powder for suspension for implantation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 3.3 mg of eptotermin alfa*

*Produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology

For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for suspension for implantation.

White to off-white granular powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of non-union of tibia of at least 9 month duration, secondary to trauma, in skeletally mature patients, in cases where previous treatment with autograft has failed or use of autograft is unfeasible.

4.2 Posology and method of administration

Posology
Osigraft should be used by an appropriately qualified surgeon.

The recommended dose is one single administration in adults. Depending on the size of the bone defect, more than one 1 g vial of Osigraft may be required. The recommended maximum dose should not exceed 2 vials since efficacy in the treatment on non-unions requiring higher doses has not been established.

Paediatric population
Osigraft is contraindicated in children and adolescents (less than 18 years old) and the skeletally immature (see section 4.3).

Method of administration:
Intraosseous use.

The reconstituted product is administered by direct surgical placement at the non-union site in contact with the prepared bone surface. The surrounding soft tissues are then closed around the implant. Experience from controlled clinical trials is limited to stabilisation of the fracture by intramedullary nailing.

1. Using sterile technique, remove the vial from its packaging.

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

3. Using your thumb, pry up the edge of the stopper. Once the vacuum is broken, remove the vial stopper while holding the vial upright to prevent loss of powder.

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

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

5. Debride fibrous, necrotic or sclerotic tissue and appropriately decorticate bone fragments so that the reconstituted Osigraft is in direct contact with bleeding bone and viable osseous tissue.

6. Provide adequate haemostasis to ensure that the implanted material is not dislodged from the surgical site. Irrigate as necessary prior to the implantation of Osigraft. Where practical, surgical manipulations to the site should be completed prior to implantation of the product.

7. Apply the reconstituted product to the prepared osseous site using a sterile instrument such as a spatula or curette. The amount of Osigraft used should approximate the size of the bone defect.

8. Do not use suction or irrigation directly at the implant site as the particles of Osigraft may be removed. Remove excess fluid if necessary by suctioning adjacent to the implant site or carefully blotting the area with sterile sponge.

9. Close soft tissues around the defect containing the product using suture material of choice. Closure is critical for containment of the implant in the area of the bone defect.

10. After closure of the soft tissues around the bone defect, irrigate field if necessary to remove any of the product which may have become dislodged during soft tissue closure.

11. Do not place a drain directly in the implant site. If required, place it subcutaneously.

4.3 Contraindications

Osigraft must not be used in patients who:

- have a known hypersensitivity to the active substance or to collagen;
- have skeletal immaturity;
- have known autoimmune disease, including rheumatoid arthritis, systemic lupus erythematosus, scleroderma, Sjögren's syndrome and dermatomyositis/polymyositis;
- have active infection at the site of non-union or active systemic infection;
- have inadequate skin coverage and vascularity of the non-union site;
- have vertebral fractures;
- have a non-union resulting from pathological fractures, metabolic bone disease or tumours;
- have any tumour in the vicinity of the non-union site;
- are receiving chemotherapy, radiation treatment or immunosuppression;

Osigraft is contraindicated in children and adolescents (less than 18 years old) and the skeletally immature (see section 4.2).

4.4 Special warnings and precautions for use

Precaution for use
Osigraft does not provide any biomechanical strength and should be used with internal or external fixation where initial mechanical stabilisation is required. However, external fixation may not provide sufficient immobilisation. Motion in the non-union site may disrupt the fracture healing process. Experience from controlled clinical trials is limited to stabilisation of tibial non-union site using concomitant intramedullary nailing. Locking intramedullary rods were used in the majority of cases.

Use of Osigraft does not guarantee repair, additional surgery may be required.

Implanted material dislodged from the non-union site can cause ectopic ossification in the surrounding tissues with potential complications. Therefore, Osigraft may only be administered to the defect site under adequate vision and with utmost care. Special care must be taken to prevent any leakage of Osigraft due to wound irrigation, defective closure of surrounding tissue or inadequate haemostasis.

Antibodies
Antibodies to OP-1 protein were detected in 66% of patients in the tibial non-union study following the administration of eptotermin alfa. Analysis of these antibodies showed that 9% had neutralizing capacity. No association with clinical outcome or adverse event could be observed in clinical studies. An immune response to Osigraft should be considered and appropriate 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 product is ineffective.

Repeat Use
Repeated use of the product cannot be recommended. Studies with anti-OP-1 antibodies demonstrated some cross-reactivity with closely related BMP 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 eptotermin alfa, a risk of developing autoimmunity towards the endogenous BMP proteins may exist.

Interaction with other medicine
The use of Osigraft with a synthetic bone void filler may lead to a risk of increase in local inflammation, infection and occasional migration of the implanted materials and is therefore not recommended (see section 4.5).

4.5 Interaction with other medicinal products and other forms of interaction

The pivotal clinical trial supporting the approval of Osigraft did not include the use of synthetic bone void fillers. Post market surveillance data has signalled that the use of the product in combination with a synthetic bone void filler may lead to an increase in local inflammation, infection and occasional migration of the implanted materials and it is therefore not recommended.

4.6 Fertility, pregnancy and lactation

Women of child-bearing potential
Women of child-bearing potential should inform their surgeon of the possibility of pregnancy prior to treatment with the medicine.

Contraception in males and females
Women of childbearing potential should be advised to use effective contraception up to at least 12 months after treatment.

Pregnancy
Animal studies were conducted that cannot rule out effects of anti-OP-1 antibodies on embryo-foetal 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, Osigraft should not be used during pregnancy unless the potential benefit justifies the potential risks to the foetus (see sections 4.4 and 5.3).

Breast-feeding
In animal studies, excretion of IgG class anti-OP-1 antibodies into milk has been shown. As human IgG is secreted into human milk, and the potential for harm to the infant is unknown, women should not breast-fed during Osigraft therapy (see section 5.3). Osigraft should be given to 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.

Fertility
There is no evidence to suggest that eptotermin alfa alters fertility.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The following table of adverse reactions was compiled from those observed and recorded during clinical trials. A similar pattern of adverse reactions has been recorded from spontaneous reporting with an incidence significantly less than that seen in the clinical trials. Some patients treated with this product were also reported to have experienced various undesirable effects associated with recent orthopaedic surgery.

The following categories are used to rank the adverse reactions by frequency of occurrence: 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); and very rare (<1/10,000), not known (cannot be estimated from the available data).

System Organ Class	**Adverse reactions** **Common**
Musculoskeletal and connective tissue disorders	Bone formation increased *(Heterotopic ossification / Myositis ossificans)*
Investigations	Antibody test positive *(Antibody formation)*
Injury, poisoning and procedural complications	Postoperative wound site erythema *(Erythema)*
	Post procedural tenderness *(Tenderness)*
	Post procedural swelling *(Swelling)*

4.9 Overdose

No case of overdose has been reported.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Osigraft is an osteoinductive and osteoconductive medicinal product.

Mechanism of action

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 cellular events induced by the active substance take place within the collagen matrix. The matrix is also osteoconductive and it allows bone in-growth into the defect area from the surrounding healthy bone.

Pharmacodynamic effects
The new bone formed is mechanically and radiographically comparable to normal bone. The new bone remodels naturally, cortices are formed and marrow elements are generated. However, use of Osigraft does not guarantee repair; additional surgery may be required.

Clinical efficacy and safety
The Tibial Nonunion pivotal trial compared Osigraft with autograft, with a primary efficacy endpoint at 9 months post-treatment. Clinical outcomes of pain and weight-bearing were comparable to the autograft (81% success in the Osigraft group, 77% success in the autograft group). The radiographic healing results of the Osigraft treatment group were slightly inferior compared to the autograft control group (68% and 79% respectively).

5.2 Pharmacokinetic properties

There are no data on the pharmacokinetics of the active substance in man. However, results from Osigraft implantation studies in animals demonstrate that the active substance eptotermin alfa is largely unavailable systemically.

5.3 Preclinical safety data

Single dose and repeat dose studies in a range of animal models (rats, dogs 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, frequently has been observed in rats where solid materials (plastics or metals) were implanted subcutaneously.

Heterotopic ossification commonly occurs in humans following accidental or surgical trauma. Heterotopic ossification may also occur following use (see section 4.8). However, there is evidence to suggest that heterotopic ossification is not linked to sarcoma in humans.

The effect of anti-OP-1 antibodies on the bone healing process was studied in dogs following two long bone defects treated with repeat implantations. The results of radiological and histological examinations in this non-clinical study showed bone healing with the initial and repeat exposure in the same animal. Antibodies to OP-1 and bovine bone collagen type 1 were found after both exposures; the antibody peak concentration was higher after the second implantation. 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 developed and were found in the serum of all exposed adult animals. Antibodies to eptotermin alfa were 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. 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 product remain uncertain (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Bovine collagen (vacuum dried).

6.2 Incompatibilities

In the absence of comparability studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

3 years.

The reconstituted product should be used immediately.

6.4 Special precautions for storage

Store in a refrigerator (2°C - 8°C).

6.5 Nature and contents of container and special equipment for use, administration or implantation

Powder in a glass vial (Type 1, borosilicate) sealed with a stopper (butyl rubber) and a crimp cap (aluminium).

The primary package is maintained sterile within a blister pack, comprised of two (inner and outer) plastic trays and lids.

Pack size of 1 vial.

6.6 Special precautions for disposal and other handling

Reconstitution
Each vial of Osigraft is reconstituted with 2 to 3 ml of sterile 9 mg/ml sodium chloride solution (0.9% w/v) prior to use. Sterile sodium chloride solution for injection and contents of the Osigraft vial are transferred to a sterile bowl and mixed with a sterile spatula or curette. To avoid breakage, do not tap the bottom of the vial when transferring contents. After reconstitution, the single use suspension for implantation should be used immediately.

Administration
When reconstituted, Osigraft has the consistency of wet sand, which facilitates its implantation and placement at bone site defects.

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

7. MARKETING AUTHORISATION HOLDER

Olympus Biotech International Limited
40 Upper Mount Street
Dublin 2
Ireland

Tel +353 87 9278653
medicalinfo@olympusbiotech.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/179/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18.05.2001
Date of latest renewal: 18.05.2011

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 MANUFACTURING AUTHORISATION HOLDER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OF THE MARKETING AUTHORISATION

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

Name and address of the manufacturer(s) of the biological active substance

Olympus Biotech Corporation
9 Technology Drive
West Lebanon
NH 03784
USA

Name and address of the manufacturer(s) responsible for batch release

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

B. CONDITIONS OF THE MARKETING AUTHORISATION

- **CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE IMPOSED ON THE MARKETING AUTHORISATION HOLDER**

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

- **OTHER CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT**

Not applicable.

- **OTHER CONDITIONS**

Risk Management Plan
The MAH commits to performing the studies and additional pharmacovigilance activities detailed in the Pharmacovigilance Plan, as agreed in version 1.0 of the Risk Management Plan (RMP) presented in Module 1.8.2. of the Marketing Authorisation and any subsequent updates of the RMP agreed by the CHMP.

As per the CHMP Guideline on Risk Management Systems for medicinal products for human use, any updated RMP should be submitted at the same time as the following Periodic Safety Update Report (PSUR).

In addition, an updated RMP should be submitted:

- When new information is received that may impact on the current Safety Specification, Pharmacovigilance Plan or risk minimisation as the result of an important (pharmacovigilance or risk minimisation) milestone being reached
- At the request of the European Medicines Agency

The Marketing Authorisation Holder will continue to submit PSURs every three years.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Osigraft 3.3 mg powder for suspension for implantation.
eptotermin alfa

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 3.3 mg eptotermin alfa*.
* Produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology.

3. LIST OF EXCIPIENTS

Bovine collagen.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for suspension for implantation.
1 vial

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 REACH AND SIGHTOF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
The reconstituted 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

Olympus Biotech International Limited
40 Upper Mount Street
Dublin 2
Ireland

Tel +353 87 9278653
medicalinfo@olympusbiotech.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/179/001

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

FOIL FOR THE BLISTER PACK (OUTER) FOR THE VIAL

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

Osigraft 3.3 mg powder for suspension for implantation.
eptotermin alfa.
Intraosseous use.

2. STATEMENT OF ACTIVE SUBSTANCE(S)

3.3 mg of eptotermin alfa

3. LIST OF EXCIPIENTS

Bovine Collagen

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for suspension for implantation.
1 vial

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 REACH AND SIGHT OF CHILDREN

Keep out of the reach and sight of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.
The reconstituted 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

Olympus Biotech International Limited
40 Upper Mount Street
Dublin 2
Ireland

Tel +353 87 9278653
medicalinfo@olympusbiotech.com

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/01/179/001

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

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

Osigraft
eptotermin alfa

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

3,3 mg

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

Osigraft 3.3 mg powder for suspension for implantation
eptotermin alfa

Read all of this leaflet carefully before you start using this medicine.
- Keep this leaflet. You may need to read it again.
- If you have further questions, ask your doctor.
- If any of the side effects gets serious, or if you notice any side effect not listed in this leaflet, please tell your doctor.

In this leaflet:

1. WHAT OSIGRAFT IS AND WHAT IT IS USED FOR

Osigraft 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. Osigraft is implanted in adult patients with fractures of the tibia which have failed to heal for at least 9 month duration in cases where treatment with autograft (transplanted bone from your hip) has failed or should not be used.

2. BEFORE YOU USE OSIGRAFT

Do not use Osigraft
- if you are allergic to eptotermin alfa or collagen, the other ingredient of Osigraft (see section 6).
- if you are an adolescent and your skeleton is not yet fully formed (still growing).
- if you are a child (below 18 years old)
- if you have an autoimmune disease (disease arising from or directed against your own tissues), including rheumatoid arthritis, systemic lupus erythematosus, scleroderma, Sjögren's syndrome and dermatomyositis/ polymyositis.
- if you have active infection at the site of non-union (inflammation and drainage at the site of injury) or active systemic infection.
- if your doctor determines that you have inadequate skin coverage (at the fracture site) and inadequate blood supply at your site of surgery.
- for vertebral (spine) fractures.
- for treating non-union resulting from pathological (disease-related) fractures, metabolic bone disease or tumours.
- when there are any tumours in the area of the non-union site.
- if you are receiving chemotherapy, radiation treatment or immunosuppression

Take special care with Osigraft
The following are precautions for use of Osigraft to be discussed with your doctor.

Osigraft stimulates the growth of new bone as part of the treatment of a fracture non-union and needs the support of specialised surgical devices to stabilise the broken bone while it heals.

Use of Osigraft does not guarantee repair; additional surgery may be required.

Special care is taken during surgery to prevent Osigraft leaking into the surrounding tissue in order to avoid the possibility of new bone growing outside the treated non-union location.

There is a possibility that new antibodies can form in your body after treatment with Osigraft. Antibodies are special proteins produced by the human body as part of the healing process in various diseases; one such illness is a virus infection. Antibodies often form as part of the body's response to treatment with some medicines one of these is Osigraft. These newly formed antibodies have not been found to cause any harm to patients. You will be monitored by your doctor if there is any medical suspicion that new antibodies have formed.

Repeated use of Osigraft is not recommended because clinical trials of multiple surgical treatments at different times have not been undertaken in patients. Laboratory studies have shown that antibodies to the eptotermin alfa component of this medicine could react with similar antibodies that the body makes naturally. The long-term impact of these antibodies is not known.

The use of Osigraft with a synthetic bone void filler may lead to a risk of increase in local inflammation, infection and occasional migration of the implanted materials and is therefore not recommended.

Using other medicines
Please tell your doctor if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

Pregnancy and breast-feeding
Osigraft should not be used during pregnancy unless the expected benefits to the mother are thought to outweigh the possible risks to the unborn child. This is something that will be decided by your surgeon. Women of child-bearing potential should inform their surgeon of the possibility of pregnancy before undergoing treatment with Osigraft. Women of childbearing potential are advised to use effective contraception up to at least 12 months after treatment.

The potential for harm to the breast-feed infant is unknown. Women should not breast-feed during the period immediately following treatment with Osigraft. If you are a nursing mother you should be treated with Osigraft only if your physician or surgeon considers the benefits to you outweigh the risks to your child.

Important information about some of the ingredients of Osigraft
Osigraft contains bovine collagen. If you have a known hypersensitivity to collagen you should not be treated with this medicine.

3. HOW TO USE OSIGRAFT

Osigraft is only used by an appropriately qualified surgeon. This is usually done under a full general anaesthetic so you will not be awake during the surgery. Depending on the size of the gap in the broken bone one or two vials of Osigraft may be administered. During surgery Osigraft is placed directly at the injury site in contact with the damaged bone surfaces. The surrounding muscle tissues are closed around the implanted medicine as is the skin on the top of the muscle.

The maximum recommended dose for this medicine is 2 vials (2g) since its effectiveness at higher doses has not been established.

4. POSSIBLE SIDE EFFECTS

Like all medicines, Osigraft can have side effects, although not everybody gets them. The frequency of possible side effects listed below is defined using the following convention:

- very common (affects more than 1 user in 10)

- common (affects 1 to 10 users in 100)
- uncommon (affects 1 to 10 users in 1,000)
- rare (affects 1 to 10 users in 10,000)
- very rare (affects less than 1 user in 10,000)
- not known (frequency cannot be estimated from the available data

In clinical studies, the following undesirable effects have been reported:
Common reported side effects included:
- discoloration of the wound site,
- erythema (redness of the skin),
- tenderness, and swelling over the implant site,
- heterotopic ossification / myositis ossificans (bone formation outside of the fracture area).

If any of the side effects gets serious or if you notice any side effect not listed in this leaflet, please tell your doctor.

5. HOW TO STORE OSIGRAFT

This medicine is only supplied to hospitals and specialist clinics. The hospital pharmacist or surgeon is responsible for the correct storage of the product both before and during its use, as well as for the correct disposal.

Keep out of the reach and sight of children.

This medicine should not be used after the expiry date which is printed on the carton and the blister.The expiry date refers to the last day of that month.

Store in a refrigerator at (2°C - 8°C).

Medicines should not be disposed of via wastewater or household waste. These measures will help to protect the environment.

6. FURTHER INFORMATION

What Osigraft contains
The active substance is eptotermin alfa (a recombinant human Osteogenic protein 1 produced in a recombinant Chinese hamster ovary (CHO) cell line). One vial of Osigraft contains 1 g of powder including 3.3 mg of eptotermin alfa and the excipient bovine collagen.

What Osigraft looks like and contents of the pack
Osigraft is supplied as white to off-white powder packaged in an amber coloured glass vial (pack size of 1) within a blister pack, comprised of a plastic tray and lid, in a carton.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder
Olympus Biotech International Limited
40 Upper Mount Street
Dublin 2
Ireland

Tel +353 87 9278653
medicalinfo@olympusbiotech.com

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

This leaflet was last approved in

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