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

Raplixa sealant powder

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each gram of powder contains 79 mg human fibrinogen and 726 IU human thrombin.
Raplixa is supplied in three different presentations 0.5 grams (39.5 mg human fibrinogen and 363 IU human thrombin), 1 gram (79 mg human fibrinogen and 726 IU human thrombin) and 2 grams (158 mg human fibrinogen and 1452 IU human thrombin).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Sealant powder
Dry white powder.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Supportive treatment where standard surgical techniques are insufficient for improvement of haemostasis. Raplixa must be used in combination with an approved gelatin sponge (see section 5.1).

Raplixa is indicated in adults over 18 years of age.

4.2 Posology and method of administration

The use of Raplixa is restricted to experienced surgeons.
Gelatin sponges must be used in combination with Raplixa. Gelatin sponges are CE marked and separately supplied and packed (see instructions for use for the specific gelatin sponge selected for use).

Posology
The amount of Raplixa to be applied and the frequency of application should always be oriented towards the underlying clinical needs for the patient. The dose to be applied is governed by variables including, but not limited to, the type of surgery, the size of the bleeding surface area, the severity of bleeding, the mode of application selected by the surgeon, and the number of applications.
Application of the product must be individualised by the treating surgeon. In clinical trials a thin layer of Raplixa produced doses that typically ranged from 0.3 to 2 g. For some procedures eg. liver resection, larger amounts may be required. 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 with a thin layer

of Raplixa which is then covered by an absorbable gelatin sponge (saline-wetted). The application can be repeated, if necessary.

The required dose of Raplixa, can vary based on the size of the area to be treated. In clinical trials, smaller bleeding sites (< 10 cm^2) used 0.5 g to 1 g on average. Larger bleeding sites used 1 to 2 grams (10-100 cm^2). It is known from in vitro testing that 1 g can cover 100 cm^2 using the RaplixaSpray device. Maximum amount of Raplixa recommended is 3 gram.

The required dose of Raplixa based on the size of the bleeding surface area to be treated is shown in the table below:

Table 1: Required Dose of Raplixa

Maximum Surface Area Direct Application from Vial	Maximum Surface Area Application Using RaplixaSpray	Raplixa Package Size
25 cm^2	50 cm^2	0.5 g
50 cm^2	100 cm^2	1.0 g

Paediatric Population
The safety and efficacy of Raplixa in children and adolescents under the age of 18 years have not been established. No data are available, Raplixa is therefore not recommended for use in children and adolescents.

Elderly
Dose adjustment not required.

Method and route of administration
For epilesional use only.
For instructions on use of the medicinal product before administration, see section 6.6.

One of the following methods of application of Raplixa may be used based on the type of surgery, location and size and severity of the bleeding:

Direct application followed by gelatin sponge
Powder is applied directly from the vial onto the bleeding surface and then applied to a CE marked gelatin sponge cut to the appropriate size and apply manual pressure with sterile gauze.

Apply first to gelatin sponge
Powder is applied directly from the vial onto a saline-wetted CE marked gelatin sponge and then applied to the bleeding site. When using a moistened gelatin sponge, a thin layer of Raplixa should be applied to the sponge immediately prior to application to the bleeding site.

Spray application using RaplixaSpray device followed by gelatin sponge
The vial and RaplixaSpray device are taken out of their respective pouches maintaining sterility. Connect the RaplixaSpray device to the RaplixaReg pressure regulator and thereby to the medical CO_2 gas supply (CO_2 is recommended; Raplixa may be also used with medical grade air) set to a pressure setting of 1.5 bar (22 psi).

The vial should be held upright, shaken gently and the aluminium cap and rubber stopper should be removed.

The vial with powder is attached to the RaplixaSpray device by inverting the device over the upright vial and pushing the vial into place.

The RaplixaSpray device is used to spray the powder on to the bleeding site and then the gelatin sponge is applied (see Instructions For Use for RaplixaSpray device and gelatin sponge).
Application must be within 2 hours after connecting the vial to the device.
The RaplixaSpray device comes with the rigid nozzle attached. This may be removed and the flexible nozzle can be attached depending on the intended use and surgeon preference.

To avoid the risk of potentially life-threatening air embolism Raplixa is recommended to be sprayed using pressurised CO_2. Raplixa may also be used with medical air (see sections 4.4 and 6.6).

4.3 Contraindications

Known hypersensitivity to the Raplixa active substances or to any of the excipients listed in section 6.1.
Raplixa must not be applied intravascularly.
Spray application of Raplixa must not be used in endoscopic or laparoscopic procedures**.**
Raplixa must not be used as a glue for the fixation of patches.
Raplixa must not be used as a glue for intestines (gastrointestinal anastomoses).
Do not use Raplixa for treatment of severe arterial bleeding.

4.4 Special warnings and precautions for use

Use and Application
For epilesional use only. Do not apply intravascularly. Follow specific instructions for use of the absorbable gelatin sponge.
Do not use Raplixa (and gelatin sponge) in contaminated areas of the body, or in the presence of active infection.

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

Air or gas emboli
Life threatening air or gas embolism has occurred with the use of spray devices employing a pressure regulator to administer fibrin sealant/haemostatic products. This event appears to be related to the use of spray devices at higher than recommended pressures and/or in close proximity to the tissue surface. The risk appears to be higher when fibrin sealants are sprayed with air, as compared to CO_2 and therefore cannot be excluded with Raplixa**.** Before administration of Raplixa care is to be taken that parts of the body outside the desired application area are sufficiently protected (covered) to prevent tissue adhesion at undesired sites. Spray application of Raplixa should only be used if it is possible to accurately judge the spray distance. Spray distance from tissue and pressure should be within the ranges recommended by the manufacturer (see table in section 6.6 for pressure and distance).

When spraying Raplixa, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism.
When using accessory nozzles with this product, the instructions for use of the nozzles should be followed.

Hypersensitivity reactions
As with any protein product, allergic type hypersensitivity reactions are possible. Signs of hypersensitivity reactions may include hives, generalized urticarial, tightness of the chest, wheezing, hypotension, and anaphylaxis. If these symptoms occur, the administration should be discontinued immediately.
In case of shock, standard medical treatment for shock should be implemented.

Transmissible infectious agents
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 and other pathogens.
The measures taken are considered effective for enveloped viruses such human immunodeficiency virus (HIV), hepatitis B virus (HBV) and hepatitis C virus (HCV).
The measures may be of limited value against non- enveloped viruses such as HAV and parvovirus B19.
Parvovirus B19 may be serious for pregnant women (fetal infection) and of individuals with immunodeficiency or increased erythropoiesis (e.g. Haemolytic anaemia).

Other
Raplixa has been studied in patients undergoing spinal surgery, vascular surgery, soft tissue surgery and hepatic resection. There is limited experience of use of Raplixa in vascular surgery when applied with the RaplixaSpray device.
Data are not available to support the use of this product in tissue gluing, neurosurgery, application through a flexible endoscope for treatment of bleeding or in gastrointestinal anastomoses.

It is strongly recommended that every time Raplixa is administered to a 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.
Raplixa may be denatured after exposure to solutions containing alcohol, iodine or heavy metals (e.g. antiseptic solutions). Such substances should be removed as much as possible before applying the product.

4.6 Fertility, pregnancy and lactation

Pregnancy and Breast-feeding
Animal reproduction studies have not been conducted with Raplixa. The safety of Raplixa for use in human pregnancy or during breast-feeding has not been established in controlled clinical trials.
The product should not be administered to pregnant and breast-feeding women.

Fertility
Fertility studies have not been conducted.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

Summary of the safety profile
Hypersensitivity or allergic reactions (which may include angioedema, burning and stinging at the application site, bronchospasm, chills, flushing, generalised urticaria, headache, hives, hypotension, lethargy, nausea, restlessness, tachycardia, tightness of the chest, tingling, vomiting, wheezing) may occur in isolated cases in patients treated with fibrin sealants / haemostatics: 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 constituents of the product.

Antibodies against components of fibrin sealant/haemostatic products may occur rarely.
Inadvertent intravascular injection could lead to thromboembolic event and disseminated intravascular coagulation (DIC), and there is also a risk of anaphylactic reaction (see section 4.4).

Life threatening air or gas embolism has occurred with the use of spray devices employing pressure regulators to administer the fibrin sealant. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface. The risk appears to be higher when fibrin sealants are sprayed with air, as compared to CO_2 and therefore cannot be excluded with Raplixa.

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

Tabulated list of adverse reactions

System organ class	**Common (≥1/100 to <1/10)**
General disorders and administrative site conditions	Insomnia Pruritus

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.

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

4.9 Overdose

In the event of overdose, patients must be closely monitored for signs or symptoms of adverse reactions and appropriate symptomatic treatment and supportive measures instituted.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: local haemostatics, other haemostatics
ATC code: B02BC30

Mechanism of Action
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 both, 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.
Clinical studies with Raplixa demonstrating haemostasis were conducted in patients undergoing spinal (n=146), vascular (n=137), liver (n=158) and soft tissue surgery (n=125).

Clinical studies in the EU were done with the CE marked Spongostan gelatin sponge. Bleeding at target sites was mild or moderate. Conventional surgical techniques such as suture, ligature and cautery were ineffective or impractical. The combination of Raplixa and a gelatin sponge reduced the median time to haemostasis at target sites by up to 2 minutes compared to a gelatin sponge alone.

The European Medicines Agency has deferred the obligation to submit the results of studies with Raplixa in one or more subsets of the paediatric population in the treatment of haemorrhage resulting from surgical procedure as per Paediatric Investigational Plan (PIP) decision, for the granted indication (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Raplixa is intended for epilesional use only. Intravascular administration is contraindicated. As a consequence, intravascular pharmacokinetic studies were not performed in man.
Fibrin Sealants/haemostatics are metabolised in the same way as endogenous fibrin by fibrinolysis and phagocytosis.

5.3 Preclinical safety data

Non-clinical data revealed no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity and genotoxicity.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trehalose
Calcium chloride
Albumin

Sodium chloride
Sodium citrate
L-arginine-hydrochloride

6.2 Incompatibilities

In absence of compatibility studies, Raplixa must not be mixed with other medicinal products.

6.3 Shelf life

3 years
In use shelf life: Once the vial is opened Raplixa should be applied within 2 hours.

6.4 Special precautions for storage

Store between + 2 °C to + 25 °C.
Keep the vial in the outer packaging in order to protect from light.
For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

0.5 g, 1 g, 2 g of powder per vial (Type I glass) with a rubber stopper and aluminium/ plastic tear-off.

Presentation
Pack of 1 vial**.**
Not all pack sizes may be marketed.

6.6 Instructions for use and handling and special precautions for disposal

Raplixa is a pre-mixed, ready to use blend of thrombin and fibrinogen supplied as a ready to use dry-powder fibrin sealant in a glass vial containing 0.5 g, 1 g or 2 g of Raplixa that is applied onto the surgical bleeding site directly from the vial or using the RaplixaSpray device. The Raplixa should be stored at controlled, ambient room temperature. The outer aluminium foil sachet may be opened in a non-sterile operating area. The vial must be opened in a sterile field.

There are three methods of application: direct application of Raplixa to the bleeding tissue followed by application of the gelatin sponge or application of Raplixa first to a gelatin sponge and application of the sponge to the bleeding tissue; or application of the Raplixa powder by using the RaplixaSpray device followed by the application of the gelatin sponge.

Prior to applying Raplixa the surface area of the wound needs to be dried by standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices).

The product should only be administered according to the instructions and with the devices recommended for this product.

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 with a thin layer of Raplixa which is then covered by an absorbable gelatin sponge (saline-wetted). The application can be repeated, if necessary.

When using the RaplixaSpray device
Take the vial and device out of their respective pouches maintaining sterility. Connect the RaplixaSpray device to the RaplixaReg air pressure regulator or CO_2 pressure regulator and thereby to the medical air or CO_2 gas supply set to a pressure setting of 1.5 bar (22 psi). Hold the vial upright, shake gently and remove the aluminium cap and rubber stopper.

Connect the vial to the device by inverting the device over the upright vial and pushing the vial into place. Raplixa should not be sprayed at a distance closer than that recommended by the spray device manufacturer and in no case closer than 5 cm from the tissue surface.

The pressure should be within the range recommended by ProFibrix. Spray application of Raplixa should only be done using the provided spray application accessories and the pressure should not exceed 1.5 bars (22 psi).

Application must be within 2 hours after connecting the vial to the device. The RaplixaSpray device comes with the rigid nozzle attached, which can be easily removed and the flexible nozzle attached depending on the intended use and surgeon preference.
To avoid the risk of potentially life-threatening air embolism, it is recommended that Raplixa should be sprayed using pressurised CO_2. Raplixa may also be used with medical air. See section 4.4.

When spraying Raplixa, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism.

Surgery	**Spray set to be used**	**Applicator tips to be used**	**Pressure regulator to be used**	**Recommended distance from target tissue**	**Recommended spray pressure**
Open surgery	1	1 or 2	RaplixaReg	5 cm	1.5 Bar (22 psi)

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

7. MARKETING AUTHORISATION HOLDER

Mallinckrodt Pharmaceuticals Ireland Ltd
College Business & Technology Park
Cruiserath
Blanchardstown
Dublin 15
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/985/001
EU/1/14/985/002
EU/1/14/985/003

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 19 March 2015

10. DATE OF REVISION OF 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. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER 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. MANUFACTURERS OF THE BIOLOGICAL ACTIVE SUBSTANCES AND MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers of the biological active substances
CSL Behring GmbH
Emil-von-Behring-Straße 76
35041 Marburg
Germany

CSL Behring GmbH
Goerzhaeuser Hof 1
35041 Marburg (Stadtteil Michelbach)
Germany

Name and address of the manufacturer responsible for batch release
Nova Laboratories Limited
Martin House, Gloucester Crescent, Wigston,
Leicester, Leicestershire, LE18 4YL,
United Kingdom

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).

- **Official batch release**

In accordance with Article 114 of Directive 2001/83/EC, the official batch release will be undertaken by a state laboratory or a laboratory designated for that purpose.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates 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.

- **Additional risk minimisation measures**

Prior to launch of Raplixa in each Member State the Marketing Authorisation Holder (MAH) must agree about the content and format of the educational programme, including communication media, distribution modalities, and any other aspects of the programme, with the National Competent Authority.

The educational programme is aimed at increasing awareness about the risk of air or gas embolism with the use of Raplixa spray device and providing instructions for the correct usage of pressure regulators.

The MAH shall ensure that in each Member State where Raplixa is marketed, all healthcare professionals who are expected to use Raplixa are provided with the following educational material:

- The Summary of Product Characteristics (SmPC)
- Guide for healthcare professionals

The Guide for healthcare professionals shall inform on the following key elements:

- Risk of life-threatening air or gas embolism if the product is sprayed incorrectly
- Use preferred pressurised CO_2 instead of pressurised air
- Use of the Raplixa spray device only in open surgery, not endoscopic surgery
- Use of the correct pressure (not exceed 1.5 bars or 22 psi) and distance from tissue not closer than 5 cm
- Requirement to dry the wound using standard techniques (e.g., intermittent application of compresses, swabs, use of suction devices) prior to using the product
- Requirement to closely monitor blood pressure, pulse rate, oxygen saturation, and end tidal CO_2 when spraying the product, for the occurrence of gas embolism
- Which regulator(s) should be used, in line with manufacturer recommendations and the SmPC instructions for use

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON

1. NAME OF THE MEDICINAL PRODUCT

Raplixa sealant powder
Human fibrinogen/Human thrombin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Human fibrinogen 79 mg/g
Human thrombin 726 IU/g

3. LIST OF EXCIPIENTS

Excipients: Trehalose, Calcium chloride, Human Albumin, Sodium chloride, Sodium citrate, L-arginine-hydrochloride

4. PHARMACEUTICAL FORM AND CONTENTS

sealant powder

1 vial 0.5 g
1 vial 1 g
1 vial 2 g

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For epilesional 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 between + 2 °C to + 25 °C.
Once the vial is opened, use within 2 hours.
Sterile

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

Any unused product should be discarded in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mallinckrodt Pharmaceuticals Ireland Ltd
College Business & Technology Park, Cruiserath, Blanchardstown, Dublin 15, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/985/001
EU/1/14/985/002
EU/1/14/985/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
ALUMINIUM-BONDED FOIL SACHET

1. NAME OF THE MEDICINAL PRODUCT

Raplixa sealant powder
Human fibrinogen/Human thrombin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Human fibrinogen 79 mg/g
Human thrombin 726 IU/g

3. LIST OF EXCIPIENTS

Excipients: Trehalose, Calcium chloride, Human Albumin, Sodium chloride, Sodium citrate, L-arginine-hydrochloride

4. PHARMACEUTICAL FORM AND CONTENTS

sealant powder

1 vial 0.5 g
1 vial 1 g
1 vial 2 g

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For epilesional 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 between + 2 °C to + 25 °C.
Once the vial is opened, use within 2 hours.
Sterile

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

Any unused product should be discarded in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Mallinckrodt Pharmaceuticals Ireland Ltd
College Business & Technology Park, Cruiserath, Blanchardstown, Dublin 15, Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/14/985/001
EU/1/14/985/002
EU/1/14/985/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS
Vial label

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

Raplixa sealant powder

2. METHOD OF ADMINISTRATION

For epilesional use

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

0.5 g
1 g
2 g
human fibrinogen 79 mg/g
human thrombin 726 IU/g

6. OTHER

B. PACKAGE LEAFLET

Package Leaflet: Information for the patient

RAPLIXA sealant powder
Human fibrinogen/ Human thrombin

▼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 the end of Section 4 for how to report side effects.

Read all of this leaflet carefully before you start using 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 of the side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Raplixa is and what it is used for

The active ingredient fibrinogen is a concentrate of clottable protein; the other active ingredient thrombin is an enzyme that causes clottable protein to coalesce to form a plug.

Raplixa is applied during surgical operations, to reduce bleeding and oozing during and after the operation in adults. In combination with a gelatin sponge, Raplixa is applied or sprayed onto cut tissue where it forms a layer that helps to stop bleeding.

2. What you need to know before you are treated with Raplixa

Do not use Raplixa:
- if you are allergic to human fibrinogen, human thrombin or any of the other ingredients of this medicine (listed in section 6)
- directly inside a blood vessel
- in endoscopic procedures (procedures that use an endoscope for viewing internal organs) or keyhole surgery
- as a glue for the fixation of patches
- as a glue for intestines (gastrointestinal anastomoses)
- on severe arterial bleeds

Warnings and precautions

- When Raplixa is applied during surgery, the surgeon must ensure that it is only applied onto the surface of tissue. Raplixa must not be injected into blood vessels because it would cause clots which could be fatal.
- Use of Raplixa has only been shown to arrest bleeding in surgery visualized through the incision (open surgery).
- Raplixa will be applied as a thin layer. Excessive clot thickness may negatively interfere with the product's efficacy and the wound healing process.

Life-threatening events have occurred with the use of other spray devices employing a pressure regulator to administer other fibrin sealants. This event occurs when an air or gas bubble or bubbles enter a vein or artery and block it. It is called an air or gas embolism. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface. The risk appears to be higher when fibrin sealants are sprayed with air as compared to CO_2 and therefore cannot be excluded with Raplixa. The Raplixa spray device (RaplixaSpray) should only be used if it is possible to accurately judge the spray distance.

When applying Raplixa using a spray device, a defined pressure within the range recommended by the spray device manufacturer is to be used. In addition, the spray device should not be used closer than the recommended distances. When spraying Raplixa, safety will be monitored because of the possibility of occurrence of air or gas embolism. The spray device and the accessory nozzle are provided with instructions for use, which should be carefully followed.

- Nearby areas should be protected to make sure that Raplixa is only applied onto the surface which is to be treated.
- When medicines are made from human blood or plasma, certain measures are put into place to prevent infections being passed on to patients. These include careful selection of blood and plasma donors to make sure those at risk of carrying infections are excluded, and the testing of each donation and pools of plasma for signs of viruses/infections. Manufacturers of these products also include steps in the processing of the blood and plasma that can inactivate or remove viruses. Despite these measures, when medicines prepared from human blood or plasma are administered, the possibility of passing on infection cannot be totally excluded. This also applies to any unknown or emerging viruses, or other types of infections.

The measures taken in the manufacture of fibrinogen and thrombin are considered effective for lipid coated viruses such as HIV (human immunodeficiency virus), hepatitis B virus and hepatitis C virus. The measures taken may be of limited value against non-enveloped viruses as hepatitis A virus and parvovirus B19 (causing fifth disease). Parvovirus B19 infection may be serious for pregnant women (foetal infection) and for individuals whose immune system is depressed or who have some types of anaemia (for example sickle cell disease or haemolytic anaemia).

It is strongly recommended that every time you receive a dose of Raplixa the name and batch number of the medicine are recorded in order to maintain a record of the batches used.

Children and adolescents

Raplixa has not been evaluated for safety and effectiveness in children.

Other medicines and Raplixa

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines.

Pregnancy and breast-feeding
Raplixa should not be administered during pregnancy and breast-feeding. There is not enough information available to know whether any particular risks are associated with the use of Raplixa during pregnancy or whilst breast-feeding.
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

3. How to Use Raplixa

The use of Raplixa is restricted to experienced surgeons who have been trained in the use of Raplixa.

The surgeon treating you will administer Raplixa during surgery.
Prior to applying Raplixa the surface area of the wound needs to be dried by standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices).

There are three methods of administration of Raplixa:
- Application of Raplixa straight from the vial to the bleeding site followed by the application of the gelatin sponge.
- Application from the vial onto a wetted gelatin sponge and then applied to the bleeding site.
- The third method is application of Raplixa onto the bleeding site using the recommended spray device followed by the application of the gelatin sponge.

The amount of Raplixa that will be applied depends on the surface area to be treated during the operation and the severity of the blood loss. When Raplixa is applied directly to the surgical bleeding site, a thin layer should be used to cover the bleeding/oozing area completely. If application of a single layer of Raplixa does not completely stop the bleeding, more may be applied.

When applying Raplixa using the recommended spray device, your surgeon must be sure to use a pressure and a distance from tissue within the range recommended by the manufacturer as follows:

Surgery	**Spray set to be used**	**Applicator tips to be used**	**Pressure regulator to be used**	**Recommended distance from target tissue**	**Recommended spray pressure**
Open surgery	1	1 or 2	RaplixaReg	5 cm	1.5 Bar (22 psi)

When spraying Raplixa, changes in blood pressure, pulse, oxygen saturation and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism.

4. Possible side effects

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

Fibrin sealants may, in rare cases (up to 1 in 1,000 people), cause an allergic reaction. If you experience an allergic reaction you might have one or more of the following symptoms: skin rash, hives or wheals (nettle-rash), tightness of the chest, chills, flushing, headache, low blood pressure, lethargy, nausea, restlessness, increased heart rate, tingling, vomiting or wheezing. If you experience any symptoms such as vomiting with blood, blood in your stool, blood in your draining tube from your abdomen, swelling or skin discolouration in your extremities, chest pain and shortness of breath, and/or any other symptoms related to your surgery, please contact your doctor or surgeon immediately.

There is also a possibility that you could develop antibodies to the proteins in Raplixa, which could potentially interfere with blood clotting. The frequency of the type of event is not known (cannot be estimated from available data).

The following side effects have also been reported:
Common side effects (may affect up to 1 in 10 people):

- Itch
- Difficulty sleeping

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

Ireland
HPRA Pharmacovigilance
Earlsfort Terrace
IRL - Dublin 2
Tel: +353 1 6764971
Fax: +353 1 6762517
Website: www.hpra.ie
e-mail: medsafety@hpra.ie

United Kingdom
Yellow Card Scheme
Website: www.mhra.gov.uk/yellowcard

5. How to store Raplixa

Keep this medicine out of the sight and reach of children.
Do not use this medicine after the expiry date which is stated on the label. Raplixa must be used within 2 hours of opening the vial.
Store Raplixa powder vials at 2 °C to 25 °C.
Do not use Raplixa if the seal on the vial has been tampered with.

6. Contents of the pack and other information

What Raplixa contains
- The active substances in Raplixa are human plasma derived fibrinogen and human thrombin.

The composition of Raplixa per gram powder is provided in Table 1.

Table 1: Composition of Raplixa (per gram powder)

Component	Target amount Quantity	Source	Function
Human Fibrinogen	79 mg/g	Human plasma	Active
Human Thrombin	726 IU/g	Human plasma	Active

- The other ingredients are trehalose, calcium chloride, albumin, sodium chloride, sodium citrate, L-arginine hydrochloride.

What Raplixa looks like and contents of the pack
Raplixa is a ready to use, pre-mixed, sterile, white dry powder supplied in a vial containing either 0.5 g, 1 g or 2 g.

Marketing Authorisation Holder and Manufacturer
Marketing Authorisation Holder
Mallinckrodt Pharmaceuticals Ireland Ltd
College Business & Technology Park, Cruiserath, Blanchardstown, Dublin 15, Ireland

Manufacturer
Nova Laboratories Limited
Martin House, Gloucester Crescent, Wigston, Leicester, Leicestershire, LE18 4YL, United Kingdom

This leaflet was last approved in 12/2016.

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

The following is intended for healthcare professionals only:

Raplixa is a pre-mixed, blend of thrombin and fibrinogen supplied as a ready to use dry-powder fibrin sealant in a glass vial containing 0.5 g, 1 g or 2 g of Raplixa. Raplixa is applied onto the surgical bleeding site directly from the vial or using the Raplixa spray delivery device, or onto a moistened gelatin sponge that is then applied to the surgical bleeding site. Raplixa and the device should be stored at controlled, ambient room temperature.

Prior to applying Raplixa the surface area of the wound needs to be dried by standard techniques (e.g. intermittent application of compresses, swabs, use of suction devices).
The gelatin sponges should be handled and used according to the manufacturer's instructions in the package insert that accompanies the gelatin sponge.

The required dose of Raplixa based on the size of the bleeding surface area to be treated is shown in the table below:

Maximum Surface Area Direct Application from Vial	Maximum Surface Area Application Using RaplixaSpray	Raplixa Package Size
25 cm^2	50 cm^2	0.5 g
50 cm^2	100 cm^2	1.0 g

Higher dosages up to 4g (including re-application and treatment of more than a single bleeding site) may be needed.

One of the following methods of application of Raplixa may be used based on the type of surgery, location and size and severity of the bleeding:

Direct application followed by gelatin sponge
Powder is applied directly from the vial onto the bleeding surface and then applied to a CE marked gelatin sponge cut to the appropriate size and apply manual pressure with sterile gauze.

Apply first to gelatin sponge
Powder is applied directly from the vial onto a saline-wetted CE marked gelatin sponge and then applied to the bleeding site. When using a moistened gelatin sponge, a thin layer of Raplixa should be applied to the sponge immediately prior to application to the bleeding site.

Spray application using Raplixa spray device followed by gelatin sponge
Use Raplixa with the Raplixa spray device.

The vial and Raplixa spray device should be taken out of their respective pouches maintaining sterility.

The Raplixa spray device is connected to the RaplixaReg pressure regulator and thereby to the medical gas supply set to a pressure setting of 1.5 bar (22 psi).

The vial should be held upright, shake gently and the aluminium cap and rubber stopper should be removed.

The vial with powder is attached to the Raplixa spray device by inverting the device over the upright vial and pushing the vial into place.

The Raplixa spray device is used to spray the powder on to the bleeding site and then the gelatin sheet is applied (see Instructions For Use for Raplixa spray device and gelatin sponge).

Application must be within 2 hours after connecting the vial to the device.

The Raplixa spray device comes with the rigid nozzle attached. This may be removed and the flexible nozzle attached depending on the intended use and surgeon preference.

Life threatening air or gas embolism has occurred with the use of spray devices employing pressure regulators to administer the fibrin sealant. This event appears to be related to the use of the spray device at higher than recommended pressures and/or in close proximity to the tissue surface. The risk appears to be higher when fibrin sealants are sprayed with air, as compared to CO_2 and therefore cannot be excluded with Raplixa.
To avoid the risk of potentially life-threatening air embolism Raplixa is recommended to be sprayed using pressurised CO_2. Raplixa may also be used with medical air.

When spraying Raplixa, changes in blood pressure, pulse, oxygen saturation, and end tidal CO_2 should be monitored because of the possibility of occurrence of air or gas embolism.
When applying Raplixa using the Raplixa spray device, the pressure should be within the range recommended by ProFibrix. Spray application of Raplixa should only be done using the provided spray application accessories and the pressure should not exceed 1.5 bars (22 psi). Raplixa should not be sprayed at a distance closer than that recommended by the spray device manufacturer and in no case closer than 5 cm from the tissue surface.

Surgery	Spray set to be used	Applicator tips to be used	Pressure regulator to be used	Recommended distance from target tissue	Recommended spray pressure
Open surgery	1	1 or 2	RaplixaReg	5 cm	1.5 Bar (22 psi)

Disposal

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