

IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA0167/131/002

Case No: 2039539

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Baxter Healthcare Limited

Caxton Way, Thetford, Norfolk IP24 3SE, United Kingdom

an authorisation, subject to the provisions of the said Regulations, in respect of the product

ARTISS LYO Powders and solvents for sealant, lyophilized

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **03/07/2009** until **02/07/2014**.

Signed on behalf of the Irish Medicines Board this

A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

ARTISS LYO Powders and Solvents for Sealant, lyophilized

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Component 1:
Sealer Protein Solution
(Sealer Protein Concentrate - Lyophilized - reconstituted with Aprotinin Solution)
Human Fibrinogen (as clottable protein) 91 mg^[1]/ml
Aprotinin 3000 KIU^[2]/ml

Component 2:
Thrombin Solution
(Thrombin - Lyophilized - reconstituted with Calcium Chloride Solution)
Human Thrombin 4 IU^[3]/ml
Calcium Chloride 40 µmol/ml

<1 ml><2 ml><5 ml> Sealer Protein Solution and <1 ml><2 ml><5 ml> Thrombin Solution, respectively, result in <2 ml><4 ml><10 ml> final product ready for use.

After mixing	1 ml	2 ml	4 ml	10 ml
Component 1: Sealer protein solution				
Human Fibrinogen (as clottable protein)	45.5 mg	91 mg	182 mg	455 mg
Aprotinin	1,500 KIU	3,000 KIU	6,000 KIU	15,000 KIU
Component 2: Thrombin Solution				
Human Thrombin	2 IU	4 IU	8 IU	20 IU
Calcium Chloride	20 µmol	40 µmol	80 µmol	200 µmol

- 1. Contained in a total protein concentration of 96-125 mg/ml
- 2. 1 EPU (European Pharmacopoeia Unit) corresponds to 1800 KIU (Kallidinogenase Inactivator Unit)
- 3. Thrombin activity is calculated using the current WHO International Standard for Thrombin

ARTISS LYO contains Human Factor XIII co-purified with Human Fibrinogen in a range of 0.6 - 5 IU/ml.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Powder and Solvent for Sealant
Freeze-dried constituents are hygroscopic, white or pale yellow powders or friable solids; liquid constituents are clear, colourless solutions.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

ARTISS is indicated as a tissue glue to adhere/seal subcutaneous tissue in plastic, reconstructive and burn surgery, as a replacement or an adjunct to sutures or staples (see 5.1). In addition, ARTISS is indicated as an adjunct to hemostasis on subcutaneous tissue surfaces.

4.2 Posology and method of administration

ARTISS LYO is intended for Hospital Use Only by suitably experienced physicians or surgeons.

Posology:

The amount of ARTISS LYO to be applied and the frequency of application should always be oriented towards the underlying clinical needs of the patient.

The dose to be applied is governed by variables including, but not limited to, the type of surgical intervention, the size of the area and the mode of intended application, and the number of applications.

Application of the product must be individualized by the treating physician. In clinical trials, the individual dosages have typically ranged from 0.2-12 ml. For some procedures (e.g. the sealing of large burned surfaces), larger volumes may be required. ARTISS has not been administered to > 65 years old in clinical trials.

The initial amount of the product to be applied at a chosen anatomic site or target surface area should be sufficient to entirely cover the intended application area. The application can be repeated, if necessary.

As a guideline for the gluing of surfaces, 1 pack of ARTISS LYO 2 ml (i.e., 1 ml Sealer Protein Solution plus 1 ml Thrombin Solution) will be sufficient for an area of at least 10 cm².

To avoid the formation of excess granulation tissue and to ensure gradual absorption of the solidified fibrin sealant, only a thin layer of the mixed Sealer Protein - Thrombin Solution, or of the individual components, should be applied.

Method and route of administration

For epilesional use.

Prepare the solution as described at 6.6.

Before application, the surface of the wound should be as dry as possible.

See 6.6 for more detailed instructions.

4.3 Contraindications

ARTISS LYO is not indicated to replace skin sutures intended to close surgical wound.

ARTISS LYO alone is not indicated for the treatment of massive and brisk arterial or venous bleeding.

ARTISS LYO must never be applied intravascularly. Hypersensitivity to the active substances or to any of the excipients.

4.4 Special warnings and precautions for use

For epilesional use only. Do not apply intravascularly.

Life threatening thromboembolic complications may occur if the preparation is unintentionally applied intravascularly.

Soft tissue injection of ARTISS LYO carries the risk of local tissue damage.

ARTISS LYO is not indicated for hemostasis and sealing in situations where a fast clotting of the sealant is required. Especially in cardiovascular procedures in which sealing of vascular anastomoses is intended ARTISS LYO should not be used.

ARTISS LYO is not indicated for use in neurosurgery and as a suture support for gastrointestinal anastomoses or vascular anastomoses as no data are available to support these indications.

ARTISS LYO should only be applied as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process.

Before administration of ARTISS care is to be taken that parts of the body outside the designated application area are sufficiently protected/covered to prevent tissue adhesion at undesired sites.

As with any protein-containing product, allergic type hypersensitivity reactions are possible. Signs of hypersensitivity reactions may include hives, generalized urticaria, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, the administration must be discontinued immediately.

ARTISS LYO contains bovine protein (aprotinin). Even in case of strict local application, there is a risk of anaphylactic reaction linked to the presence of bovine aprotinin. The risk seems to be higher in cases where there was previous exposure, even if it was well tolerated. Therefore any use of aprotinin or aprotinin containing products should be recorded in the patients' records.

In the event of anaphylactic or severe hypersensitivity reactions, administration is to be discontinued and state-of-the-art emergency measures are to be taken. In case of shock, standard medical treatment for shock should be implemented.

Standard measures to prevent infections resulting from the use of medicinal products prepared from human blood or plasma include selection of donors, screening of individual donations and plasma pools for specific markers of infection and the inclusion of effective manufacturing steps for the inactivation/removal of viruses. Despite this, when medicinal products prepared from human blood or plasma are administered, the possibility of transmitting infective agents cannot be totally excluded. This also applies to unknown or emerging viruses or other pathogens.

The measures taken are considered effective for enveloped viruses such as HIV, HBV, and HCV, and for the non-enveloped virus HAV.

The measures taken may be of limited value against non-enveloped viruses such as parvovirus B19. Parvovirus B19 infection may be serious for pregnant women (fetal infection) and for individuals with immunodeficiency or increased erythropoiesis (e.g., hemolytic anemia).

It is strongly recommended that every time that ARTISS LYO is administered to the patient, the name and batch number of the product are recorded in order to maintain a link between the patient and the batch of the product.

4.5 Interaction with other medicinal products and other forms of interaction

No formal interaction studies have been performed. Similar to comparable products or thrombin solutions, the product may be denatured after exposure to solutions containing alcohol, iodine or heavy metals (e.g. antiseptic solutions). Such substances should be removed to the greatest possible extent before applying the product.

4.6 Pregnancy and lactation

The safety of fibrin sealants/haemostatics for use in human pregnancy or breastfeeding has not been established in controlled clinical trials. Animal studies have also not been performed.

Therefore, the product should be administered to pregnant and lactating women only if clearly needed.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Inadvertent intravascular injection could lead to thromboembolic events and DIC and there is also a risk of anaphylactic reactions (see 4.4).

Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the application site, bradycardia, bronchospasm, chills, dyspnoea, flushing, generalized urticaria, headache, hives, hypotension, lethargy, nausea, pruritus, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in rare cases in patients treated with fibrin sealants/hemostatics.

In isolated cases, these reactions have progressed to severe anaphylaxis. Such reactions may especially be seen if the preparation is applied repeatedly, or administered to patients known to be hypersensitive to aprotinin (see section 4.4) or any other constituents of the product.

Even if a first treatment with ARTISS was well tolerated, a subsequent administration of ARTISS or systemic administration of aprotinin may result in severe anaphylactic reactions.

Antibodies against components of fibrin sealant may rarely occur.

For safety with respect to transmissible agents, see section 4.4.

Adverse reactions reported from clinical studies as well as from postmarketing surveillance are summarized in the following. Known frequencies of these adverse reactions are based on a controlled clinical study in 138 patients where skin grafts were fixed to excised burn wounds using ARTISS. None of the events were classified as serious. Unknown frequencies are based on spontaneous reports from postmarketing surveillance of Baxter's fibrin sealants.

The ADRs and their frequencies are summarized below:

Common ($\geq 1/100$ to $< 1/10$)

Uncommon ($\geq 1/1000$ to $< 1/100$)

Unknown (cannot be estimated from the available data)

Immune system disorders:

Frequency unknown: anaphylactic responses, hypersensitivity;

Cardiac disorders:

Frequency unknown: bradycardia, tachycardia;

Vascular disorders:

Frequency unknown: hypotension, haematoma;

Respiratory, thoracic and mediastinal disorders:

Frequency unknown : dyspnoea;

Gastrointestinal disorders:

Frequency unknown: nausea;

Skin and subcutaneous tissue disorders:

Common*: pruritus;

Uncommon* : dermal cyst;

Frequency unknown: urticaria;

General disorders and administration site conditions:

Frequency unknown: flushing, impaired healing, oedema, pyrexia;

Injury, poisoning and procedural complication:

Common* : skin graft failure;

Frequency unknown: seroma;

*In the controlled clinical study these adverse reactions also occurred at the control site without ARTISS application.

4.9 Overdose

No case of overdose has been reported.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: local hemostatics, ATC code: B02BC; tissue adhesives, ATC code: V03A K

ARTISS can replace sutures or staples when used for fixation of skin grafts to burned or otherwise injured wound areas. ARTISS can be used as an adjunct to sutures or staples to adhere and seal skin flaps in cases where sutures/staples are expected to yield unsatisfactory results with respect to postoperative hematoma or seroma formation.

The fibrin adhesion system initiates the last phase of physiological blood coagulation. Conversion of fibrinogen into fibrin occurs by the splitting of fibrinogen into fibrin monomers and fibrinopeptides. The fibrin monomers aggregate and form a fibrin clot. Factor XIIIa, which is activated from factor XIII by thrombin, crosslinks fibrin. Calcium ions are required for the conversion of fibrinogen and the crosslinkage of fibrin.

As wound healing progresses, increased fibrinolytic activity is induced by plasmin, and decomposition of fibrin to fibrin degradation products is initiated. Proteolytic degradation of fibrin is inhibited by anti-fibrinolytics. Aprotinin is present in ARTISS LYO as an antifibrinolytic to prevent premature degradation of the clot.

For efficacy, *in vivo* studies in an animal model closely imitating the situation in patients were used. ARTISS (frozen and lyophilized presentations) demonstrated efficacy regarding sealing autologous split skin grafts and mesh grafts.

ARTISS (frozen) was investigated for fixation of split thickness sheet skin grafts in burn patients in a prospective, randomised, controlled, multicenter clinical study. In each of the 138 patients, two comparable test sites were identified. In one test site the skin graft was fixed with ARTISS (frozen), in the other test site the graft was fixed with staples (control). ARTISS (frozen) proved to be non-inferior to staples with respect to the primary efficacy endpoint, complete wound closure at Day 28 was evaluated by a blinded evaluator panel from photographs. This was achieved in 55/127 patients (43.3%) treated with ARTISS (frozen) and 47/127 patients (37%) treated with staples.

With respect to secondary endpoints, ARTISS (frozen) showed a significantly lower incidence and size of hematoma/seroma on Day 1 ($p < 0.0001$ for incidence as well as size). Incidence and area of engraftment on Day 5 and wound closure on Day 14, as well as area of wound closure on Day 28 were not different. ARTISS (frozen) was also superior to staples with respect to patient satisfaction ($p < 0.0001$) and patients experienced significantly less anxiety about pain with ARTISS (frozen) than with staples ($p < 0.0001$). Moreover, ARTISS (frozen) was significantly superior to staples with respect to the investigator's assessment of quality of graft adherence, preference of fixation method and satisfaction with graft fixation, overall quality of healing and overall rate of healing ($p < 0.0001$).

5.2 Pharmacokinetic properties

ARTISS LYO is intended for episodic use only. Intravascular administration is contraindicated. As a consequence, intravascular pharmacokinetic studies were not performed in man.

Pharmacokinetic studies in different species of laboratory animals were not conducted.

Fibrin sealants/hemostatics are metabolized in the same way as endogenous fibrin by fibrinolysis and phagocytosis.

5.3 Preclinical safety data

No preclinical safety data are available for ARTISS (thrombin 4 IU/ml). Toxicity studies were done with Fibrin Sealants containing thrombin 500 IU/ml, as representative for products containing thrombin 4 IU/ml. Single-dose toxicity studies in rats and rabbits indicated no acute toxicity of Fibrin Sealant VH S/D (500 IU/ml). Fibrin Sealant VH S/D (500 IU/ml) also proved well tolerated in wound healing models in rats and rabbits, and in in vitro human fibroblast cultures.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Component 1: Sealer Protein Solution

Human Albumin Solution
L-Histidine
Niacinamide
Polysorbate 80 (Tween 80)
Sodium Citrate Dihydrate
Water for Injections

Component 2: Thrombin Solution

Human Albumin Solution
Sodium Chloride
Water for Injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products other than appropriate solvents mentioned in 6.6.

6.3 Shelf Life

2 years

6.4 Special precautions for storage

Keep out of the reach and sight of children.

Do not store ARTISS LYO above 25°C. Do not freeze.

Keep ARTISS LYO in the outer carton in order to protect from light.

Use the reconstituted sterile solutions within 4 hours. Keep the reconstituted sterile solutions at 37°C or at room temperature without stirring if not used immediately. Reconstituted solutions must not be refrigerated or frozen.

6.5 Nature and contents of container

All components of ARTISS LYO are filled into glass containers (Sealer Protein Concentrate - Lyophilized, type I glass and type II glass, all other vials: type I glass) conforming to Ph. Eur. requirements. The vial containing Sealer Protein Concentrate - Lyophilized is equipped with a magnetic stirrer.

Each pack of ARTISS LYO contains:

- 1 vial Powder for Sealant - Component 1 (Lyophilized) containing Human Fibrinogen 91 mg/ml
- 1 vial Powder for Sealant - Component 2 (Lyophilized) containing Thrombin 4 IU/ml
- 1 vial Solvent for Component 1 (Solution) containing Aprotinin 3000 KIU/ml
- 1 vial Solvent for Component 2 (Solution) containing Calcium Chloride 40 µmol/ml
- 1 Kit for reconstitution and application (DUPLOJECT System: 4 transfer needles, 2 blue-scaled syringes, 2 black-scaled syringes, 1 Dupolject two-syringe clip, 2 joining pieces and 4 application canulas)

ARTISS LYO is available in the following pack sizes:

- ARTISS LYO 2 ml
(reconstituted product contains: 1 ml of Sealer Protein Solution and 1 ml of Thrombin Solution)
- ARTISS LYO 4 ml
(reconstituted product contains: 2 ml of Sealer Protein Solution and 2 ml of Thrombin Solution)
- ARTISS LYO 10 ml
(reconstituted product contains: 5 ml of Sealer Protein Solution and 5 ml of Thrombin Solution)

The Kit for Reconstitution and Application (DUPLOJECT System) is for single use only. Do not re-sterilize!

Not all pack sizes may be marketed.

Other accessories for application of the product can be obtained from BAXTER.

6.6 Special precautions for disposal and other handling

General

To prevent ARTISS LYO from adhering to gloves and instruments, wet these with sodium chloride solution before contact.

As a guideline for the gluing of surfaces, 1 pack of ARTISS LYO 2 ml (i.e., 1 ml Sealer Protein Solution plus 1 ml Thrombin Solution) will be sufficient for an area of at least 10 cm².

The required dose of ARTISS LYO depends on the size of the surface to be covered. Preparation and reconstitution

Prior to reconstitution of the fibrin sealant components the rubber stoppers of all vials should be cleansed.

Direct contact between disinfectant and product must be avoided (see section 4.5).

I. Preparation of Component 1 - Sealer Protein Solution

The Sealer Protein Concentrate – Lyophilized is dissolved with the Aprotinin Solution to form the Sealer Protein Solution.

Sealer Protein Concentrate – Lyophilized is reconstituted using the FIBRINOTHERM warming and stirring device (recommended method). Alternatively, a sterile water bath at a temperature of 33 - 37°C can be used.

Reconstitution using the FIBRINOTHERM device:

The FIBRINOTHERM device maintains a constant temperature of 37°C. It also shortens the dissolution time of the Sealer Protein Concentrate – Lyophilized by rotating the magnetic stirrer contained in each Sealer Protein Concentrate – Lyophilized vial.

- Place the vials containing Sealer Protein Concentrate - Lyophilized and Aprotinin Solution into the appropriate openings of the pre-heated FIBRINOTHERM device and heat the vials for approximately 3 minutes.
- Transfer the Aprotinin Solution into the vial containing the Sealer Protein Concentrate - Lyophilized using one needle and the blue-scaled syringe provided in the single-sterile kit for reconstitution. Place the sealer Protein vial into the stirring well of the FIBRINOTHERM device (use the adaptor, if necessary) and stir until complete dissolution. Reconstitution is complete as soon as no particles are visible anymore when holding the vial against the light. If particles are present, keep on stirring the solution at 37°C for a few more minutes until complete dissolution. Turn off the magnetic stirrer when dissolution is complete.

Note: Excessive stirring might compromise product quality!

- Keep the Sealer Protein Solution at 37°C or at room temperature without stirring if it is not used immediately. Before use the solution must be warmed to 37°C. To ensure homogeneity stir or swirl briefly before drawing up the Sealer Protein Solution into the blue-scaled syringe provided in the double-sterile kit for application.
- Withdraw the reconstituted Sealer Protein Solution from the vial under sterile conditions.

For further instructions please refer to the instructions for use of the FIBRINOTHERM device.

Reconstitution using a water bath:

- Preheat the vials containing the Sealer Protein Concentrate - Lyophilized and the Aprotinin Solution for approximately 3 minutes in a water bath at a temperature of 33 - 37°C. (Heating beyond 37°C must be avoided!)
- Transfer the Aprotinin Solution into the vial containing the Sealer Protein Concentrate - Lyophilized using one needle and the blue-scaled syringe provided in the single-sterile Kit for reconstitution.
- Return the Sealer Protein vial to the water bath at 33°C - 37°C for one minute.
- Swirl briefly but avoid excessive frothing. Then return the vial to the water bath and check periodically for complete dissolution. Reconstitution is complete as soon as no particles are visible when holding the vial against the light. If particles are present, keep the vial at 33°C - 37°C for a few more minutes and agitate the solution until complete dissolution.
- Keep the Sealer Protein Solution at 33°C - 37°C or at room temperature if not used immediately. Before use the solution must be warmed to 33°C - 37°C. To ensure homogeneity swirl briefly before drawing up the Sealer Protein Solution into the blue-scaled syringe provided in the double-sterile kit for application.
- Withdraw the reconstituted Sealer Protein Solution from the vial under sterile conditions.

Note: When using a water bath for reconstitution instead of the FIBRINOTHERM device, special precautions must be taken against submersing the vial, particularly the septum, to avoid possible contamination.

II. Preparation of Component 2 - Thrombin Solution

The Thrombin – Lyophilized is dissolved with the Calcium Chloride Solution to form the Thrombin Solution. Transfer the contents of the Calcium Chloride Solution vial into the Thrombin – Lyophilized vial. Use the second needle and the black-scaled syringe provided in the single-sterile Kit for reconstitution.

Swirl briefly to dissolve the lyophilized material. To warm the Thrombin Solution either the FIBRINOTHERM device or a water bath can be used. Keep the Thrombin Solution at 33 - 37°C or at room temperature if not used immediately. Before use, the solution must be warmed to 33 - 37°C. Prior to use, draw up the Thrombin Solution from the vial using the second needle and the black-scaled syringe provided in the double-sterile Kit for application.

Note: Syringes and needles used for the reconstitution of one component must not be re-used for the reconstitution of the other component, as this would lead to solidification of that component in the vial or syringe.

III. Use of reconstituted ARTISS LYO Components

Both fibrin sealant components must be used within 4 hours after reconstitution. Reconstituted solutions must not be refrigerated or frozen.

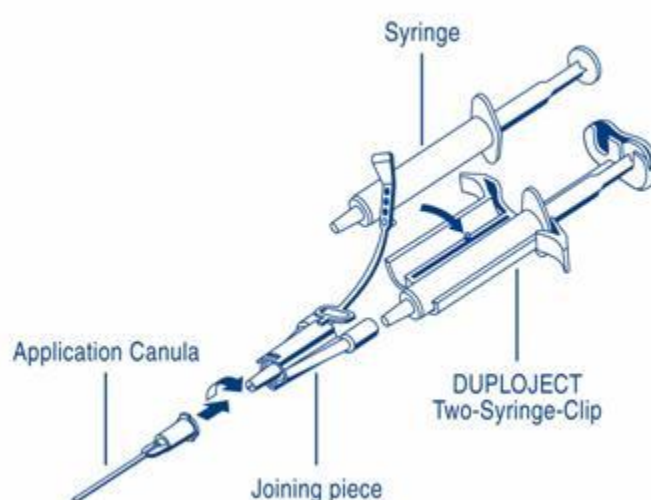
The Sealer Protein and the Thrombin Solutions should be clear or slightly opalescent. Do not use solutions that are cloudy or have deposits. Inspect reconstituted products by eye for particulate matter and discoloration prior to administration.

Administration

For application, clip the two single-use syringes with the reconstituted Sealer Protein Solution and Thrombin Solution into the DUPLOJECT Two-Syringe Clip and connect this assembly to a joining piece and an application cannula. The double-sterile Kit contains all devices necessary for application.

The common plunger of the DUPLOJECT Two-Syringe Clip ensures that equal volumes are fed through the joining piece, before being mixed in the application needle and ejected.

Operating Instructions



Place the two syringes filled with Sealer Protein Solution and with Thrombin Solution into the clip. Both syringes should be filled with equal volumes.

Connect the nozzles of the two syringes to the joining piece ensuring that they are firmly fixed. Secure the joining piece by fastening the tether strap to the DUPLOJECT Two-Syringe Clip. Should the pull strap tear, use the spare joining piece. If none is available, further use is still possible but tightness of the connection needs to be ensured to prevent any risk of leaking.

- Fit an application cannula onto the joining piece.
- Do not expel the air remaining inside the joining piece or application cannula until you start actual application as the aperture of the cannula may clog otherwise.

Apply the mixed Sealer Protein - Thrombin Solution onto the recipient surface or surfaces of the parts to be sealed.

If application of the fibrin sealant components is interrupted, clogging may occur in the cannula. Replace the application cannula with a new one only immediately before application is resumed. If the apertures of the joining piece are clogged, use the spare joining piece provided in the package.

Application is also possible with other accessories supplied by BAXTER that are particularly suited for, e.g. minimally invasive surgery, application to large or difficult-to-access areas. When using these application devices, strictly follow the Instructions for Use of the devices.

After the two components have been applied, approximate the wound areas. Fix or hold the glued parts with continuous gentle pressure in the desired position for about 3–5 minutes to ensure that the setting fibrin sealant adheres firmly to the surrounding tissue.

Disposal

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

7 MARKETING AUTHORISATION HOLDER

Baxter Healthcare Ltd.
Caxton Way
Thetford
Norfolk IP24 3SE
UK

8 MARKETING AUTHORISATION NUMBER

PA 167/131/2

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 3rd July 2009.

10 DATE OF REVISION OF THE TEXT