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Summary of the risk management plan (RMP) for Raplixa (human fibrinogen / human thrombin)

This is a summary of the risk management plan (RMP) for Raplixa, which details the measures to be taken in order to ensure that Raplixa is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Raplixa, which can be found on Raplixa's EPAR page.

Overview of disease epidemiology

Raplixa is a medicine used in adults to help stop bleeding during surgery when standard surgical methods for controlling bleeding, such as stitches, are insufficient. Raplixa is used with a gelatin sponge.

Approximately 540 vascular, spinal, hepatic and soft tissue surgeries are performed in every 100,000 people in the EU each year. About 44% of these procedures (around 237 procedures in every 100,000 people) require methods or medicines to control bleeding. Bleeding history, use of medicines which prevent abnormal bleeding, and the type of procedure, medical condition and associated illnesses are risk factors for surgical bleeding.

Summary of treatment benefits

Raplixa contains the active substances human fibrinogen and human thrombin. It is available as a powder and is used with an approved sponge made of gelatin. Raplixa is applied onto the area of bleeding directly, or by using a spray device, followed by application of the sponge. When applied to a moist surface, the thrombin is activated and converts fibrinogen into fibrin, which then aggregates (sticks together) and forms a fibrin clot that holds the gelatin sponge tightly to the wound surface, preventing bleeding and sealing the tissue. The sponge is left in the body, where it dissolves and disappears completely.

Raplixa has been shown to be effective in helping to stop bleeding during surgeries in one main clinical study. This study involved 721 randomised patients undergoing surgery of the spine, liver, blood vessels or soft tissue, and who had mild or moderate bleeding that could not be controlled by standard techniques. The study compared Raplixa used with a gelatin sponge, or with a gelatin sponge used on its own. Across all surgery types, patients in the Raplixa group had their bleeding stopped within 1 to 2 minutes compared with 2 to 4 minutes for patients in the control group. On average, using Raplixa reduced the bleeding time by about 2 minutes.

Unknowns relating to treatment benefits

Raplixa has been studied in patients above 18 years of age undergoing surgery of the spine, liver, blood vessels or soft tissue. Most patients were white but the study also included black patients. There is limited experience of use of Raplixa in vascular surgery when applied with the Raplixa spray device.

Raplixa has not been studied in tissue gluing or neurosurgery, or for application through a flexible endoscope.

Studies in children (patients below 18 years) began in 2014.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Severe allergic reactions (hypersensitivity)	Rare but severe allergic reactions were seen in the clinical trials for Raplixa. Allergic reactions are a potential concern with any protein-based medicine and are not preventable. Since human fibrinogen and human thrombin are proteins extracted from human blood, allergic reactions to Raplixa's active substances or to any of its other ingredients might occur and if this is the case, the administration must be stopped immediately.	Not preventable. Patients with allergies to any of the ingredients in Raplixa must not be given the medicine.

Important potential risks

Risk	What is known
Incorrect application of Raplixa (inside blood vessels), which could potentially lead to blood clots (thromboembolic events)	Although this is a potential risk, in one study, blood clots were seen in about the same number of patients who received Raplixa with a gelatin sponge patients as in those who received the gelatin sponge alone.
Air/gas bubbles in the blood stream (air/gas embolism)	Air or gas embolism has occurred with the use of spray devices that are used to administer other fibrin sealants. This side effect appears to be related to the use of the spray device at higher than recommended pressure and/or in close proximity to the tissue surface. The risk appears to be higher when fibrin sealants are sprayed with air, rather than with CO_2. This event could lead to serious effects or death. The spray used with Raplixa has been designed with several safeguards (e.g. air vented through the back) to reduce the likelihood of air/gas embolism. Based on clinical trial experience, the use of this spray was not associated with any increased risk of air emboli. However, air/gas embolism remains a potential risk with pressurised gas fibrin sealant spray devices.
Viral infection	The active substances in Raplixa, human fibrinogen and human thrombin, are proteins extracted from human blood. Although the process for the manufacture of Raplixa includes steps to effectively inactivate/remove viruses, as with any human blood product, viral

Risk	What is known
	infections will remain a potential risk.

Missing information

Risk	What is known
Safety and effectiveness in children and pregnant or breastfeeding women	Adequate safety and efficacy data are not yet available to support the use in children and therefore Raplixa is not recommended in this population. Animal reproduction studies have not been conducted with Raplixa. The safety of Raplixa in pregnancy or breastfeeding has not been established in controlled studies. Therefore, Raplixa should not be given to pregnant or breastfeeding women.
Safety in patients with other illnesses like kidney, liver, or heart conditions (safety data in patients with co-morbidities such as renal/ hepatic/cardiac impairment)	Raplixa has not been studied in patients with other illnesses like kidney, liver, or heart conditions.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine, and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Raplixa can be found on Raplixa 's EPAR page.

Raplixa has special conditions and restrictions for its safe and effective use (additional risk minimisation measures). Full details on these conditions and the key elements of any educational material can be found in Annex II of the product information which is published in Raplixa's EPAR page; how they are implemented in each country however will depend upon agreement between the manufacturer and the national authorities.

These additional risk minimisation measures are for the following risk:

Air/ gas embolism

Risk minimisation measure: To provide healthcare professionals with educational material regarding the risk of air/gas embolism
Objective and rationale: Increase awareness about the risk of air or gas embolism with the use of Raplixa spray device and

Risk minimisation measure: To provide healthcare professionals with educational material regarding the risk of air/gas embolism
provide instructions for the correct usage of pressure regulators.
Description: Educational materials will be provided to surgeons who are expected to use Raplixa to advise on the correct use of the Raplixa spray device.

Planned post-authorisation development plan

List of studies in post-authorisation development plan

Study/activity (including study number)	**Objectives**	**Safety concerns /efficacy issue addressed**	**Status**	**Planned date for submission of (interim and) final results**
FC-007 Paediatrics programs in the US: A Multi-centre, randomized, single blind, controlled Trial of Raplixa in liver resection, soft tissue dissection, or vascular surgery	To characterise the safety and efficacy of Raplixa administered as an aid to control bleeding in liver, soft tissue, or vascular surgery, in a paediatric population	Overall safety, as determined by the incidence, severity and relationship of adverse events, clinical laboratory abnormalities and post-surgery bleeding complications, changes on clotting tests, thrombogenicity and antibody formation.	Start Q1 2014	Part of the Paediatric Investigation Plan Q1 2015
FC-005: A phase 3b, randomized, single-blind, controlled, comparative efficacy and safety study of topical Fibrocaps™ (Raplixa™) and Tachosil® in surgical hemostasis during hepatic resection	To demonstrate the superiority of Raplixa plus gelatin sponge compared with Tachosil and to further evaluate the efficacy and safety of Raplixa plus gelatin sponge compared with Tachosil	Overall safety, as determined by the incidence, severity and relationship of adverse events, clinical laboratory abnormalities and post-surgery bleeding complications, changes on clotting tests, thrombogenicity	Ongoing	Q2 2015

Studies which are a condition of the marketing authorisation

None of the studies above are a condition of the marketing authorisation

Summary of changes to the risk management plan over time

Not applicable

This summary was last updated in 02-2015.