Part VI: Summary of the risk management plan by product

VI.1 Elements for summary tables in the EPAR

VI.1.1 Summary table of Safety concerns

Summary of safety concerns	
Important identified risks	• Hematoma / haemorrhage / bleeding • Danaparoid worsening of thrombocytopenia • Skin and subcutaneous tissue disorders
Important potential risks	• Medication error
Missing information	• None

VI.1.2 Table of on-going and planned studies in the Post-authorisation Pharmacovigilance Development Plan

Not applicable.

VI.1.3 Summary of Post authorisation efficacy development plan

Not applicable.

VI.1.4 Summary table of Risk Minimisation Measures

Safety concern	**Routine risk minimisation measures**	**Additional risk minimisation measures**
Important Identified Risk		
Haemorrhages, hematomas, bleeding	• Haemorrhages and hematomas are labelled AEs in SmPC Section 4.8. • Warning statements are in SmPC Section 4.4. • A contraindication statement is in SmPC Section 4.3.	None
Danaparoid Worsening of Thrombocytopenia	• A warning statement is in SmPC Section 4.4. • This event is labelled in SmPC Section 4.8.	None
Cutaneous Reactions	• This event is labelled in SmPC Section 4.8. • A contraindication statement is in SmPC Section 4.3.	None
Important Potential Risk		
Medication Error	Detailed dosage and administration instructions in the SmPC Section 4.2.	None
Missing Information		
None	None	None

VI.2 Elements for a Public Summary

Danaparoid was approved in June 1991 as a medication for preventing blood clots in the deep veins (deep venous thrombosis [DVT]) in patients undergoing skeletal, major abdominal or chest surgery. In a few countries it has also been registered for the prevention of DVT in patients with strokes which have not been caused by bleeding in the brain.

Every patient undergoing surgery runs a certain risk of blood clotting, dependent on the type of operation (e.g. major or minor), patient's age, and presence of other risk factors (e.g. cancer). In 2004 in Europe, the number of main surgical operations and procedures performed in hospitals varied between 168 per 10,000 (Cyprus) and 5743 per 10,000 (Belgium). Blood clotting prevention has been recommended in the majority of hospitalized patients in clinical practice guidelines issued by the 2016 American College of Chest Physicians (ACCP). Death rates in patients undergoing skeletal, major abdominal, or chest surgery strongly depend on a variety of factors such as the type of surgery, age of the patient, health status etc. No general death rates can be presented for this indication.

From 1996, danaparoid was approved in various countries (as a variation to the original DVT-prevention indication), for preventing and treating blood clot complications in patients with low blood platelets caused by use of an anti-blood clotting treatment called heparin (heparin-induced thrombocytopenia [HIT]). One third of hospitalized patients in the United States, or about 12 million a year, receive heparin (type not further described), with an estimated incidence of 120,000 to 600,000 HIT patients per year. From European countries, no incidence data is available. Low blood platelets in itself rarely poses a threat to affected patients, but disorders associated with it can produce severe disease and death.

VI.2.2 Summary of treatment benefits

Danaparoid is one of a group of medicines that are called antithrombotics.

Danaparoid is used for prevention of deep vein thrombosis and its possible consequences, in particular in patients undergoing orthopaedic, major abdominal or thoracic surgery. Danaparoid is similarly used to prevent blood clots in patients who can no longer be given heparin, including patients with a condition called heparin-induced thrombocytopenia (HIT). Thrombocytopenia is a large drop in the number of platelets due to hypersensitivity to heparin.

- Thirteen studies (including 1,382 patients) confirmed the efficacy of danaparoid in the prevention of blood clots in patients having elective hip surgery, fractured hip surgery or general surgery and in patients with acute thrombotic stroke and acute spinal cord injury. Danaparoid was also shown to be better than heparin, warfarin and acetylsalicylic acid at preventing blood clots. In most studies, the development of blood clots was monitored using technology that was state-of-the art at the time.

Danaparoid can also be used to treat blood clots that have already formed in the blood vessels, and is used in patients who require urgent prevention of blood clotting because of the development or a history of HIT.

- An important part of the data used to evaluate treatment of patients with HIT came from a compassionate use program that ran for ~16 years. Although danaparoid was not yet approved, physicians requested to use it in patients with HIT or other patients who could not tolerate heparin. The compassionate use program included 631 patients (678 treatment episodes).
- Additional data came from a literature search (699 patients/712 treatment episodes) and spontaneous serious adverse event reports (88 patients) to the manufacturer.

- Of all 1478 treatment episodes (all data sets combined), 1234 (83.5%) were free of a "lack of efficacy" endpoint (fatal or non-fatal events involving blood clots, unplanned amputations, or persistent/new decrease in platelet count). Events involving blood clots occurred in 11.0% of the treatment episodes.

VI.2.3 Unknowns relating to treatment benefits

Danaparoid has been studied in over 8,000 patients in the clinical development program. Though experience is limited, danaparoid has also been studied in children (aged 2 weeks to 17 years), the elderly, and in pregnant and lactating women. Importantly, there is experience with danaparoid since its first approval in 1991, during which time the efficacy of the product has been well established.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Hematoma (bruising) / Haemorrhage / Bleeding	Danaparoid has the potential to increase the risk of bleeding. Therefore, all events of bleeding are considered expected except when the outcome is fatal. In a report of 1478 clinical outcomes of patients treated with danaparoid, major bleeding events were reported during 8.1% of treatment episodes (120/1478). There were 55 events in relation to 130 heart-lung bypass procedures (42.3%), 12 events in relation to 197 major general blood vessel operations (6.1%) and 53 events in the 1,155 episodes (4.6%) of medical use only. Minor bleeding was reported in 12% of treatment episodes. The reported incidence of bleeding before and/or after surgery appears to depend on the definition of bleeding, the type of surgery, and the risk-profile of the patient. Overall, the reported incidences of major bleeding vary between 1% and 20%. Major bleeding significantly affects the risk of death.	Doctors prescribing danaparoid will refer to prescribing information called the Summary of Product Characteristics (SmPC) provided to them by the manufacturer. This information for prescribers is taken from the danaparoid Core Company Data Sheet (CDDS), which is the document that specifies contraindications, special warnings, and precautions for use.
Danaparoid worsening of low blood platelets	Low blood platelets as can be caused by (low molecular weight) heparin (HIT) was observed during the use of danaparoid, but only in patients who already had an immune system response to either heparin or low molecular weight heparin. Low blood platelets in danaparoid-treated HIT patients may occur due to cross-reactivity to a molecule called antiplatelet antibody that may be triggered by heparin. In fact it is a	No information is available in the danaparoid CCDS on the preventability of low blood platelets due to cross-reactivity of antiplatelet antibody caused by heparin, since it appears to be an individual reaction and is unlikely to have clinical consequences.

Risk	What is known	Preventability
	natural progress of the underlying HIT. In a report of 1478 clinical outcomes of patients treated with danaparoid, clinical cross-reactivity was reported in 78 (5.3%) patients: 45 with a positive finding of antiplatelet antibody either before or developing during danaparoid treatment, and 33 who were not tested at either time. Not much data on the incidence of various forms of low blood platelets are available.	
Skin and tissue disorders beneath the skin	Various types of rash may occur during treatment with danaparoid, including rash with bleeding spots, spotted and raised rash, rash with red appearance, itching, hives, generalized rash, blistery rash, and injection or infusion site rash. The majority of the rashes are mild.	These reactions are summarized in the CCDS. No specific data are available on the preventability of adverse skin reactions but the majority of these resolve promptly after danaparoid is withdrawn.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
Medication error	Reports of medication error with danaparoid have been rare (7.4 per 100,000 patients treated) and have mostly involved the patient receiving a dose lower than the recommended dose. Doctors prescribing danaparoid will refer to prescribing information called the Summary of Product Characteristics (SmPC) provided to them by the manufacturer. This information for prescribers is taken from the danaparoid Core Company Data Sheet (CCDS), which is the document that specifies the dose and how danaparoid should be given.

Danaparoid may be used together with other oral anti blood clotting drugs which interfere with platelet function (such as aspirin and non-steroidal anti-inflammatory drugs), clot-dissolving or potentially ulcer producing drugs (such as corticosteroids), but caution remains necessary. There are no data available on the effect of danaparoid on thyroid function tests. Interaction studies have only been performed in adults.

After danaparoid was available on the market, one case with a drug interaction was reported, causing blood clot formation during the use of danaparoid and Heparin together.

Missing information

No important missing information is currently identified.

VI.2.5 Summary of risk minimisation measures by safety concern

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimizing them. An abbreviated version of this in lay language is provided in the form of the Package Leaflet (PL). The measures in these documents are known as routine risk minimization measures.

This medicine has no additional risk minimization measures.

VI.2.6 Planned post authorisation development plan

Not applicable.

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

VI.2.7 Summary of changes to the Risk Management Plan over time

Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1.0	29-Feb-2008 (at the time of authorization)	Important identified risks: - Hematoma / haemorrhage / bleeding - Danaparoid worsening of Thrombocytopenia - Skin and subcutaneous tissue disorders No important potential risks or missing information.	
2.0	10-Jul-2014	Medication error added as an important potential risk.	Added at the request of the P-RMS in the assessment report for the PSUR covering the period 16-NOV-2010 to 15-NOV-2013 (IE/H/PSUR/0004/003)
3.0	12-Oct-2017	No new/removed to safety concerns	Updated for application of additional indication for MRP and national procedures, updated data since last DLP and transfer to new MAH template