VI.2 Elements for a Public Summary

VI.2.1 Overview of disease epidemiology

- **Indication: Treatment of blood clots**

Blood clots in the large veins of the legs, known as deep vein thrombosis (DVT), are a common medical problem, especially with older people, as 1% of those aged more than 75 years will suffer a DVT in any given year. More than 7 out of every 10 DVTs occur in those aged over 60 years.

Clots in the blood vessels of the lungs, known as a pulmonary embolism (PE), occur quite frequently and are almost always caused by blood clots forming in the large veins of the legs which can detach and travel through the body via the blood vessels to finally block a blood vessel in the lung, causing serious damage and may cause death.

Cancer is a major risk factor and blood clots in cancer patients tend to be more dangerous than in other patients, and hence require extended treatment. Other risk factors include surgery, poor mobility, trauma, obesity and certain medicines.

- **Indication: Prevention of blood clots in patients undergoing surgery**

Blood clots in the veins of the legs, known as deep vein thrombosis (DVT), are a common medical problem. Surgery is a well-known risk factor for getting a blood clot. Some of the DVTs that occur after surgery can detach and travel to the blood vessels of the lungs via the blood vessels and cause a pulmonary embolism (PE), which may even cause death. Some types of surgery are associated with higher risks of DVT/PE, e.g. hip and knee replacements have relatively high associated rates of DVT. Surgery in patients with cancer is also associated with a higher rate of DVT. Obesity, advanced age, poor mobility, infections and prolonged recovery from a disease increase the risk of DVT after surgery.

- **Indication: Prevention of blood clots in non-surgical adult patients**

Patients who have not had surgery, but have other illnesses such as; heart failure, acute infections, cancer, neurological- and rheumatological conditions are also at risk of blood clots. The blood clots that may occur in connection to such illnesses can be just as dangerous as the ones that may form after surgery.

- **Indication: Prevention of blood clotting during haemodialysis**

Patients with very advanced kidney disease are often treated with haemodialysis, where they are connected to an artificial kidney machine. The kidney machine removes waste products from the blood, a task normally handled by the kidneys. In this procedure, blood is

transported from the body by tubes to the kidney machine, where it passes through filters and is returned to the body by further tubes. The contact between the blood and these artificial surfaces increases the risks of blood clots forming in the tubes and this can result in a failed dialysis treatment. innohep® is used in connection with haemodialysis to prevent these blood clots from forming.

VI.2.2 Summary of treatment benefits

- **Initial treatment of blood clots**

Two trials included 1,050 patients with a blood clot in the leg or lung receiving either innohep® or heparin. The aim was to compare numbers of patients in either group who had another blood clot, a major bleeding, or died after 3 months. The treatments were shown equally effective and safe.

- **Extended treatment of blood clots**

A trial included 900 patients with cancer and a blood clot in the leg or lung receiving long term innohep® or warfarin. The aim was to compare numbers of patients in either group who developed another blood clot. innohep® was more effective than warfarin for prevention of a new blood clot.

- **Prevention of blood clots in patients undergoing surgery**

A trial included 1,271 patients undergoing general surgery receiving innohep® or heparin for 6-10 days after surgery, with the aim of comparing numbers of patients in either group who developed a blood clot. The 3,500 unit dose of innohep® was equally effective as heparin; the innohep® 2,500 unit dose less effective.

Three trials including 2,345 patients undergoing knee or hip replacement surgery compared innohep® to placebo or other anticoagulant therapy. innohep® showed a reduction of risk of blood clots compared to placebo.

The reduction of blood clots was more pronounced with innohep® than with warfarin, and equally effective for prevention of blood clots as enoxaparin.

- **Prevention of blood clots in non-surgical adult patients**

Five trials including 350 non-surgical patients showed that innohep® was effective in in preventing blood clots. The trials included patients immobilised due to spinal cord injury, elderly patients with impaired kidneys and patients with a plaster cast.

- **Prevention of blood clotting during haemodialysis**

Three trials with 219 patients having multiple dialyses showed that innohep® prevented blood clotting during haemodialysis.

VI.2.3 Unknowns relating to treatment benefits

innohep® has been used for more than 25 years in approximately 1 billion patients in 50+ countries. Use of innohep® beyond 6 months hasn't been studied. Limited data is available with use of innohep® in patients with severely impaired kidneys, in children, during lactation and regarding the effect on fertility.

VI.2.4 Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Serious allergic reactions	Hypersensitivity may affect 1 in 100 people. Life-threatening allergic reactions (anaphylaxis) can occur; it may affects up to 1 in 1,000 people. Possible symptoms include sudden onset of rash, itching or lumpy rash, swelling of the face, lips, tongue, throat or other parts of the body, shortness of breath, wheezing or difficulty breathing.	The patient information leaflet explains that if a patient experiences allergic signs or symptoms and innohep® is suspected to be the cause, medical advice should be sought straight away as urgent medical help may be needed. Additionally, use of innohep® must be avoided in patients with known hypersensitivity to the active substance or any of the excipients.
Bleeding (Haemorrhage)	Bleeding of any kind and severity is a known side effect of innohep®. Severe bleedings may affect up to 1 in 100 people. Possible symptoms may include red or brown urine, black tarry stools, unusual bruising (very painful, large or dark bruises), bleeding from your nose or mouth or any wound that will not stop.	Patients at high risk of bleeding cannot receive innohep®. The patient information leaflet explains that if a patient experiences signs of a severe bleeding, medical advice should be sought straight away.

Decrease in blood platelets (Thrombocytopenia and heparin-induced thrombocytopenia)	Heparin-induced thrombocytopenia (HIT) is rare, may affects up to 1 in 1,000 people. The most common symptom is a decrease in blood platelets. Blood platelets are cell fragments which are involved in the formation of blood clots. HIT can result in either bleeding or blood clots	It is advised that before and during the treatment, routine blood tests should be performed in order to monitor the effect of innohep®, including control of blood platelet counts. Regular monitoring of blood platelet count in cancer patients at extended treatment for cancer associated thrombosis is advised, especially during the first month, considering that cancer and its treatments such as chemotherapy may also cause a decrease in blood platelets. Additionally, it is advised that innohep® must be discontinued in patients who develop a decrease in blood platelets, and that innohep® should not be used in cases of current or history of decrease in blood platelets caused by innohep® therapy.
Decrease in bone density in connection with long-term treatment incl. bone fractures (Osteoporosis in connection with extended use incl. bone fractures)	A decrease in bone density (osteoporosis) is rare, may affects up to 1 in 1,000 people. It may occur if treated with innohep® for a long time. The bones may get weak and break more easily. Of note, in a large human study of 450 patients treated with innohep® for up to 6 months, no incidents of osteoporosis was seen.	It is advised that patients treated for a long time with innohep® are monitored closely, including monitoring of possible undesirable effects.

Increased level of blood potassium (Hyperkalaemia)	Increased level of blood potassium is rare, may affects up to 1 in 1,000 people. Symptoms include general discomfort, abnormality of heartbeat that ranges from often unnoticed skipped beats or accelerated heart rate to very noticeable changes accompanied by dizziness or difficulty breathing and muscle weakness.	Blood potassium levels are monitored regularly by blood analyses before and during the treatment for patients at risk of abnormal blood potassium levels.

Important potential risks

Risk	**What is known (Including reason why it is considered a potential risk)**
None	N/A

Missing information	What is known
Use in patients with severely reduced kidney function	Limited information is available about how innohep® works in patients with a very low kidney function, defined as having a creatinine clearance level below 20 ml/minute. Caution is advised when innohep® is used for patients with severely reduced kidney function.
Use in children	Limited information is available about how innohep® works in children below 18 years of age. innohep® is not approved for use in children.
Use during breast-feeding	It is unknown whether tinzaparin (the active ingredient in innohep®) is transferred into human breast milk and there may therefore be a risk of transmission to the breast-feeding infant if the mother is treated with innohep®. For the mother, the risk of blood clots is particularly high during the first six weeks after child birth. Therefore, in collaboration with a healthcare professional, a decision must be made whether to stop breast-feeding or to stop innohep® treatment, taking into account the benefit of breast-feeding for the child and the benefit of innohep® treatment for the mother.
Effect on fertility	It is unknown whether innohep® has an effect on human fertility. Experience from animals did not indicate any harmful effects on reproduction.
Safety information in use beyond 6 months duration	Studies in patients have tested safety and efficacy for use of innohep® for up to 6 months. Safety information on treatment beyond 6 months is limited as there are no studies with innohep® used beyond 6 months.

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 minimising 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.

The Summary of Product Characteristics and the Package Leaflet for innohep® can be found on the homepages of the national Health Authorities.

This medicine has no additional risk minimisation measures.

VI.2.6 Planned post-authorisation development plan

None planned.

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

Table 1 Major changes to the Risk Management Plan over time

Version	Date	Safety Concerns	Comment
1	18/09/2013	*Important identified risks* 1. Serious allergic reactions 2. Haemorrhage 3. Thrombocytopenia and heparin-induced thrombocytopenia 4. Osteoporosis in connection with extended use incl. bone fractures 5. Hyperkalaemia *Important potential risks* None *Missing information* None	Version under original review
2	18/06/2014	*Important identified risks* 1. Serious allergic reactions 2. Haemorrhage 3. Thrombocytopenia and heparin-induced thrombocytopenia 4. Osteoporosis in connection with extended use incl. bone fractures 5. Hyperkalaemia *Important potential risks* None *Missing information* 1. Use in renal impairment (creatinine clearance <20 ml/min) 2. Use in children 3. Use during lactation 4. Effect on fertility	Version originally approved 4 Missing information added based on assessment by the DHMA (MRP procedure RMS).
3	15/06/2015	“Safety information in use beyond 6	New version

Version	Date	Safety Concerns	Comment
		months" has been added as missing information. Proposed safety concerns for this version are: *Important identified risks* 1. Serious allergic reactions 2. Haemorrhage 3. Thrombocytopenia and heparin-induced thrombocytopenia 4. Osteoporosis in connection with extended use incl. bone fractures 5. Hyperkalaemia *Important potential risks* None *Missing information* 1. Use in patients with creatinine clearance <20 ml/min 2. Use in children 3. Use during lactation 4. Effect on fertility 5. Safety information in use beyond 6 months	submitted for assessment. New missing information added based on assessment by the MHRA, UK. Editorial change in Missing information for Use in patients with severe renal impairment.
4	16/06/2016	*Important identified risks* 1. Serious allergic reactions 2. Haemorrhage 3. Thrombocytopenia and heparin-induced thrombocytopenia 4. Osteoporosis in connection with extended use incl. bone fractures 5. Hyperkalaemia *Important potential risks* None *Missing information* 1. Use in patients with creatinine clearance	Version approved based on assessment by the DHMA (MRP procedure RMS).

Version	Date	Safety Concerns	Comment
		<20 ml/min 2. Use in children 3. Use during lactation 4. Effect on fertility 5. Safety information in use beyond 6 months	
5	27/02/2017	*Important identified risks* 1. Serious allergic reactions 2. Haemorrhage 3. Thrombocytopenia and heparin-induced thrombocytopenia 4. Osteoporosis in connection with extended use incl. bone fractures 5. Hyperkalaemia *Important potential risks* None *Missing information* 1. Use in patients with creatinine clearance <20 ml/min 2. Use in children 3. Use during lactation 4. Effect on fertility 5. Safety information in use beyond 6 months	No changes in Important identified and potential risks and missing information compared to version 4.