Australian Government
Department of Health
Therapeutic Goods Administration

# AusPAR Attachment 2

# Extract from the Clinical Evaluation Report for Nadroparin

Proprietary Product Name: Fraxiparine

Sponsor: Aspen Pharmacare Australia Pty Ltd

**First round report: February 2017**
**Second round report: June 2017**

TGA Health Safety Regulation

# About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health, and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <https://www.tga.gov.au>.

# About the Extract from the Clinical Evaluation Report

- This document provides a more detailed evaluation of the clinical findings, extracted from the Clinical Evaluation Report (CER) prepared by the TGA. This extract does not include sections from the CER regarding product documentation or post market activities.
- The words [Information redacted], where they appear in this document, indicate that confidential information has been deleted.
- For the most recent Product Information (PI), please refer to the TGA website <https://www.tga.gov.au/product-information-pi>.

# Contents

# List of abbreviations

| Abbreviation | Meaning |
|---|---|
| AEs | Adverse events |
| AMI | Acute myocardial infarction |
| ASA | Acetylsalicylic acid |
| BMI | Body mass index |
| CHMP | Committee on Human Medicinal Products |

| Abbreviation | Meaning |
|---|---|
| CI | Confidence Intervals |
| CNS | Central nervous system |
| COPD | Chronic obstructive pulmonary disease |
| CVA | Cerebrovascular accident |
| CY216D | Nadroparin |
| DVT | Deep vein thrombosis |
| EB | Elastic bandages |
| FDR | Risk factors for thromboembolism (as indicated in the Pottier, 2000 reference). |
| FUT | Fibrinogen uptake test |
| GCS | Graded compression stockings |
| GI | Gastro-intestinal |
| HAT | Heparin-associated thrombocytopenia |
| Hgb | Haemoglobin |
| HIT | Heparin-induced thrombocytopenia |
| HITTS | Heparin-induced thrombotic thrombocytopenia syndrome |
| HIV | Human immunodeficiency virus |
| IU | International units |
| LMWH | Low molecular weight heparin |
| MTC | Mixed treatment comparison |
| NHMRC | National Health and Medical Research Council |
| NSAIDs | Non-steroidal anti-inflammatories |
| NYHA | New York Heart Association functional classification |
| OR | Odds ratio |
| PE | Pulmonary embolism |
| PT | Prothrombin time |

| Abbreviation | Meaning |
|---|---|
| RR | Relative risk |
| SAEs | Serious adverse events |
| SD | Standard deviation |
| SEM | Standard error of the mean |
| UFH | Unfractionated heparin |
| VTE | Venous thromboembolism |

# 1. Introduction

## 1.1. Submission type

This is a literature-based submission (LBS) to extend indications for Fraxiparine (nadroparin calcium).

## 1.2. Drug class and therapeutic indication

Fraxiparine (nadroparin calcium) is a low-molecular weight heparin.

The current TGA-approved indications for Fraxiparine are:

- *Prophylaxis against deep vein thrombosis (DVT) associated with general or orthopaedic surgery.*
- *Treatment of DVT.*
- *Prevention of clotting during haemodialysis.*

This application seeks to register the following additional indication for Fraxiparine:

- *Prophylaxis of venous thromboembolism in medical patients bedridden due to acute illness*

## 1.3. Dosage forms and strengths

Fraxiparine is a sterile, clear preservative-free solution usually for subcutaneous injection. Disposable glass pre-filled single use syringes containing nadroparin calcium 9,500 IU anti-Xa/mL in water for injections with sufficient calcium hydroxide or dilute hydrochloric acid to adjust the pH to between 5 and 7.5.

**Table 1: Types of products.**

| Volume | Type of Syringe | Nadroparin Calcium (IU anti-Xa) | Pack size |
|---|---|---|---|
| 0.2 mL | Ungraduated | 1,900 | 2 and 10 |
| 0.3 mL | Ungraduated | 2,850 | 2 and 10 |
| 0.4 mL | Ungraduated | 3,800 | 2 and 10 |
| 0.6 mL | Graduated | 5,700 | 2 and 10 |
| 0.8 mL | Graduated | 7,600 | 2 and 10 |
| 1.0 mL | Graduated | 9,500 | 2 and 10 |

Comment: The proposed PI states that all volumes and pack sizes may not be available in Australia.

## 1.4. Dosage and administration

The proposed dosage and method of administration for the additional indication is as follows (as mentioned in the proposed PI):

***Medical Patients bedridden due to acute illness:***

*Nadroparin is administered subcutaneously once daily. The dose should be adjusted for body weight according to the table below. Treatment should be continued throughout the risk period of thromboembolism.*

| Body weight (kg) | Once daily | |
|---|---|---|
| | Volume injected (ml) | Anti-Xa IU |
| ≤70 | 0.4 | 3,800 |
| >70 | 0.6 | 5,700 |

*In elderly patients, dose reduction to 0.3ml (2,850 Anti-Xa IU) may be appropriate.*

*Fraxiparine is administered by subcutaneous injection; the usual site for injection is the lateral abdominal wall, although the thigh may be used as an alternative. The needle should be inserted perpendicularly into a pinched-up fold of skin which should be held gently but firmly until the injection has been completed. Do not rub the injection site. Fraxiparine is not intended for intramuscular administration*

*Fraxiparine 0.2 mL - 1,900 IU anti-Xa, 0.3 mL - 2,850 IU anti-Xa and 0.4 mL - 3,800 IU anti-Xa prefilled syringes are intended for administration of unit dosages only. The entire contents of the syringe should be injected. There may be a small air bubble in the syringe, but this does not have to be removed.*

*Fraxiparine 0.6 mL - 5,700 IU anti-Xa, 0.8 mL - 7,600 IU anti-Xa and 1.0 mL - 9,500 IU anti-Xa prefilled graduated syringes may be used to administer adjusted dosages. Hold the syringe vertically with the needle uppermost and ensure the air bubble is at the top of the syringe. Advance the plunger to the volume/dosage required, expelling air and any excess.*

Comment: The instructions regarding duration of treatment are not specific and do not reflect the data provided in the submission.

# 2. Background

## 2.1. Information on the condition being treated

Venous Thromboembolism (VTE) is one of the most important preventable causes of morbidity and mortality in hospital patients, having an annual incidence of one per 1000 individuals (Dahlback 2008). During the past 40 years numerous studies have shown that UFH and LMWH are effective and safe for the prevention of VTE in surgical patients (Geerts 2008). This has led to the widespread use of these agents for thromboprophylaxis in surgical patients with a resultant reduction in the incidence of fatal PE (Cohen 1996). However, there have been fewer trials investigating the benefits and risks of thromboprophylaxis in medical patients. Most of these studies have concentrated on specific conditions such as myocardial infarction (MI) (Collins 1996) and ischaemic stroke (Gubitz 2004). The incidence of DVT in medical disorders varies considerably. It can range from 8 to 25% for patients with mild disease who are incompletely immobilised (Prescott, 1981, International Consensus Statement. 1997 Prevention of Thromboembolism) to 40% for patients with hemiplegia after a nonhaemorrhagic-ischaemic, cerebrovascular event (Kay, 1995; Sandset, 1990; Turpie, 1987). These differences are a reflection of the populations in studies and the different assessment methods used. The few studies that have compared LMWH with unfractionated heparin (UFH) in medical patients with various diseases have not demonstrated any significant difference in efficacy, but only a trend towards improved safety with LMWH (Bergmann, 1996; Dahan, 1986; Forette, 1995; Manciet, 1996; Thromboembolic Risk Factors (Thrift) Consensus Group. 1992). Four large studies were analysed in a review (Lederle, 1998) involving 15,795 patients hospitalised in general medicine departments and at risk for DVT who were treated with prophylactic doses of heparin. The odds ratio for the effect of low-dose heparin on mortality was 0.91 (95 CI: 0.80 to 1.04) which provided preliminary evidence suggesting the possibility that prophylactic treatment of general medical patients may reduce the mortality.

## 2.2. Current treatment options

LMWHs are as effective as unfractionated heparin (UFH) in deep-vein thrombosis (DVT) prophylaxis for major surgery. However, there is limited evidence or consensus for prophylaxis in medical patients. In Australia, another LMWH Enoxaparin sodium (Levenox) is approved for the same indication as the one proposed for nadroparin:

*Prophylaxis of VTE in medical patients bedridden due to acute illness*

However, the other available LMWH in Australia, Dalteparin (Fragmin) is not approved for thromboprophylaxis in medical patients bedridden due to acute illness.

## 2.3. Clinical rationale

Nadroparin is a LMWH made by depolymerisation of standard heparin. Nadroparin has both immediate and prolonged antithrombotic action. Nadroparin exhibits a high-affinity binding to the plasma protein anti-thrombin III (ATIII). This binding leads to an accelerated inhibition of factor Xa and to a lesser extent, factor IIa leading to a high ratio of anti-Xa activity to anti-IIa activity (ranges from 2.5 to 4.0) compared to unfractionated heparin for which this ratio is one. Compared with unfractionated heparin, nadroparin has less effect on thrombocyte function and aggregation *in vitro* and only a slight effect on primary haemostasis.

## 2.4. Evaluator's commentary on the background information

The stated rationale for use of Fraxiparine for thromboprophylaxis in bedridden patients with acute medical illnesses is acceptable.

# 3. Contents of the clinical dossier

## 3.1. Scope of the clinical dossier

Fraxiparine injections have been approved in several countries (including Australia) for the treatment and prophylaxis of thromboembolic disorders for greater than 10 years, which is in accordance with the requirements of the TGA Guideline on Literature Based Submissions.

Following initial consultation with and endorsement by TGA, the applicant has prepared a LBS to support the proposed indication and dosage for this new indication. The following inclusion and exclusion criteria were used to select papers relevant to this application:

- Include studies (RCTs in the first instance) investigating the use of nadroparin in prophylaxis/ prevention of thromboembolic disorders in medical patients bedridden due to acute illness.
- Include studies investigating doses of ≤ 5700 Anti-Xa IU.
- Include studies utilising appropriate diagnostic criteria and relevant clinical efficacy endpoints.
- Include studies that are of sufficient duration to allow efficacy and safety assessment.
- Include reference check for systematic reviews and meta-analyses to ensure all relevant publications have been identified in the main search.
- Exclude studies investigating the use of nadroparin in prophylaxis/prevention in general or orthopaedic surgery and use in haemodialysis patients.

- Exclude studies investigating use of nadroparin in treatment of thromboembolic disorders or treatment unrelated to thromboembolic disorders.
- Exclude studies investigating use in ambulatory patients.

The submission contains the following clinical study reports:

- 2 systematic meta-analyses (Alikhan, 2014 and Dooley, 2014);
- 2 pivotal studies (Fraisse, 2000; Harenberg, 1992, 1996);
- 2 supportive efficacy studies (Luba, 2007; Pottier, 2000);
- 2 studies which only evaluated safety (Forette, 1995; Pessina, 2003).

### 3.2. Paediatric data

No data in paediatric patients was provided. This drug is not indicated in children and adolescents as there are insufficient safety and efficacy data to establish dosage in patients aged <18 years.

### 3.3. Good clinical practice

Most of the studies were conducted in compliance with GCP guidelines and/or adequate ethics approval from local regulatory authorities.

### 3.4. Evaluator's commentary on the clinical dossier

The relevant published articles were identified through a structured and systematic review of scientific data bases and selected using screening criteria designed to select those studies which met the objectives of the application.

The Risk Management Plan (RMP) was not provided in this submission. TGA may require a RMP to be submitted for existing registered products if an application proposes a major change to the way the product will be used, or if a new safety concern has been identified. This application does not propose a major change to the way the product is currently used and no new safety concerns were identified from the adverse event data provided with this application from studies evaluating the safety and efficacy of prophylactic nadroparin in medical patients bedridden with acute illness. Hence, the sponsors concluded that a RMP was not required for this application and the argument is acceptable Overall, the submitted dossier was adequate and well-presented.

## 4. Pharmacokinetics

### 4.1. Studies providing pharmacokinetic information

No new pharmacokinetic information was provided. The following information is taken from the approved PI for nadroparin (Fraxiparine).

## 4.2. Summary of pharmacokinetics

### 4.2.1. Physicochemical characteristics of the active substance

Fraxiparine is a sterile, clear preservative-free solution usually for subcutaneous injection containing nadroparin calcium 9,500 IU anti-Xa[1] per 1.0 mL dissolved in water for injections.

Nadroparin is a low molecular weight heparin made by depolymerisation of standard heparin. It is a glycosaminoglycan with a mean molecular weight around 4,500 daltons. It possesses a high ratio of anti-Xa activity to anti-IIa activity between 2.5 to 4.0 compared to unfractionated heparin for which this ratio is one. One ICU is equivalent to 0.38 IU anti-Xa.

### 4.2.2. Pharmacokinetics in healthy subjects

The pharmacokinetic properties of nadroparin have been assessed in plasma on the basis of biological activity, i.e. measurement of anti-factor Xa activity. Following subcutaneous administration, the peak anti-Xa activity (Cmax) is reached after approximately 3 to 6 hours (Tmax). Bioavailability is almost complete (around 88%). After IV injection, the peak plasma anti-Xa level is reached within less than 10 minutes and the half-life is around 2 hours. The elimination half-life is approximately 3.5 hours. However, in one study anti-Xa activity was detectable for at least 18 hours following a subcutaneous dose of 100 anti-Xa IC U/kg (38 anti-Xa IU/kg) in nine out of twelve study subjects.

### 4.2.3. Pharmacokinetics in the target population

No PK studies were conducted in the target population for the extended indication of prevention of thromboembolism in medical patients bedridden due to acute illness.

### 4.2.4. Pharmacokinetics in special populations

No new data was provided. The following is already included in the approved PI for nadroparin:

> *Elderly: Renal function generally decreases with age so elimination is slower in the elderly (see Pharmacokinetics: Renal Impairment below). The possibility of renal impairment in this age group must be considered and the dosage adjusted accordingly (see DOSAGE AND ADMINISTRATION and PRECAUTIONS).*
>
> *Renal Impairment: In patients with severe renal failure, a reduced dosage should be considered as elimination of anti-Xa activity is prolonged in such patients.*

### 4.2.5. Population pharmacokinetics

Not applicable.

### 4.2.6. Clinical implications of in vitro findings

Not applicable.

## 4.3. Evaluator's overall conclusions on pharmacokinetics

The pharmacokinetics of nadroparin is well established and no additional PK data was provided in this submission.

[1] Anti-Xa denotes anti factor Xa activity.

# 5. Pharmacodynamics

## 5.1. Studies providing pharmacodynamic information

No new pharmacodynamic information was provided.

## 5.2. Summary of pharmacodynamics

### 5.2.1. Mechanism of action

Nadroparin has both immediate and prolonged antithrombotic action. Nadroparin exhibits a high-affinity binding to the plasma protein anti-thrombin III (ATIII). This binding leads to an accelerated inhibition of factor Xa and to a lesser extent, factor IIa (Anti-Xa:Anti-IIa ratio of 3.6:1), which contributes to the antithrombotic potential of nadroparin. Other mechanisms that contribute to the antithrombotic activity of nadroparin include stimulation of tissue factor pathway inhibitor (TFP1), activation of fibrinolysis via direct release of tissue plasminogen activator from endothelial cells and the modification of haemorrheological parameters (decreased blood viscosity and increased platelet and granulocyte membrane fluidity). Compared with unfractionated heparin, nadroparin has less effect on thrombocyte function and aggregation *in vitro* and only a slight effect on primary haemostasis.

### 5.2.2. Pharmacodynamic effects

#### *5.2.2.1. Primary pharmacodynamic effects*

No new data provided.

#### *5.2.2.2. Secondary pharmacodynamic effects*

No new data provided.

#### *5.2.2.3. Time course of pharmacodynamic effects*

No data provided.

### 5.2.3. Relationship between drug concentration and pharmacodynamic effects

No data provided.

### 5.2.4. Genetic, gender and age related differences in pharmacodynamic response

No data provided.

### 5.2.5. Pharmacodynamic interactions

No data provided.

## 5.3. Evaluator's overall conclusions on pharmacodynamics

The antithrombotic action of nadroparin is well established and no new pharmacodynamics data was provided in this submission.

# 6. Dosage selection for the pivotal studies

## 6.1. Pharmacokinetics and pharmacodynamics: dose finding studies

Not applicable.

## 6.2. Phase II dose finding studies

No data provided.

## 6.3. Phase III pivotal studies investigating more than one dose regimen

In the pivotal Fraisse (2000) study, dosage was based on patients' body weight (3,800 AXa IU, i.e., 0.4 mL for 45 to 70 kg; 5,700 AXa, i.e., 0.6 mL for 71 to 110 kg) and this was based on previous clinical experience with nadroparin in high-risk surgical patients. In this study, treatment was started immediately after enrolment and continued until the patient was weaned off mechanical ventilation; the duration of treatment could not exceed 21 days. The mean duration of treatment was 11-12 days in the nadroparin and placebo groups.

In the pivotal active-controlled study (Harenberg, 1992, 1996), patients were randomly assigned to UFH or LMWH treatment group and received either 5000 IU UF heparin (Calciparine) subcutaneously thrice daily or 3100 IU (anti Xa)/ 0.3 mL LMW heparin (Fraxiparine) once daily (plus 2 placebo injections containing 0.9% saline in prefilled syringes). The dose of nadroparin used in this study was not weight-based and it is not clear how dosing was determined. Treatment was started within 12 hours of hospital admission and duration of treatment was 10 days.

The randomised, open-label study (Luba, 2007) in 300 medical inpatients hospitalised with acute medical evaluated the efficacy and safety of two dosing models of thromboprophylaxis. In one group, patients were treated with nadroparin for the duration of immobilisation and in the second group, patients received nadroparin treatment during immobilisation and for 10 days after. All patients received weight-based dosing with nadroparin (similar to that in the pivotal Fraisse study). A tendency for a rarer occurrence of end points in patients receiving LMWH, for longer than only during immobilization was observed in the open-label study but interpretation was limited by open-label study design and low occurrence of events.

## 6.4. Evaluator's conclusions on dose finding for the pivotal studies

Dosage was based on similar dosing schedule which is already approved for thromboprophylaxis for surgery patients and patients undergoing haemodialysis (which are the already approved indications for nadroparin).

The main limitation or information gap regarding dose finding for proposed new indication was that no specific dose-finding studies were conducted in medical patients bedridden due to acute medical illness. All dosing for new indication was based on dosing schedule which is already approved for thromboprophylaxis for surgery patients and patients undergoing haemodialysis.

# 7. Clinical efficacy

## 7.1. Studies providing evaluable efficacy data

Overall, 8 published reports were included in this submission to provide evidence of efficacy for the proposed indication of nadroparin as a thromboprophylactic agent in hospitalised, acutely ill medical patients. The two systematic meta-analyses (Alikhan, 2014 and Dooley, 2014) and 2 RCTs (Fraisse, 2000; Harenberg, 1992, 1996) are discussed. These 4 published studies provide the main evidence to support efficacy.

## 7.2. Pivotal or main efficacy studies

### 7.2.1. Fraisse, 2000

#### *7.2.1.1. Study design, objectives, locations and dates*

This was a prospective, randomised, double-blind, placebo-controlled trial. The objective was to evaluate the therapeutic benefits of the LMWH- nadroparin calcium (Fraxiparine) in patients with acute, decompensated chronic obstructive pulmonary disease (COPD) who required mechanical ventilation, using clinical examination and Doppler ultrasonography to detect thromboembolic events. The study was conducted at 34 medical intensive care units in France from March 1992 through April 1995.

#### *7.2.1.2. Inclusion and exclusion criteria*

The main inclusion criteria were: patients admitted with acute, respiratory-decompensated COPD, who required mechanical ventilation; age 40 to 80 yrs; weight 45 to 110 kg; written, informed consent.

Main exclusion criteria were: history of a confirmed DVT within the previous 6 months or presence of signs of a DVT on the Doppler ultrasonography at inclusion, an organic lesion that could bleed, i.e., an active gastroduodenal ulcer or a recent haemorrhagic cerebrovascular accident; severe liver failure leading to a decrease of the prothrombin time (PT) to less than 50% (normal values between 70 and 100%); severe renal impairment (serum creatinine>300 mmol/L); confirmed or uncontrolled hypertension (diastolic blood pressure > 120 mm Hg); a congenital or acquired coagulation disorder; a history of hypersensitivity or thrombocytopenia to heparins of any type; were contraindicated to anticoagulant therapy, venography, or angiography; or were receiving any form of acetylsalicylic acid, ticlopidine, or oral anticoagulants.

**Comment:** The published study (study methods) mentions the following: "From March 1992 through April 1995, consecutive patients admitted with acute, respiratory-decompensated COPD, who required mechanical ventilation, were enrolled if they were aged 40 to 80 years and weighed 45 to 110 kg. Patients were *included* if they had: a history of a confirmed DVT within the previous 6 mo or presence of signs of a DVT on the Doppler ultrasonography at inclusion, an organic lesion that could bleed, i.e., an active gastroduodenal ulcer or a recent haemorrhagic cerebrovascular accident; severe liver failure leading to a decrease of the prothrombin time (PT) to less than 50% (normal values between 70 and 100%); severe renal impairment (serum creatinine > 300 mmol/L); confirmed or uncontrolled hypertension (diastolic blood pressure > 120 mm Hg); a congenital or acquired coagulation disorder; a history of hypersensitivity or thrombocytopenia to heparins of any type; were contraindicated to anticoagulant therapy, venography, or angiography; or were receiving any form of acetylsalicylic acid, ticlopidine, or oral anticoagulants."

There appears to be an error as the authors seem to imply that these patients were *excluded* from the study. Clarification has been sought from the sponsors regarding this. Furthermore, it was not specified if the study excluded patients with stroke and unstable angina although it would be implied as this study is included in the Alikhan meta-analysis which excluded studies in patients with stroke, AMI and admission to ICU.

#### *7.2.1.3. Study treatments*

Patients were randomised to receive either nadroparin (Fraxiparine; Sanofi-Winthrop, Gentilly, France) or matching placebo by subcutaneous injection once daily. Based on previous clinical experience with nadroparin in high-risk surgical patients, dosage was based on patients' body weight (3,800 AXa IU, that is, 0.4 mL for 45 to 70 kg; 5,700 AXa, i.e., 0.6 mL for 71 to 110 kg).

Nadroparin was supplied as a concentrated solution of 9,500 AXa IU/mL in disposable, prefilled syringes. Placebo 0.9% physiological saline was supplied in an identical manner.

Study treatment started immediately after enrolment and continued until the patient could be weaned from mechanical ventilation. However, according to study protocol, the duration of study treatment could not exceed 21 ± 1 days. The time between the start of mechanical ventilation, enrolment and first injection of LMWH was as short as possible and was not supposed to exceed 24 h. Patients with less than 48 h of ventilator were excluded from the study. If the mechanical ventilation had to be continued more than 21 ± 1 days after inclusion, the studied treatment was stopped at 21 ± 1 day after inclusion. The study observation period was then considered to be ended and the patients were evaluated for primary end point (bilateral venography) and included in the intention-to-treat analysis. Treatment was discontinued if a major critical event (lack of therapeutic efficacy or serious adverse event) or a major protocol violation occurred. In case of lack of efficacy, or DVT, treatment at a therapeutic dose was usually initiated.

#### *7.2.1.4. Efficacy variables and outcomes*

Patients were examined daily for DVT on usual signs or symptoms (pain, heat, redness and oedema), haemorrhage and other adverse events. Doppler ultrasonography[2] was performed before inclusion and weekly during the study and in all cases of clinically suspected DVT. Thrombosis was suspected by the presence of echogenic endoluminal material and/or the absence of total vein compressibility.

The primary efficacy criterion was incidence of DVT diagnosed by venography. Venography was performed at normal planned completion, in cases of early permanent discontinuation, or during the study, for positive, doubtful, or uninterpretable Doppler ultrasonography. Early permanent discontinuation of treatment was due to either a lack of efficacy, a serious adverse event (SAE), patient decision, an intercurrent event presenting a potential risk for the patient, or a major protocol violation (including noncompliance with therapy). Diagnosis was confirmed by two independent radiological experts' assessments of the venographies. Experts were not informed of the treatment allocated or the conclusions of the radiologist who performed venography.

Presence of pulmonary embolism was clinically assessed by daily physical examinations. This was confirmed by digital or conventional pulmonary angiography only in cases with clinical features suggestive of this diagnosis.

Comment: Details regarding clinical assessment of pulmonary embolism were not provided in the publication.

#### *7.2.1.5. Randomisation and blinding methods*

Patients were randomised to receive either nadroparin (Fraxiparine; Sanofi-Winthrop, Gentilly, France) or matching placebo by subcutaneous injection once daily.

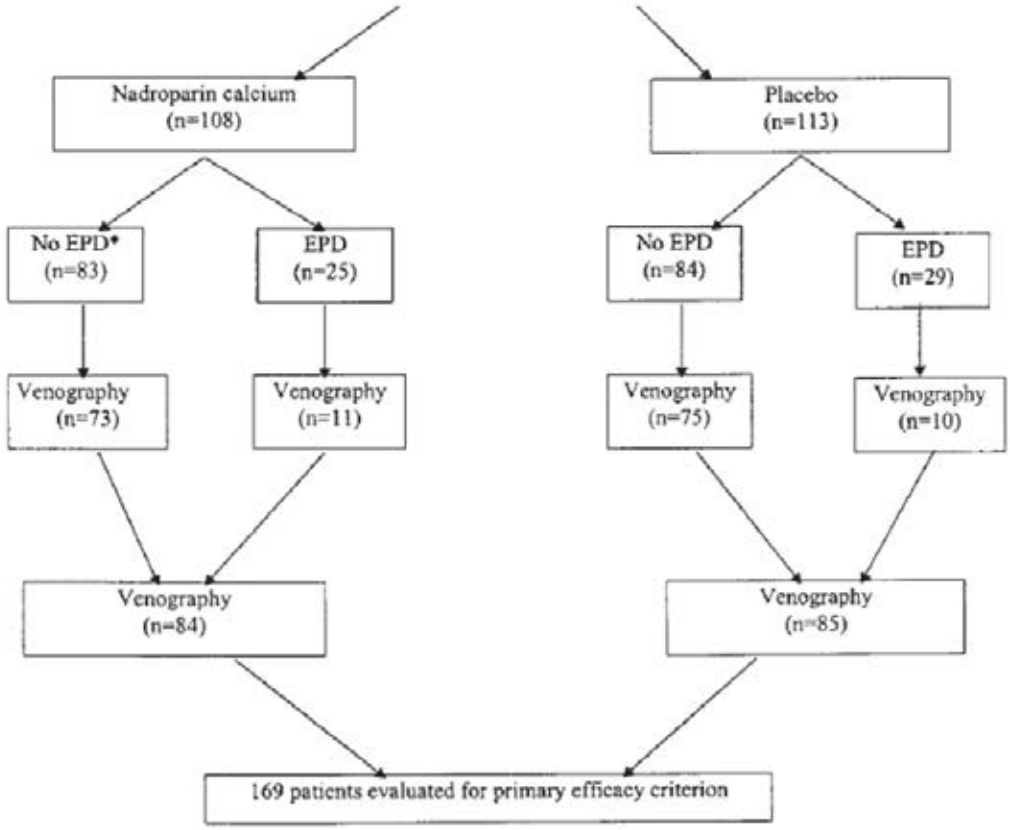
Comments: Details regarding randomisation methods or blinding techniques were not provided in the published study.

#### *7.2.1.6. Analysis populations*

Efficacy was analysed using evaluable patients, i.e., those with a venography, and safety was analysed using an intention-to-treat (ITT) analysis in all patients who received at least one injection.

[2] Examinations, performed by a single operator in each centre using Duplex compression ultrasonography, were bilateral, compared both legs and included systematic study of each venous segment.

**Figure 1: Fraisse, 2000. Patients evaluable for the primary efficacy criterion**




*EPD= Early Permanent Discontinuation

#### *7.2.1.7. Sample size*

Published data suggest that patients with acute, decompensated COPD who received no prophylaxis dose have a potential incidence of symptomatic DVT ranging between 8% and 25% (Rubenstein, 1988; Vesconi, 1988; Winter, 1983; Planes, 1996). With a beta error of 10% and an alpha error of 5%, these estimates may be reduced to 3% and 8%, respectively. Thus, 200 patients were required for each group, although an interim analysis of data was performed to review whether the study should continue after the first 100 patients had been enrolled in each group. As a result, the study was stopped after 223 patients had been enrolled.

#### *7.2.1.8. Statistical methods*

All statistical tests (unpaired, two-sided *t* test for quantitative variables; chi-square test for discrete variables or Fisher's exact test when conditions for using a chi-square test were not met; and Mann-Whitney nonparametric U test for ordinal variables) were two-tailed, with an alpha error of 5%.

#### *7.2.1.9. Participant flow*

All 223 enrolled patients were randomised, but two (one in each group) did not receive any treatment, giving 221 treated patients. In the nadroparin group, 56% and 44% of patients received 0.4 mL and 0.6 mL, respectively compared to 64% and 36%, respectively in the placebo group. There was no significant difference in the number of patients with an early permanent discontinuation of therapy in the two groups (nadroparin vs placebo: 23.2% vs 25.7%). The decrease in sample size over time was similar in both groups. However, patients receiving nadroparin were less likely to discontinue treatment because of DVT than were those

receiving placebo (12% vs 37.9%, p = 0.06). Although incidence of discontinuations due to thrombocytopenia, death and other causes was slightly higher in the nadroparin group, the difference from placebo was not statistically significant.

#### *7.2.1.10. Major protocol violations/deviations*

Of the 221 treated patients, 52 (23.5%) were not assessed by venography, thus giving 169 patients (nadroparin, n = 84; placebo, n = 85) who were evaluable for the assessment of efficacy. The reason for the lack of assessment in 52 patients (24 vs 28) was similar in both groups and included: technical difficulty, contrast media hypersensitivity, septic shock, cardiogenic shock, congestive heart failure, arrhythmia, thrombocytopenia, bleeding, acute renal failure, patient refusal and premature weaning of mechanical ventilation.

#### *7.2.1.11. Baseline data*

Both groups were comparable for all demographic and clinical characteristics, except for age; patients receiving nadroparin were significantly (p = 0.02) older that those receiving placebo. These relatively elderly patients, with a history of COPD for an average of 10 years, presented with serious risk factors for DVT such as immobilisation (100%), respiratory disease (100%), bronchial superinfection (74%), congestive heart failure (29%), age > 65 year (50%), obesity (23%), venous insufficiency (13%), neoplastic disease (5%) and previous thromboembolic disorders (4%). Risk factors for venous thromboembolism were also similar in both groups, as were all laboratory parameters measured at inclusion. Mean duration of therapy was 11.9 ± 6.0 (SD) and 11.4 ± 6.0 (SD) days in nadroparin and placebo groups, respectively.

#### *7.2.1.12. Results for the primary efficacy outcome*

There was a lower incidence of total DVT in patients receiving nadroparin (15.5%, 13/84) than in those receiving placebo (28.2%, 24/85) and the difference between treatment groups approached statistical significance (p = 0.045). However, interpretation was limited by lack of data on odds ratios or 95% CIs. Proximal DVT (including extended DVT with both proximal and distal localisations) occurred in three patients in the nadroparin group versus seven patients in the placebo group suggesting a trend in favour of nadroparin although difference from placebo was not statistically significant due to small number of events. This trend was reinforced by the fact that there was one (one of three) versus six (six of seven) patients with extended proximal DVT in the nadroparin and the placebo groups, respectively.

**Table 2: Primary efficacy criterion (DVT diagnosed by venography)**

| | Nadoparin (*n* = 84) | Placebo (*n* = 85) | p Value |
|---|---|---|---|
| DVT | | | |
| Present, n (%) | 13 (15.5) | 24 (28.2) | 0.045 |
| Absent, n (%) | 71 (84.5) | 61 (71.8) | 0.045 |
| Localizations | | | |
| Proximal, n* | 3 | 7 | 1.00 |
| Distal only, n | 10 | 17 | > 0.05 |
| Segmental localization | | | |
| Subpopliteal, n | 11 | 23 | |
| Popliteal, n | 1 | 5 | |
| Superficial femoral, n | 1 | 4 | |
| Deep femoral, n | 2 | 2 | |
| External iliac, n | 0† | 1 | |
| Common iliac, n | 0† | 0† | |
| Inferior vena cava, n | 0† | 0† | |

For definition of abbreviations, *see* Table 1.

* Some of these patients had an extended thrombus to proximal + distal localizations. This was the case for one patient in the nadroparin group (one of three) and six patients in the placebo group (six of seven).

† One missing data.

#### *7.2.1.13. Results for other efficacy outcomes*

Only one patient in the nadroparin group presented with clinical features of suspected PE during the trial, although both venography and pulmonary angiography were normal in this patient. Another patient receiving nadroparin presented with acute respiratory insufficiency, followed by cardiovascular failure and died 48 h after the scheduled completion of the trial. Although PE was suspected in this patient it was not confirmed as neither pulmonary angiography nor autopsy was performed.

Mortality rate was high in this study (27-32%) which was not unexpected considering the serious condition of these patients, but number of deaths was similar in the nadroparin (8/108, 32%) and placebo (8/113, 27.6%) groups. Furthermore, all patients had daily clinical check-ups and weekly Doppler examinations and any diagnosed DVT was immediately treated by curative dosage of heparin which may probably account for the very low rate of symptomatic pulmonary embolism observed in the study.

#### *7.2.1.14. Evaluator commentary*

Although there are no precise data on the prevalence of thromboembolic disease in patients hospitalised for pulmonary disease, it has been estimated at 8% to 25%. There is no consensus regarding the efficacy of thromboembolism prophylaxis in critically ill patients with no clear guidelines as to drug dose and regimen. Hence, a placebo-controlled study design was acceptable to evaluate the therapeutic benefits of the LMWH- nadroparin calcium (Fraxiparine) in patients with acute, decompensated COPD who required mechanical ventilation, using clinical examination and Doppler ultrasonography to detect thromboembolic events.

The study included elderly patients (mean age of 67-69 years) with a history of COPD for an average of 10 years, with serious risk factors for DVT such as immobilization (100%), respiratory disease (100%), bronchial superinfection (74%), congestive heart failure (29%), age> 65 yr (50%), obesity (23%), venous insufficiency (13%) and neoplastic disease (5%). Overall, the study patients were representative of the target patient population and the dose of nadroparin used in this study was similar to the proposed dose. It was not specified if the study

excluded patients with stroke and AMI. However, this study was included in the Alikhan meta-analysis which excluded patients with stroke, AMI and admission to ICU.

Although the study was reasonably well-designed, it did have certain limitations which confounded interpretation of results such as lack of details regarding clinical assessment of pulmonary embolism or of randomisation/blinding methods. Furthermore, 52 (23.5%) of the 221 treated patients were not assessed by venography. However, detailed analysis of patients with uninterpretable venographies did not reveal any significant differences between the two groups with even distribution of reasons why venography was not performed.

Although the diagnosis of DVT with Doppler ultrasonography can be considered as good with 93% specificity and 95% sensitivity, as far as proximal DVTs are concerned, the difficulties encountered in performing the initial examination may have resulted in an underestimate of cases at enrolment. Only one patient was excluded for this reason, which implies a very low incidence of DVT in these potentially high-risk patients, in contrast to the much higher incidence observed during the study. The incidence of total DVT in the nadroparin group was significantly lower than in the placebo group (13 versus 23, $p = 0.045$). The distribution of proximal (3 versus 7, $p = 1.00$) and distal (10 versus 17, $p > 0.05$) thrombi was not statistically different between groups. However, it should be noted that only one patient receiving nadroparin had an extended thrombus, that is, proximal and distal, compared with six patients receiving placebo.

No proven pulmonary embolism was observed during the study although it was not systematically investigated by objective tests. Clinical symptoms for pulmonary embolism are neither specific nor reliable and furthermore, these were not clearly specified in the methods. Pulmonary embolism was thought to have contributed to only one patient's death, but both venography and pulmonary angiography were normal in that patient. In addition, neither pulmonary angiography nor autopsy was routinely performed in patients who died (which include 8 patients in each treatment group).

Overall, despite some limitations, this was a reasonably well-conducted, randomised, double-blind, placebo-controlled study which provided evidence for efficacy of Fraxiparine (nadroparin) in 221 patients with acute, decompensated chronic obstructive pulmonary disease (COPD) requiring mechanical ventilation. Compared with placebo, nadroparin (dose-adjusted to body weight with mean duration of 11 days) showed a 45% reduction in incidence of DVT, which was not associated with a high incidence of serious bleeding or thrombocytopenia. This study provided Level II evidence (NHMRC) and was included in both the Alikhan 2004 and Dooley 2014 meta-analyses.

### 7.2.2. Harenberg (1992, 1996)

Comment: The Harenberg 1992 paper only provides the study protocol and the preliminary results of the trial. The final study results are reported in Harenberg 1996 article. Both these papers have been evaluated and discussed together in the following sections.

#### *7.2.2.1. Study design, objectives, dates and locations:*

The Heparin Study in Internal Medicine (HESIM) compares the efficacy and safety of an unfractionated heparin (UFH) with a low molecular weight heparin (LMWH), specifically CY216D or nadroparin for prevention of proximal DVT and pulmonary embolism (PE) in medical inpatients with a high risk for development of thromboembolism. The main objective of this study was to demonstrate equivalence in the incidence of proximal DVT and PE during 10-day prophylaxis with UFH versus LMWH. Ten centres in Germany took part in this study and it complied with the revised Declaration of Helsinki and the protocol was approved by the ethical committee of Faculty of Clinical Medicine Mannheim, University of Heidelberg.

#### *7.2.2.2. Inclusion and exclusion criteria*

The main inclusion criteria were: age between 50 and 80 years, expected duration of bed rest and hospital stay >10 days, indication for prophylaxis of thromboembolism and informed consent. One or more risk factors for development of thrombosis should be present in patients: obesity, varicosis, chronic venous insufficiency, postthrombotic syndrome, intake of oral contraceptives or oestrogen, thrombocytosis > 450,000/µL or hyperviscosity syndrome (fibrinogen > 500 mg/dL), previous myocardial infarction, thrombotic cerebral infarction or peripheral arterial ischemia.

The main exclusion criteria were: known intolerance towards heparin, thrombocytopenia (< 80,000/µL), hereditary or acquired coagulation disorder, acute DVT, pretreatment with heparin other than study medication, regular intake of medication influencing blood coagulation, indication for treatment with medication with effect on blood coagulation, fibrinolysis or platelets, indication for high dose treatment with heparin, diseases with unfavourable short term prognosis, septicaemia with gram negative bacteria, disseminated intravascular coagulation, known vascular aneurysm, fixed hypertension, severe diabetic microangiopathy history of cerebral bleeding, recent haemorrhage of the gastrointestinal tract, the urogenital tract and other organs, severe renal impairment (creatinine > 3 mg/dL), acute glomerulonephritis, necrotic pancreatitis, severe liver dysfunction (prothrombin time/Quick c 60 %) and/or decompensated hepatic cirrhosis and endocarditis lenta (subacute bacterial endocarditis).

**Comment:** The published study did not specify if all patients were actually bedridden as the inclusion criteria: 'expected duration of bed rest and hospital stay > 10 days' was generalised. The only information regarding actual duration of bed rest mentions that the median duration of bed rest ranged from 0 to 20 days in both treatment groups. Furthermore, it was not clarified if patients with stroke or AMI were excluded from this study.

#### *7.2.2.3. Study treatments*

Patients were randomly assigned to UFH or LMWH treatment group and received either UFH (Calciparine) 5000 IU subcutaneously thrice daily or 3100 IU (anti Xa)/ 0.3 mL LMWH (Fraxiparine) once daily (plus 2 placebo injections containing 0.9% saline) in prefilled syringes.

Comment: The dose of nadroparin used in this study was not weight-based. The reduced dose of 0.3 mL was still acceptable as the patient population enrolled in this study was elderly (with mean age of 70 years and 55% aged 70 to 80 years). However, it is not clear why 0.3 mL of Fraxiparine used in this study had 3100 anti-Xa IU while the proposed PI mentions 0.3 mL as 2850 anti-Xa IU.

In eligible patients, prophylaxis had to be commenced within 12 hours after admission to the hospital. The injection was given three times daily at 8 hours intervals. In the LMWH group the first injection contained nadroparin while the other two injections contained placebo. The first injection was given between 6 and 7 a.m., the second injection between 2 and 3 p.m. and the third injection between 10 and 11 pm.

Treatment of patients with study heparin was to be terminated in the following cases: DVT before or at the end of the treatment period of 10 days, PE before or at the end of the treatment period, haemorrhage which requires therapy and necessitates discontinuation of heparin treatment, thrombocytopenia (< 80,000/µL) and other severe adverse reactions which occurred during the treatment period.

#### *7.2.2.4. Efficacy variables and outcomes*

Patients were examined at days 1, 4, 6, 8 and 10 for clinical symptoms of DVT and PE according to standardised examination protocol (Figure 2). Compression sonography was performed on admission at Day 1, within 24 hours of randomisation as well as between Days 8 and 11 at the

end of the study. The proximal veins (popliteal, femoral and iliac) of the legs were investigated and documented when acute DVT was present. The distal veins were not examined due to low sensitivity of real-time compression sonography in asymptomatic patients. Due to high specificity and sensitivity of compression sonography[3] in detecting proximal DVT, phlebography was performed only in patients with negative or uncertain sonographic results and clinical suspicion of DVT. The sensitivity of the sonographic techniques of the popliteal and femoral veins in asymptomatic patients varies from 80 to 90 % and the specificity from 94 to 100 % (Barnes R, et al, 1990; Borris LC, et al, 1990; Woolson ST, et al, 1990). The sensitivity of the sonography of asymptomatic calf vein thrombosis is only 39 to 43% (Jonbloets, et al, 1992). Due to these limitations, the study investigators decided to adopt the sonographic techniques for screening of DVT in the large scale clinical trial and to restrict statistical evaluations to results obtained upon ultrasound examination of the popliteal and femoral area of the lower limbs. In patients with symptomatic DVT, the sensitivity and specificity of B-mode compression and duplex sonography ranges from 87 to 100% and from 91 to 100%, respectively.

**Figure 2: Harenberg, 1992. Flow chart screening for DVT and PE in the HESIM trial-heparin study in internal medicine**

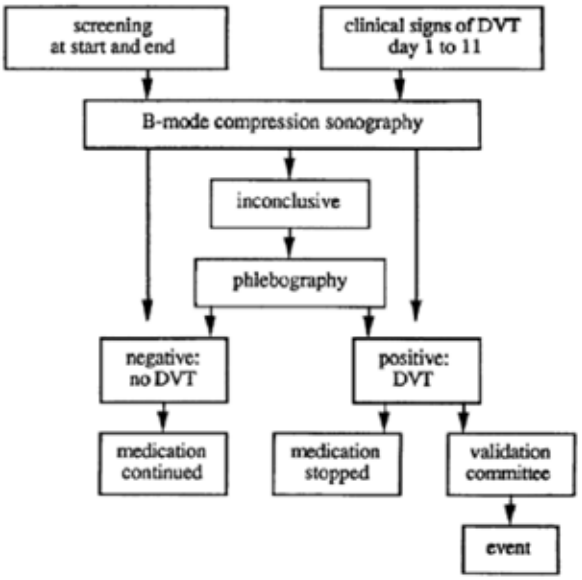



Figure 2: Flow chart of the screening for DVT in the HESIM trial - heparin study in internal medicine

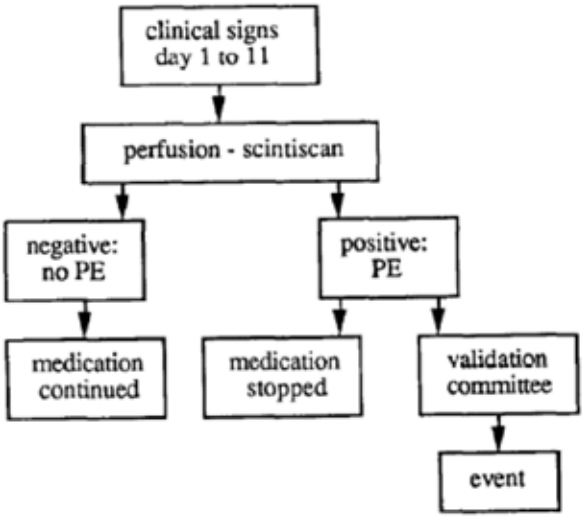



Figure 3: Flow chart of screening for PE in the HESIM trial - heparin study in internal medicine

If PE was clinically suspected, chest radiography, ECG, laboratory tests and perfusion scintigraphy were performed. If the pulmonary scintiscan showed defects with high probability for PE, the patients was treated with high-dose heparin. A ventilation scan or pulmonary angiography had to be performed in case of low-probability defects.

[3] The diagnosis of proximal DVT is made by comparison of the results of the compressibility of the veins using B-mode or duplex sonography at the end of the study (day 8 - 11) with the initial (day 1) findings. Proximal veins are the popliteal, femoral and iliac veins. B-mode compression sonography is performed as described by Habscheid et al (1990). The compressibility of the veins using duplex-sonography is carried out according to Millewich et al (1989). All positive or indecisive sonographic results are documented photographically or by video. Incomplete or complete incompressibility of a vein is considered to prove the presence of venous thrombosis. Phlebography is performed in patients with a negative or inconclusive sonographic result but clinical symptoms suggestive of thromboembolism.

Primary endpoint was the occurrence of symptomatic proximal DVT (of the lower limbs) and/or pulmonary embolism (PE)[4] or asymptomatic proximal DVT detected by compression sonography. The presence of a primary endpoint was screened in all patients using repeated clinical examinations and compression sonography. Only one endpoint per patient is counted for statistical evaluation. Secondary endpoints were venous thrombosis of other locations, arterial embolism, myocardial infarction and death within the study period. The comparison of the treatment efficacy relates to patients with an observation period of 8 to 10 days.

Patients were followed until discharge to assess the incidence of primary and secondary endpoints after termination of study treatment period. The results of the primary endpoints and of positive compression sonography at day 1 were validated by the blinded validation committee. Data on patients who died during the study were analysed by the critical event committee (which was also blinded to treatment received by patient) and the CEC established whether PE or bleeding complications were the cause of death.

**Comment:** The assessment of DVT by sonography was acceptable and complied with CHMP guidelines for 'Clinical investigation of medicinal products for the prophylaxis of venous thromboembolic risk in non-surgical patients.' (2006).

#### *7.2.2.5. Randomisation and blinding methods*

The study protocol included stratified randomisation of patients on admission to the hospital according to one of the following subgroups: malignant disease, cardiovascular disease, bronchopulmonary disease, neurologic disease, or other diseases.

**Comment:** Details regarding randomisation methods or blinding techniques were not provided in the published study.

#### *7.2.2.6. Sample size*

Since general screening of all patients by perfusion lung scanning is not feasible, the estimated combined rate of occurrence of DVT and PE was set at 4 % for a clinical trial in medical inpatients on prophylaxis of thromboembolism with low dose heparin. Pn and Ps are probabilities of thromboembolic endpoints with the new and the standard treatment, respectively. After about 800 patients had been included in the trial, a global incidence for thromboembolic events of approximately 1% was observed. The low incidence of primary endpoints was mainly due to the fact, that an unexpectedly high proportion of about 1.5% of the patients exhibited clinically unapparent DVT upon the initial sonographic examination and had to be excluded from the study. Other reasons for this unexpectedly low incidence could be the lack of an acute event as in operative medicine and the rather short observation period as compared to the long duration of the illness. In order to prove superiority of one treatment with overall incidences as low as those observed, necessary sample sizes would be two to three times as large as those calculated initially. Due to these facts the study committees decided to change the hypothesis of the trial from superiority of the new drug to equivalence of the two treatment groups. With type one error probability a = 0.05 and power 1 - p = 0.80 if actually Pn = Ps, about 1100 patients were necessary for each treatment group.

#### *7.2.2.7. Statistical methods*

The hypothesis of equivalence had to be considered for one interim analysis with about 700 patients per treatment group as well as for the final analysis. The error probabilities for

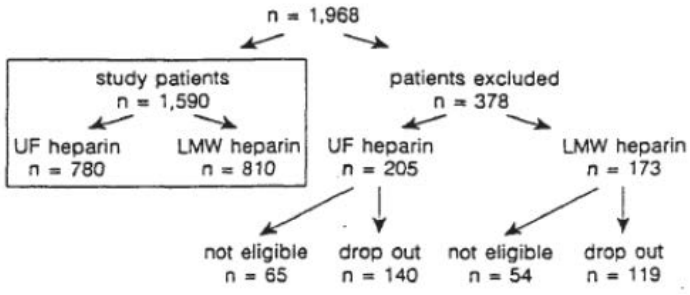
[4] Patients will be examined for clinical symptoms of PE on day 1, 4, 6, 8 and 10. The examination protocol includes the following: tachycardia, dyspnea, tachypnoea of recent onset , cough with or without haemoptysis, signs of arterial hypoxemia in blood gas analysis, chest pain when breathing, rise of body temperature, pleural friction sound or signs of infarction pleuro pneumonia. If pulmonary embolism is clinically suspected, chest radiography, ECG, laboratory tests and perfusion scintiscan are performed. If possible, a ventilation scintiscan is made additionally. Otherwise it is attempted to perform a control perfusion scintiscan. If necessary for diagnosis of pulmonary embolism, pulmonary angiography will be performed in addition to the scintigraphic procedures.

multiple tests were controlled according to Bonferroni's inequality. For analysis of other variables, Fischer's exact test was used and the y2 test for contingency tables and the U test to compare the distributions of continuous parameters.

#### *7.2.2.8. Participant flow*

The study started in May 1990 with 10 trial centres. By the time of the 1992 publication, 1672 patients were included in the trial with an inclusion rate of about 90 patients per month and the drop-out rate was about 15 %. Of the 2915 registered patients, 947 were not randomised, mainly for organisational reasons. A total of 1968 patients were randomised to receive UFH or LMWH heparin. Of these 378 were excluded after randomisation: 119 patients were excluded from the efficacy analysis for one of the following reasons: no initial sonography, initial DVT, contraindication to heparin, no initial thrombocyte count, prothrombin time <60%, creatinine >3.0mg, interfering medication, inclusion criteria not met, age >80 years, thrombocytes <80,000/ul, previous heparin and initial PE. They were distributed similarly in the two treatment groups (p = 0.13); another 259 patients presented one of the following exclusion criteria after randomisation: early discharge, transfer to different ward, AE, no final sonography, informed consent withdrawn, other diseases, late or missing injection, medication error, high heparinisation and late first examination. However, rate of drop-outs from the study was similar in both treatment groups (p-0.76). However, premature termination of prophylaxis was twice as common with UFH compared with LMWH (nadroparin). Hence, 1590 patients were included in the final analysis with 780 receiving UFH and 810 receiving LMWH-nadroparin.

**Figure 3: Description of Study Population**




#### *7.2.2.9. Major protocol violations/deviations*

Data not provided.

#### *7.2.2.10. Baseline data*

The baseline demographics (age, height, body weight and previous bed rest) were similar in both groups. The presence of risk factors was also similar in both groups with exception of gender and varicose veins (more common in females). Based on the validated case reports, 13 % of the patients were stratified to group 1 (malignant disease), 34 % to group 2 (cardiovascular disease), 11 % to group 3 (bronchopulmonary disease), 19 % to group 4 (neurologic disease) and 23 % to group 5 (other diseases). The stratification of the patients in groups of cardiovascular (n = 516), neurologic (n = 319), malignant (n = 189), bronchopulmonary (n = 175) and other diseases (n = 391) was comparable for both treatments (p = 0.82). Overall, 56% of the patients were female and 44 % male. The mean age of the patients was 70 years (17% were aged from 50 to 60 years, 28 % from 60 to 70 years and 55 % from 70 to 80 years). The distribution of main diagnosis was also similar in both groups. The concomitant medications during the 10-day study period did not show any significant differences between the two treatment groups.

Comment: There was no table summarising the concomitant medications taken during the 10-day study period.

#### *7.2.2.11. Results for the primary efficacy outcome*

The interim analysis was performed on 710 evaluable patients treated with UFH and 726 treated with LMWH (nadroparin). The primary endpoint was observed in 4 and 6 patients during prophylaxis with UFH and LMWH, respectively. Hence, equivalence of the 2 treatments was proven (p = 0.012) and the trial was terminated after the interim analysis. The ITT analysis showed equivalence of the efficacy of both treatments with an upper confidence limit of 0.012.

Comment: The 95% CI were not provided in the published paper.

The incidence of thromboembolism in the stratification groups were as follows: Cardiovascular: 4/516 (0.78%), malignant: 2/189 (1.06%), neurologic: 1/319 (0.31%), pulmonary: 1/175 (0.57%) and other diseases: 2/391 (0.51%). Differences between the incidences in the stratification groups were not verified (p = 0.86).

Primary endpoints in the UFH group occurred once at day 7 (PE), twice at day 9 (PE) and once at day 10 (DVT). During treatment with LMWH-nadroparin, thromboembolism occurred once at day 3 (PE), once at day 8 (DVT) and twice at day 10 (DVT and PE).

Overall 6 endpoints were observed in females and 4 in male patients. In 2 ineligible patients with increased serum creatinine, venous thrombosis occurred at day 10; these patients were randomised to LMWH, but received low dose heparin from day 2 due to presence of exclusion criteria.

#### *7.2.2.12. Results for other efficacy outcomes*

There was no relation between the incidence of thromboembolism and risk factors of age, height, body weight, sex, previous bed rest and smoking. However, histories of DVT (p = 0.092) and PE (p = 0.015) were more frequent in patients with thromboembolic event during the study. Other risk factors did not appear to be related to the incidence of thromboembolism.

The probability of PE or haemorrhage as the cause of death was evaluated by the blinded CEC. One definite PE was a primary endpoint. A probable presence of PE was assumed in 6 patients (3 in each group). The presence of PE as cause of death was classified as possible (n = 16), unlikely (n = 3) and excluded (n = 6) in the other study patients. Haemorrhage as the cause of death was regarded as unlikely or excluded by the CEC in all patients.

The incidence of deaths was significantly higher in the nadroparin group (n = 23) compared to the UFH group (n = 9) (p = 0.02); pneumonia, stroke and cardiac insufficiency as clinical causes of death were more common in the LMWH (nadroparin) treatment group. There was a difference in number of deaths at centres depending on whether or not primary endpoints were observed as the primary endpoints were only observed in 4 of the 10 centres. At the centres where primary endpoints were observed, 13 of 935 patients died compared to 19 of 635 patients at centres without primary endpoint observation. It is important to note that no differences were observed between treatment groups at centres with primary endpoints (UFH vs LMWH: 1.09% vs 1.6%, p = 0.6). In contrast, the incidence of death was 3.5 fold higher in the LMWH group at centres without endpoint observation (1.25% vs 4.49%, p = 0.02). There were no changes in the occurrence of deaths during study period at centres with primary endpoint observation. At the other centres, 10/19 patients died within first 2 days of the study period. This may suggest that patients who died had underlying general disease with a worse prognosis compared to patients who did not die during the study.

Other secondary thrombotic events did not occur and only 1 myocardial infarction was diagnosed in each heparin group. After the end of the study, 661 patients were observed until discharge and the mean observation period was 8 days for the UFH group and 7.5 days for the LMWH group. One patient developed a primary endpoint at day 2 and another at day 10 after the end of the study period (both occurred while receiving prophylactic treatment of thromboembolism with UFH).

#### *7.2.2.13. Evaluator commentary*

This was a randomised, active-controlled study in 1590 elderly patients with high risk of thromboembolism. Placebo control was not acceptable as low dose heparin is routinely administered in these patients with high risk of thromboembolism. The study design assumed a 1% incidence of proximal DVT by sonography compared to the 4% incidence of DVT (proximal and distal) when detected by fibrinogen uptake test in a similar study population (Dahan et al, 1986). The low incidence of DVT in this study may be attributed to the low sensitivity of compression sonography in asymptomatic compared to symptomatic patients, a fact which was not known during the planning of the actual study (Wells, et al, 1995).

This study demonstrated equivalence of LMWH- nadroparin and UFH for prophylaxis of thromboembolism in hospitalised, bedridden patients with medical diseases. The incidence of primary endpoint of DVT or PE was about 1% in both treatment groups. The main advantage of nadroparin over UFH was the equal efficacy with only one daily SC injection and a lower incidence of AEs.

Female gender, excess weight, prolonged bed rest, cardiac insufficiency, MI, embolic or haemorrhagic stroke, malignancy, pulmonary or intestinal infection, thrombocytosis and hyperviscosity syndrome are established risk factors for development of thromboembolic complications (Wyshock, 1988; Coon, , 1976). However, analysis of these risk factors in this study demonstrated that only history of DVT and PE significantly contributed to the incidence of thromboembolic complications in hospitalised, medical patients. This may have been due to low number of events in this study and also the long course of malignant, CV or inflammatory diseases. However, this could also be interpreted as the study population not truly reflective of the target patient population of medical patients bedridden due to **acute** medical illness.

The authors conclude that this randomised, double-blind, comparative non-inferiority study demonstrates that once daily subcutaneous LMWH (nadroparin) is as effective as administering UFH three times a day for the prophylaxis of thromboembolic diseases in bedridden hospitalised medical patients (Level II NHMRC evidence). This study was also included in Dooley 2014 meta-analysis.

However, interpretation of results from this pivotal non-inferiority study was limited by the following factors:

- The published study did not specify if all patients were actually bedridden as the inclusion criteria: 'expected duration of bed rest and hospital stay ≥ 10 days' was too generalised. The only information regarding actual duration of bed rest mentions that the median duration of bed rest ranged from 0-20 days in both treatment groups. Furthermore, details regarding patient care such as early mobilisation and physiotherapy were not provided or considered in the analysis and may limit interpretation.
- Low incidence of primary endpoint (proximal DVT/PE) and lack of 95% CIs for the primary efficacy results. The authors state that in contrast to development of postoperative thromboembolism, where surgical intervention triggers the thrombotic complications, thrombosis may develop slowly in medical diseases such as CV, malignancy or inflammatory and may have been initiated before admission to hospital. This assumption may be supported by detection of 21 asymptomatic patients with recent DVT by compression sonography at entry into study. However, this only highlights the fact that the patient population in this pivotal study was not well-defined and may not reflect the target patient population of medical patients bedridden due to **acute** illness.
- Furthermore, it was not clear if patients with stroke and acute myocardial infarction were excluded- this is important as the need for thromboprophylaxis differs in these patients and needs to be evaluated separately.

- Dose of nadroparin used in this study was not weight based. There was some discrepancy in the anti-Xa activity of the same 0.3 mL dose of Fraxiparine used in this study and that proposed in the PI provided in this submission.
- Details regarding randomisation/ blinding methods not provided; furthermore, details regarding concomitant medications taken during the study were also not provided.

## 7.3. Other efficacy studies

### 7.3.1. Luba, 2007

Study design, objectives: This was a randomised, open-label study in 300 medical inpatients hospitalised for acute illnesses. The objective of this study was to evaluate the efficacy and safety of two models of thromboprophylaxis with nadroparin in medical inpatients hospitalised for acute illnesses in the hospital in Rabka-Zdroj (Poland).

Inclusion/exclusion criteria: The main inclusion criteria were: age >40 years; hospitalization period of at least 6 days; immobilization period of 3-14 days (an immobilised patient was defined as one who due to his disorder is unable to independently take a few steps); the absence of clinical (lower leg or lower extremity oedema, lower extremity pain) or ultrasound (positive ultrasound compression test result) symptoms of lower extremity DVT.

The exclusion criteria were: an immobilizing disease in the past 6 months; currently ongoing anticoagulant therapy (apart from acetylsalicylic acid); contraindications to LMWH (haemorrhage high risk or previously found allergy to this medication); cancer;[5] mental disorders; alcoholism.

Study methods: The study was conducted in 2 stages: stage 1: from the day of admittance until the completion of prophylactic treatment with nadroparin, stage 2: 90 days from the completion of prophylactic treatment with nadroparin. In stage 1 the patients were randomised in one of the two groups (I, II) in a 1:1 ratio. Nadroparin (Fraxiparine GlaxoSmith-Kline) prophylactic treatment was administered following the manufacturer's instructions, according to their body mass: patients under 70 kg received 0.4 mL of nadroparin daily (that is 3800 I.U.), patients >70 kg – 0.6 mL of nadroparin daily (that is 5700 I.U.). The dosage was chosen according to the Fraisse et al. study. In group I nadroparin prophylactic treatment was administered only during patient immobilization, in group II during immobilization and for following 10 days.

During nadroparin administration patients were observed for any possible complications due to its administration, such as bleeding or allergic reactions. During hospitalization the complete blood count with platelet count was calculated at least twice (at 3–5 days intervals), for possible thrombocytopenia. Haemorrhagic ecchymosis in medication injection areas were not considered a complication due to their very frequent occurrence in patients receiving heparin.

Study endpoints (efficacy and safety variables): Lower extremity DVT confirmed by a four point ultrasound compression test, upon completion of prophylactic treatment or during a 3-month follow-up, or death regardless of its reason, was considered end points. Adverse effects of nadroparin, especially haemorrhagic complications were assessed.

For confirmation or exclusion of DVT an ultrasound compression test in four points was performed three times in each patient: on the day of admission, upon completion of prophylactic treatment and upon completion of a 3-month follow-up. During stage 2 of the study patients were assessed for any potential venous thromboembolism symptoms.[6] Patients

[5] Cancer patients were excluded mainly due to being followed up in specialist centres which made permanent control impossible. The number of studied population being limited, the completeness of observation played a major role for the power of analysis.

[6] Upon discharge each patient received printed information about such venous thromboembolism symptoms as: 1) lower extremity oedema, 2) pain or erythema of a lower extremity, 3) syncope, 4) sudden heart throbbing sensation,

who had no alarming symptoms during observation, underwent an assessment in 90 (±10) days. Patients' data was collected by means of a questionnaire[7] based on patients' history and the performed examination.

Statistical analysis: The collected data on incidence of thromboembolic events was summarised and descriptive statistics - statistical mean and standard deviation (SD) were derived. For qualitative variables, the number and percentage of patients in each group were obtained. Shapiro and Wilk test was employed to check if the data distribution was normal. The comparison of the two groups was done with the use of the Student's t test and if the data distribution was not normal with the Mann and Whitney test. The correlation analysis was performed for the assessment of relations between variables. In all analyses, the results for which test probability value p was lower than the assumed relevance level ($p < 0.05$), were considered significant.

Patient disposition, Baseline characteristics: In 2 years, 300 patients including 145 females (48.4%) and 155 males (51.6%) were enrolled. The majority of patients were over 70 years of age (62.7%). The mean age was 64.3 (±3.5) and 69.2 (±4.5) years for females and males, respectively. The identification of the thromboembolism risk factors was based on the following sources: the MEDENOX (Samana, 1999), the PROTECT study (PROphylaxis of Thromboembolic Events by Cetroparin Trial) (Diner, 2006) and Cohen's collective analysis (Cohen, 2006). The most frequent thromboembolism risk factors in the presented study were: the age over 70 and heart failure. Both groups did not differ with regard to demographic characteristics or reasons for immobilisation. It is important to note that the main reasons for immobilisation were severe respiratory diseases (55%), heart failure (24.3%) and ischaemic stroke (12.3%). The duration of immobilization was 3-11days (mean 4.8 and 5.1 days in Group I and II, respectively). The most common thrombotic risk factors were age > 70 years (62.7%), heart failure (51.3%), cigarette smoking (10% and obesity (9%). The average number of risk factors was similar in both groups (1.43 and 1.44 in Groups I and II, respectively). Among thrombotic risk factors, patients in Group I had a statistically significantly higher incidence of cigarette smoking (14% vs 6%, $p = 0.02$) and dehydration (4.67% vs 0.67%, $p = 0.03$). The mean duration of nadroparin thromboprophylaxis in group I was 5.1 days, in group II 14.5 days ($p = 0.03$). During prophylactic treatment no patient dropped out of the study and there were no deaths.

Comment: The paper provided in the submission mentions the following: "The immobilization duration was 37 days (mean 4.8 days; in group I – 5.1 days and in group II – 4.5 days)." However, there appears to be a typographical error as table mentions duration of immobilisation was 3-11 days with mean of 4.8 days (group I=5.1 days and group II=4.5 days). Clarification is sought from the sponsors regarding this.

Efficacy results: During the follow-up of 3 months' duration, the end points (DVT or death) occurred in 17 (5.6%) of all 300 patients. This group did not differ from the other patients regarding demographics and the reason for hospitalization. Two sudden deaths were observed on day 30 and 52 after completion of prophylactic treatment (cause of death was not verified at autopsy) and 15 (5%) cases of documented proximal lower extremity deep vein thrombosis (positive result of ultrasound compression test). The incidence of end points in the group of shorter prophylactic treatment period was slightly higher (8%, 12 persons) compared to longer duration prophylaxis group (3.3%, 5 persons). There were 2 deaths (1.3%) observed in the shorter duration prophylactic treatment group. Of 17 patients with demonstrated end points,

5) sudden dyspnoea or chest pain, 6) sudden unexplained arterial blood pressure drop. In the event of occurrence of any of the above mentioned symptoms, the patient was to immediately present at the hospital or to call the physician conducting the study.

[7] Such information as: age, sex, the reason for and duration of immobilization, the duration of nadroparin administration, the thromboembolism risk factors, the risk for thromboembolism, the ultrasound compression test results and venous thromboembolism symptoms found, as well as anticoagulant treatment complication symptoms, was included in the questionnaire.

the prophylactic treatment time matched the immobilization time in 12 and in 5 patients it lasted 10 days longer.

The mean age of patients with ultrasound proximal DVT symptoms was 71 years and 9 of them were females (52.9%). In 10 patients (66.6%) the period of nadroparin administration equalled the immobilization time (group I), in the remaining 5 patients it lasted 10 days longer (group II). Patients in whom DVT occurred despite the extended period of prophylactic treatment were in the high venous thromboembolism risk group. The mean number of risk factors in this group was 3.4 (mainly elderly age, heart insufficiency, obesity and cigarette smoking) compared to 2.3 in the short duration prophylactic treatment group. In individuals with a positive end point (n = 17). The most frequent reason for immobilization was a severe respiratory disease (52.9%). The immobilization time in the confirmed deep vein thromboembolism group (n = 15) was 8 days on the average and was nearly twice as long as the mean immobilization time in the rest of the patients. The most frequent venous thromboembolism risk factor in these 15 patients was heart insufficiency found in 13 patients (86.6%).

Elderly age is an important venous thromboembolism risk factor, so patient population evaluated in this study was appropriate with enrolment of patients over 40 years (mean age was 64-69 years); this was similar to the MEDENOX study, PROTECT study and Cohen collective analysis. The percentage of patients in whom venous thrombosis occurred despite the prophylactic treatment was comparable throughout all the quoted studies. In this study, 3800 - 5700 I.U. dose of nadroparin was used (which is similar to the proposed dose) and the percentage of venous thrombosis found in patients despite the administered prophylactic treatment was 5.8%. This result was very close to the one obtained in the Cohen [2006] collective analysis in which the administration of a 2.5 mg fondaparinux prophylactic treatment correlated with documented venous thrombosis in 5.6% of patients.

Inpatients with cerebral ischaemic stroke are at an especially high risk of venous thrombosis due to lower extremity paresis and, pulmonary embolism is often a cause of death (Kampheusein, 2006; Kelly, 2004) in these patients. It has been estimated that the incidence of venous thromboembolism in these patients ranges from 30 to 75% and mortality for pulmonary embolism is 1-2% (Hillborn, 2002). This study also evaluated 37 inpatients with cerebral ischemic stroke (12.3% of study population) and symptoms of the venous thromboembolism occurred in 3 patients (8.1%) despite prophylactic treatment with nadroparin. These results were similar to those observed in the PROTECT study (Diener, 2006) in which the symptoms of venous thromboembolism occurred in 7% and 9.7% of the patients treated with LMWH (certoparin) and standard heparin, respectively.

Overall results from this open-label study confirmed the safety and efficacy of thromboprophylaxis with nadroparin in medical patients hospitalised for acute illness. The proposed dose of nadroparin was used in this study. A tendency for a reduced occurrence of endpoints in patients receiving LMWH for longer than only during immobilisation, was also observed. However, larger, controlled medical inpatient studies need to be conducted in order to assess if prophylactic treatment prolongation beyond the immobilization time will result in larger clinical benefits than prophylaxis limited to the immobilization time.

#### 7.3.2. Pottier, 2000

This was an open-label, epidemiological study to evaluate, in mixed medical settings, a preventive scheme including the rationalization (streamlining) of risk factors and the use of low molecular weight heparin. The study was conducted over 2 years in patients hospitalised between 1 November 1995 to 31 October 1997 in five medical departments at Nantes University Hospital (France) treating acute patients. This study had two main aims: to create streamlined groupings of indications for prevention in a variety of medical environments and to assess the clinical incidence of MTE. This rationalization involved analysing FDR in terms of their thrombogenicity and their stability (temporary or permanent).

All patients were included, except those who: 1) were expected to stay for fewer than 3 days, 2) had recently had surgery (within one month), 3) were receiving anticoagulant treatment on admission, 4) received different preventative measures to those outlined below. One of three levels of risk (high, intermediate and low) was assigned based on the risk factors encountered. Among the permanent FDR which are most often observed in medical settings are age, chronic loss of mobility or venous insufficiency. The most common temporary factors are being bed bound and acute inflammation.

Patients with a high or intermediate risk level were eligible for prophylactic treatment, a fixed dose of Nadroparin 0.3 mL per day (3075IU).

Comment: The dose of nadroparin used in this open-label, epidemiological study was not weight-based. The dose used in this epidemiological study is only recommended in the elderly, but this study included patients > 18 years. Furthermore, it is important to note that 0.3 mL of Nadroparin used in this study had 3075 anti Xa while the proposed PI mentions 0.3 mL as 2850 anti Xa. Clarification regarding this has been sought.

The primary endpoint was the occurrence, during hospital stay, of a deep or superficial venous thrombosis of the lower limbs, a pulmonary embolism or unexplained sudden death. Diagnostic confirmation was required in each case using Doppler sonography of lower limbs and/or ventilation-perfusion lung scanning. Phlebography and/or pulmonary angiography were carried out if the non-invasive examinations outlined above were inconclusive. All requests for additional examinations for clinical suspicion of MTE (major thromboembolic event) were centralised and recorded by a single vascular function testing department. These examinations were conducted "blind" with regards to whether the patient was at risk or being treated.

Incidence and risk factors for thromboembolisms were evaluated for three groups: 1) patients receiving preventive treatment, 2) patients not receiving preventative treatment as they did not meet the criteria, 3) patients where prevention was overlooked. Prescriber compliance with the study methodology was checked by a daily sampling of 5 patients.

The number of in-patient admissions during the study was 24,497. Amongst the 24,497 patients admitted, 13,963[8] did not meet the criteria for inclusion. Of the remaining 10,534 patients, 1,264 (12%) had no FDR (risk factors), - 412 (4%) received other preventative treatment and were excluded, - 3,730 (35.4%) were considered high risk or intermediate risk and treated in accordance with the study criteria, 3,602 (34.2%) were considered to be at low risk and not treated in accordance with the criteria of the study, 1,022 (9.7%) were considered high risk or intermediate risk and not treated, in contravention of the study criteria, 495 (4.7%) were considered high risk or intermediate risk and not treated due to contraindications.

Overall, 53 clinical thromboembolic events were reported. The incidence of venous thromboembolisms was:

- 0.75% (28 thromboembolisms for 3,730 patients) in the group treated with Nadroparin,
- 1.7% (18 thromboembolisms for 1,022 patients) in the group "prevention overlooked",
- 0.14% (5 thromboembolisms for 3,602 patients) in the untreated low risk group,
- 0.4% (2 thromboembolisms for 495 patients) in the group with contraindications,
- Less than 0.08% (no thromboembolisms for 1,264 patients) in the group with no FDR.

[8] 3,429 (14%) were receiving anticoagulant treatment when admitted, 9,554 (39%) stayed for less than 3 days, 980 (4%) had had an operation in the previous month.

No significant difference was detected regarding the multiplicity of FDR encountered in each group. A comparison of the different types of FDR observed across the groups with or without thrombosis, treated or untreated, shows the following significant differences:

- unexplained previous history of MTE was more frequent in patients who had thrombosis whilst on Nadroparin;
- C reactive protein (CRP) was higher in patients who had thrombosis whilst on Nadroparin. Further studies would be required to evaluate thrombophilia and inflammatory processes as possible explanations of failures of Nadroparin.

Only five patients[9] presented with a deep vein thrombosis when no preventative treatment was justified by the criteria of the study.

This study suggests that Nadroparin is effective in preventing MTE in a variety of acute medical in-patient environments because the thromboembolic risk was significantly reduced by 55% (0.75% in the treated group *versus* 1.7% in the "prevention overlooked" group). This efficacy does not seem to depend on weight or the number of FDR observed. The treated and 'prevention overlooked' patient populations were comparable in terms of frequency and accumulation of FDR. The incidence of MTE with Nadroparin (0.75%) is close to those reported in the literature studies with the same methodological criteria (large study, clinical assessment). Incidence in the low risk, no prevention group (0.14%) was very low, suggesting that isolated non-major temporary FDR or combined with other non-major temporary FDR but not linked to a permanent FDR are of low clinical significance. The authors conclude that their study confirms that a rigorous analysis of FDR in terms of pathogenicity allows a population exposed to a risk of 1.7% of thromboembolic complications to be isolated. For these patients, prescribing LMWH-nadroparin may be useful due to the 55% reduction in risk it brings.

#### 7.3.3. Evaluator commentary: other efficacy studies

Luba (2007) reported a randomised, open-label study in 300 patients (aged >40 years) hospitalised with acute medical illnesses During a further 3-month follow-up of all the 300 patients, death of unknown causes or deep-vein thrombosis were found in 17 (5.6%) patients, including 2 patients who suddenly died. No such events were observed during the thromboprophylaxis period. In medical patients receiving thromboprophylaxis for a longer period of time than the immobilization there was a tendency to lower occurrence of death and deep-vein thrombosis within the first months following hospitalization (12 *vs* 5; p = 0.08). There were no major bleedings or thrombocytopenia in both groups during thromboprophylaxis and the subsequent follow-up. Despite certain limitations, this study confirmed the effectiveness and safety of thromboprophylaxis with nadroparin in acutely ill medical inpatients; results also, suggested additional benefits from prolonged use of low molecular-weight heparins observed during the first months after hospitalization, although this will require confirmation in larger, controlled studies.

Pottier (2000) was an open-label, epidemiological study which showed that a rigorous analysis of FDR in terms of pathogenicity allows a population exposed to a risk of 1.7% of thromboembolic complications to be isolated and that thromboprophylactic treatment with nadroparin results in a 55% reduction in risk of DVT. Overall, this study only provided supportive evidence for use of nadroparin for proposed indication. All patients in this study were not bedridden and results from this study suggest that the clinical significance of being bed bound as an isolated FDR or in combination with others is unknown. Furthermore, the authors suggest that the physical therapy care (mobilisation, elastic compression) to at-risk

[9] Their FDR were as follows:1) two temporary FDR: young bed bound subject with dehydration (acute pancreatitis), 2) 1 temporary FDR: young bed bound subject, 3) 2 permanent FDR: venous insufficiency in an older patient, 4) 1 temporary FDR: young bed bound subject (38 years), mg per day of Enoxaparin and 5) 2 temporary FDR: young bed-bound subject with acute inflammation (CRP > 100mg/l).

patients would enable a reduction of a further 70% in the number of patients given anticoagulant treatment. However, role of physical therapy care was not considered in the evaluation of efficacy of nadroparin in any of the pivotal RCTs and meta-analysis in this submission

## 7.4. Analyses performed across trials: pooled and meta-analyses

The two systematic analyses submitted in this application both aimed to evaluate the efficacy and safety of LMWHs, including nadroparin, when used as a thromboprophylactic agent in acutely ill medical patients with reduced mobility or bedridden.

### 7.4.1. Alikhan 2014

Objectives, search methods, selection criteria: The aim of this review is to determine the efficacy and safety of heparin (UFH or LMWH) thromboprophylaxis in acutely ill medical patients admitted to hospital, excluding those admitted to hospital with an acute myocardial infarction or stroke (ischaemic or haemorrhagic) or those requiring admission to an intensive care unit.

The types of studies included in this review were:

- Randomised controlled trials comparing UFH with placebo or no treatment
- Randomised controlled trials comparing LMWH with placebo or no treatment
- Randomised controlled trials comparing UFH with LMWH

The participants included in this review were: People over the age of 18 years admitted to hospital with an acute medical illness, such as heart failure, respiratory failure, cancer, acute infection, episode of inflammatory bowel disease, acute rheumatic disorder. Studies that primarily involved cancer patients not in an acute medical setting were excluded, such as receiving chemotherapy in tandem with thromboprophylaxis. Studies involving participants with only myocardial infarction or stroke were excluded because the risk of VTE and the need for thromboprophylaxis differs in this population (Collins 1996 and Geerts 2001).

Data collection and analysis: For this update[10] the Cochrane Peripheral Vascular Diseases Group Trials Search Co-ordinator (TSC) searched the Specialised Register (last searched November 2013) and the Cochrane Central Register of Controlled Trials (CENTRAL) (2013, Issue 10), part of *The Cochrane Library*. The Specialised Register[11] was maintained by the TSC and constructed from weekly electronic searches of MEDLINE, EMBASE, CINAHL and AMED and through hand searching relevant journals. One review author identified possible trials and the trial reports were assessed independently by another review author to confirm eligibility for inclusion in the review.

The primary efficacy outcomes evaluated in the analysis were: asymptomatic or symptomatic DVT of the lower limbs detected by fibrinogen uptake test, ultrasound, venography or plethysmography; symptomatic non-fatal PE detected by ventilation perfusion scan, computed tomography, pulmonary angiography, or confirmed at autopsy. The secondary efficacy outcomes were all-cause mortality, fatal PE and combined clinically symptomatic non-fatal PE and fatal PE. The primary safety outcome was major haemorrhage[12]; the secondary safety outcomes were minor haemorrhage and thrombocytopenia.

[10] In the previous version of this review (2009), authors consulted with colleagues and investigators as well as the manufacturers of the various LMWH preparations to identify unpublished or missed studies. This was not done for the current version

[11] The full list of the databases, journals and conference proceedings which have been searched, as well as the search strategies used are described in the Specialised Register section of the Cochrane Peripheral Vascular Diseases Group module in The Cochrane Library.

[12] As defined by individual authors.

The data was individually extracted by both the review author and all information was recorded on data extraction forms. The methodological quality of included trials was assessed independently by both review authors using the 'Risk of bias'[13] tool from The Cochrane Collaboration. Disagreements were resolved by discussion.

Statistical analysis was performed according to the statistical guidelines for authors recommended by the Cochrane Peripheral Vascular Diseases Group. The studies were divided into two groups and analysed separately:

- heparin (UFH or LMWH) prophylaxis versus placebo or no treatment;
- LMWH versus UFH.

For each of the two groups, data was pooled from each study on DVT, non-fatal PE, fatal PE, combined non-fatal and fatal PE, all-cause mortality, major bleeding, minor bleeding and thrombocytopenia in order to arrive at an overall estimate of efficacy and safety of heparin versus no treatment or placebo and LMWH versus UFH. The results of each trial were summarised on an intention- to-treat basis (including all randomised patients) in 2 x 2 tables for each outcome measurement. Where possible, all randomised participants were included, even if the original trial authors excluded them. The results obtained from different methods were similar (risk ratios, Mantel-Haenzel and odds ratios), therefore the meta-analysis was performed using odds ratios (ORs) with 95% confidence intervals (CIs). A test for heterogeneity examined the null hypothesis that all studies are evaluating the same effect; P values were obtained comparing the test statistic with a $Chi^2$ distribution[14]. To detect reporting bias, funnel plots were constructed for meta-analyses that included at least 10 studies, as funnel plots with less than 10 studies lack the power to distinguish chance from real asymmetry. Heterogeneity test was performed and random-effects model was used if the test was positive but unless otherwise stated the meta-analysis was performed using a fixed effect model. Where data were available, subgroup analysis was performed to evaluate outcomes based on medical diagnosis at hospital admission.

The following Sensitivity analyses were also performed:

- Four studies included in the review had a loss of >20% of the study population between randomisation and evaluation for DVT or PE (CERTAIN 2010; CERTIFY 2010; Fraisse 2000; MEDENOX 1999). Although the majority of the missing participants were accounted for with suitable reasoning, it was still possible these losses could alter the outcome.
- DVT diagnosis using a fibrinogen uptake test and plethysmography is often less accurate than by ultrasound or venography. In order to establish that the meta-analysis results were not dependent on studies using these low-accuracy tests, sensitivity analysis was conducted by removing three studies using a fibrinogen uptake test or plethysmography to detect DVT (Belch 1981; Dahan 1986; EMSG 1996).
- The safety data for the CERTAIN 2010 study was collected after a three month follow-up period, which was different to the other studies that collected the efficacy and safety data during the same study time period. With this additional time allotted for these endpoints it was possible this study unduly altered the meta-analysis, therefore sensitivity analysis was performed by removing this study from the meta-analyses for major and minor bleeding, as

[13] The following domains were assessed: selection bias (random sequence generation, allocation concealment), performance bias (blinding of participants and personnel and blinding of outcome assessment), attrition bias (incomplete outcome data), reporting bias (selective reporting) and other bias. The domains were classified as low risk of bias, high risk of bias, or unclear risk of bias according to the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2011).

[14] To help readers assess the consistency of results of studies in a meta-analysis, RevMan 5 software includes a method ($I^2$ statistic) that describes the percentage of total variation across studies due to heterogeneity rather than by chance. A value of 0% indicates no observed heterogeneity and larger values show increasing heterogeneity.

well as thrombocytopenia. In two studies (Belch 1981; Dahan 1986) major bleeding was not clearly defined and was only described as 'major bleeding'. In order to determine if these studies with inadequate definitions of major bleeding were not having an overt effect on the meta-analysis they were removed in a sensitivity analysis to evaluate the effect.

- Two studies (EMSG 1996; MEDENOX 1999) included a low dosage (20 mg) of the LMWH enoxaparin. For EMSG 1996 this was the only LMWH dosage, but for MEDENOX 1999 there was also a higher dosage of 40 mg. Sensitivity analysis was performed by removing the 20 mg dosages and the effect was evaluated.

Comments: However, results of the sensitivity analysis performed by removing the 20mg enoxaparin dose will not be discussed as these do not provide any information relevant to this nadroparin submission.

Details of included studies, assessment of risk of bias, etc.: This review included 16 studies (45 published articles) with 34,369 participants. Ten of these studies compared heparin prophylaxis with no treatment or placebo (Belch 1981; Bergmann 1996; Dahan 1986; Fraisse 2000; Gallus 1973; Gardlund 1996; Ibarra-Perez 1988; LIFENOX 2011; MEDENOX 1999; PREVENT 2004) and six studies compared LMWH with UFH (CERTAIN 2010; CERTIFY 2010; EMSG 1996; Forette 1995; PRIME 1996; THE-PRINCE 2003). Fifteen of the included studies were written in English and one in French (Forette 1995), but English translation was provided by authors.

Four trials took place in a single centre (Belch 1981; Dahan 1986; Gallus 1973; Ibarra-Perez 1988). Nine trials were European multicentre trials: four in France (Bergmann 1996; EMSG1996; Forette 1995; Fraisse 2000), one in Sweden (Gardlund 1996), three in Germany (CERTAIN 2010; CERTIFY 2010; THE-PRINCE 2003) and one in Germany and Austria (PRIME 1996). One trial was performed in multiple centres across Europe and Canada (MEDENOX 1999) and two trials were truly multi-national, one performed in centres across Europe, North and South America, Canada, North and Southern Africa, Israel, Lebanon and Australia (PREVENT2004) and the other in China, India, Korea, Malaysia, Mexico, Philippines and Tunisia (LIFENOX 2011).

Heparin vs placebo or no treatment: Four trials compared UFH with no treatment (Belch 1981; Gallus 1973; Gardlund 1996; Ibarra-Perez 1988). One study compared UFH 5000 IU twice daily (Gardlund 1996) and the other two studies compared UFH 5000 IU three times daily with no treatment (Belch 1981; Gallus 1973). Six trials compared LMWH with placebo, three trials were with enoxaparin (Dahan 1986; LIFENOX 2011; MEDENOX 1999), two trials with nadroparin (Bergmann 1996; Fraisse 2000) and one trial with dalteparin (PREVENT 2004). One of the enoxaparin trials (MEDENOX 1999) compared two doses (20 mg and 40 mg) of enoxaparin with placebo.

LMWH versus UFH: Six trials compared LMWH with UFH (CERTAIN 2010; CERTIFY 2010; EMSG 1996; Forette 1995; PRIME 1996; THE-PRINCE 2003). Three of these trials compared enoxaparin with UFH (EMSG 1996; PRIME 1996; THE-PRINCE 2003). Two trials compared enoxaparin 40mg once daily with UFH5000 IU three times daily (PRIME 1996; THE-PRINCE 2003); one trial compared enoxaparin 20 mg once daily with UFH 5000 IU twice daily (EMSG 1996). One trial compared nadroparin 3075 anti Xa units once daily with UFH 5000 to 7500 IU three times daily (Forette 1995). One trial compared certoparin 3000 anti Xa units with UFH 5000 IU three times daily (CERTIFY 2010).

Excluded studies: Ten studies were excluded from the original review (Aquino 1990; Cade 1982a; Cade 1982b; Halkin 1982; Harenberg 1990; HESIM; Manciet 1990; Mottier 1993; Poniewierski 1988; PROMPT) and 1 additional study (EXCLAIM) was excluded for this update[15].

[15] In brief, one study did not strictly fit the criteria for a randomised control trial (Halkin 1982), six studies included patients meeting the exclusion criteria of MI (or acute coronary disease), recent surgery, stroke (or cerebrovascular

Efficacy results: Heparin (LMWH and UFH) versus placebo or no treatment:
Deep vein thrombosis (DVT): Data were available for DVT in seven trials[16] and the heparin treatment group had statistically significantly reduced odds of DVT (OR=0.41; 95% CI: 0.25 to 0.67; P = 0.0004). When sensitivity analysis was performed to assess the effects of a loss of > 20% of the study population, there was little effect on the results with an OR of 0.26 (95% CI 0.12 to 0.52; P = 0.0004). There was little effect on the overall outcome with an OR of 0.48 (95% CI: 0.29 to 0.81; P = 0.006) by removing Belch 1981 and Dahan 1986 studies for sensitivity analysis for low-accuracy testing of DVT.

Pulmonary embolism (PE): Symptomatic, non-fatal PE was measured in all seven trials (Belch 1981; Dahan 1986; Fraisse 2000; Gardlund 1996; Ibarra-Perez 1988; MEDENOX 1999; PREVENT 2004) although meta-analysis was only conducted for six, excluding Gardlund 1996 (as non-fatal PE was only assessed through necropsy data and not in all participants). Non-fatal PE had an OR of 0.46 (95% CI: 0.20 to 1.07; P = 0.07). Fatal PE was recorded in six trials (Bergmann 1996; Dahan 1986; Gardlund 1996; LIFENOX 2011; MEDENOX 1999; PREVENT 2004) with an OR of 0.71 (95% CI: 0.43 to 1.15; P = 0.16). Combined non-fatal PE and fatal PE was reported for nine studies (Belch 1981; Bergmann 1996; Dahan 1986; Fraisse 2000; Gardlund 1996; Ibarra-Perez 1988; LIFENOX 2011; MEDENOX 1999; PREVENT 2004) with an OR of 0.66 (95% CI: 0.43 to 1.02; P = 0.06). When the Fraisse 2000 and MEDENOX 1999 studies were removed for sensitivity analysis to assess the effects of a loss of > 20% of the study population, there was little change in results for non-fatal PE (OR 0.55; 95% CI: 0.22 to 1.39; P = 0.20), no change for fatal PE as neither study was contributing and there was no difference between the treatment groups for combined non-fatal and fatal PE (OR 0.68 95% CI 0.44 to 1.07; P = 0.09).

All-cause mortality: All-cause mortality was assessed in eight trials (Bergmann 1996; Dahan 1986; Fraisse 2000; Gardlund 1996; Ibarra-Perez 1988; LIFENOX 2011; MEDENOX 1999; PREVENT 2004) but meta-analysis was only performed for seven, excluding Ibarra-Perez 1988 because not enough information was given to fully understand which treatment groups the deaths occurred in. There was no clear evidence of a difference in mortality between the two treatment groups, with an OR of 0.97 (95% CI: 0.87 to 1.08; P = 0.57).

Heterogeneity and reporting bias: For the comparison between heparin and placebo or no treatment there was little or no heterogeneity between the studies, therefore all meta-analyses, except for the DVT outcome, were conducted using a fixed-effect model. None of the comparisons had 10 or more studies so an assessment for reporting bias by constructing funnel plots could not be performed.

Deep vein thrombosis (DVT): Six studies evaluated DVT (CERTAIN 2010; CERTIFY 2010; EMSG 1996; Forette 1995; PRIME 1996; THE-PRINCE 2003). For the LMWH treatment group there was a statistically significant decreased odds compared to the UFH group (OR 0.77; 95% CI: 0.62 to 0.96; P = 0.02). However, there was no longer any evidence of a difference between the treatment groups (OR 0.80; 95% CI: 0.50 to 1.29; P = 0.37) in the sensitivity analysis to assess the effects of a loss of > 20% of the study population (removal of the CERTAIN 2010 and CERTIFY 2010 studies). There was very little effect on the overall outcome (OR 0.76; 95% CI 0.61 to 0.96; P = 0.02) following removal of EMSG 1996 for sensitivity analysis for both a low-accuracy test for DVT and low dosage of enoxaparin.

Pulmonary embolism (PE): Symptomatic, non-fatal PE was measured in six studies ( CERTAIN 2010; CERTIFY 2010; EMSG 1996; Forette 1995; PRIME 1996; THE-PRINCE 2003). There was

disease) that could not be removed from the analysis (Cade 1982a; Cade 1982b; Harenberg 1990; HESIM; Mottier 1993; PROMPT), two studies included patients receiving orthopaedic rehabilitation (Aquino 1990; Manciet 1990), one study had all participants receiving the study medication before randomisation to continue the medication or move to placebo (EXCLAIM) and one study's method for identifying DVT was not considered sensitive enough (PROMPT).

[16] Belch 1981; Dahan 1986; Fraisse 2000; Gallus 1973; Ibarra-Perez 1988; MEDENOX 1999; PREVENT 2004

no clear evidence of a difference between LMWH and UFH for non-fatal PE (OR 0.93; 95% CI: 0.42 to 2.08; P = 0.86). Fatal PE was measured in only two studies (CERTAIN 2010; CERTIFY 2010) for which there was no difference between the two treatment groups (OR 0.33; 95% CI: 0.01 to 8.13; P = 0.50). Combined non-fatal and fatal PE was evaluated in the same six studies as non-fatal PE, with no evidence of a difference between UFH and LMWH (OR 0.86; 95% CI: 0.39 to 1.90; P = 0.71). When CERTAIN 2010 and CERTIFY 2010 were removed for sensitivity analysis to assess the effects of a loss of >20% of the study population, the nonfatal PE OR was lowered to 0.47, but the association remained non-significant (95% CI 0.13 to 1.68; P = 0.25). As CERTAIN 2010 and CERTIFY 2010 were the only two studies evaluated for fatal PE, this outcome was no longer estimable and the combined non-fatal and fatal PE was identical to non-fatal PE.

All-cause mortality: All-cause mortality was assessed in five studies (CERTIFY 2010; EMSG1996; Forette 1995; PRIME 1996; THE-PRINCE 2003). There was no clear evidence for a difference immortality (OR 0.79; 95% CI: 0.54 to 1.16; P = 0.23).

Subgroup analysis: Subgroup analysis based on medical diagnosis at hospital admission could not be performed as there are currently insufficient data within published studies on outcomes within subgroups of interest.

Heterogeneity and reporting bias: For the comparison between UFH and LMWH there was little or no heterogeneity between the studies, therefore all meta-analyses were conducted using a fixed-effect model. None of the comparisons had 10 or more studies so an assessment for reporting bias by using a funnel plot could not be performed.

Comments: In this meta-analysis, 16 studies were used to compile evidence, 10 comparing heparin (UFH and LMWH) prophylaxis with no treatment or placebo and six which compared LMWH to UFH, with a total of 34,369 participants. For the majority of the outcomes there was general agreement between the studies. Overall quality of the studies was good, although there was risk of performance bias in the studies that were open label, which made up just under half of all the studies. Also, most of the studies were lacking in an explanation of how random sequence generation and allocation concealment were performed, although this is most likely due to the fact that many included studies are older and were not held to as high reporting standards when published.

Heparin (UFH and LMWH) resulted in a reduction in DVT and a borderline statistically significant reduction in combined non-fatal and fatal PE when compared with placebo or no treatment. The reduction in VTE risk is comparable to that previously reported in prophylaxis studies of patients following acute myocardial infarction (Collins 1996), acute ischaemic stroke (Gubitz 2004), colorectal surgery (Wille-Jørgensen 2004) and orthopaedic surgery (Collins 1988). The analysis found no clear difference in all-cause mortality in patients receiving heparin prophylaxis although these studies were not powered to show a difference in mortality, which would require over 200,000 patients (assuming an overall 5% mortality, 10% of deaths due to VTE and a 50% relative risk (RR) reduction in events).

The authors state that results of this meta-analysis demonstrated that patients hospitalised with acute medical illnesses who receive UFH or LMWH thromboprophylaxis have a reduced risk of DVT, however there is an increase in major haemorrhage when compared to those who do not receive heparin thromboprophylaxis. LMWH reduced the odds of DVT compared with UFH as well as reduced the odds of major bleeding, suggesting LMWH has a better efficacy profile and carries a lower risk of adverse events compared with UFH. There are

currently insufficient published data to allow analysis of outcomes of interest based on patient medical diagnosis at hospital admission.

However, the evaluators feel that this meta-analysis provided supportive evidence for use of nadroparin for proposed new indication and do not consider the evidence to be level I (NHMRC) as stated by the sponsors. This is mainly due to the following limitations:

Only 3 individual studies included in the meta-analysis evaluated prophylactic nadroparin, one compared nadroparin to UFH (Forette, 1995) and the others to placebo (Fraisse, 2000; Bergman, 1996).

The meta-analysis did not specify that all studies included only patients who were bedridden. Further, cancer patients in an acute medical setting, patients with AMI and stroke were excluded.

LMWHs are not clinically interchangeable and so the general evidence provided for heparin (UFH and LMWH) and for all LMWHs cannot be extrapolated as evidence for efficacy/ safety of nadroparin for proposed new indication of thromboprophylaxis of medical patients bedridden due to acute medical illness.

### 7.4.2. Dooley 2014

Design, objectives and dates: This was a systematic review and mixed-treatment comparison (MTC) meta-analysis with its primary objective being to compare the efficacy and safety LMWHs for venous thromboembolism (VTE) prophylaxis in hospitalised medically ill patients. The secondary objective was to compare all therapies within the network to each other.

Methods: A systematic literature search was done of MEDLINE and Cochrane Central databases and a manual search was also performed using the references of clinical trials and review articles to identify additional relevant articles. The following main criteria had to be met for an article to be included in the analysis:

- randomised controlled trials of parallel design that evaluate hospitalised medically ill patients and compare VTE prophylaxis with either UFH, LMWH or fondaparinux monotherapy to each other or inactive 'control' (either placebo or no prophylaxis') and report at least one of the following outcomes of interest – deep vein thrombosis (DVT), pulmonary embolism (PE), VTE, mortality, major bleeding and minor bleeding.
- DVT was further inclusive of all DVTs that were objectively confirmed, either symptomatic or asymptomatic. PE was further inclusive of fatal and nonfatal cases. VTE, major bleeding and minor bleeding were extracted using the definition used by the individual trials.
- Trials evaluating the acute stroke population were excluded due to the risk of bleeding being significantly higher in this patient population.
- Trials allowing mechanical prophylaxis were allowed only if mechanical prophylaxis was applied equally to all randomised patients.

The methodological quality of the included trials was assessed by using the Jadad score[17]. All trials were reviewed by two separate investigators and conflicts were resolved through discussion. The following data were collected from each trial: author identification, year of publication, funding source, study design characteristics, study population (inclusion and exclusion criteria, geographic location, length of study, duration of patient follow-up), patient baseline characteristics, thromboprophylaxis regimen (name, strength, frequency, dose, route of administration, duration of therapy, mobilization status of the patient, use of concurrent

[17] The Jadad score evaluates trials based on randomization, double blinding and patient withdrawal producing an aggregate score between 0 and 5 (0¼weakest, 5¼strongest). Trials less than 3 are deemed to have lower methodological quality.

medical therapies) and outcomes data (number of events, definitions, period of follow-up and diagnostic tests for confirmation).

Statistical methods: (1) a traditional meta-analysis[18] was conducted for all pairwise comparisons, using a random-effects model and weighted averages were reported as relative risks (RR) with 95% confidence intervals. (2) a MTC meta-analysis was conducted using a Bayesian Markov Chain Monte Carlo framework using WinBUGs version 1.4.3. A random-effects model was fitted and odds ratios (ORs) with associated 95% intervals were calculated. To assess consistency, results were compared between the MTC and the traditional meta- analysis qualitatively. To evaluate model fit, the residual deviance for each outcome was calculated and convergence was evaluated using caterpillar plots.

Characteristics of included studies: A total of 20 trials enrolling 37,284 patients met inclusion criteria. Fourteen trials reported mortality, 11 reported VTE, 13 reported PE, 13 reported DVT, 15 reported major bleeding and 13 reported minor bleeding. Mortality was evaluated at various time points in the trials including during hospitalization up to 1 year. The time at which DVT and PE were measured was more consistent with all trials reporting within the 21–28 day period with the exception of one trial reporting PE at 90 days. Similarly, for the reporting of VTE most trials reported events during hospitalization and up to 21 days although two trials used 90 days. Bleeding events were reported on therapy with exception of two trials which measured bleeding events at 60 and 90 days.

Comment: However, only 4 of these trials involved nadroparin and compared nadroparin to placebo (Fraisse, 2000 and Mahe, 2000) or to UFH (Harenberg, 1996; Forette, 1995). It is important to note that the Mahe study is not relevant to this submission as it involved a very high dose of nadroparin and only enrolled patients hospitalised and immobilised for <24hrs due to an acute medical illness**.**

Patient characteristics: The patient population among the trials generally consisted of hospitalised patients admitted for a variety of different medical conditions such as heart failure or COPD exacerbations, respiratory decompensation requiring mechanical ventilation, infection and recent myocardial infarction. Trials consistently excluded patients with recent or planned surgical interventions, major risk factors for bleeding (i.e. recent major bleed), liver or renal impairment. Patients enrolled were typically immobilised for several days (6–28 days). The majority of the trials enrolled similar proportions of males and females with the exception of Lederle et al., which consisted of over 97% of males. The average age was greater than 60 years and patients averaged weights between 57 and 85.5 kg, although eight trials did not report weight. Majority of the studies were of high methodological quality (14 of the 20 trials had Jadad scores greater than 3), while the other trials were of lower methodological quality (4 trials had a score of 2 and two trials had a score of 1).

Efficacy Results: The primary objective was to evaluate LMWHs compared to each other. It is important to note that the results are based on indirect evidence as no trials directly compared one LMWH to another. Mortality and VTE were compared among all four LMWHs (nadroparin, enoxaparin, dalteparin and certoparin), with no statistically significant differences reported for any comparison. Dalteparin was not included in the network for PE or DVT due to lack of reported outcomes. The odds of PE or DVT did not vary significantly among the three LMWHs evaluated (nadroparin, enoxaparin and certoparin). Major and minor bleeding was evaluated for all four LMWHs with no statistically significant findings. The residual deviance was 22.98 for VTE, 21.88 for PE, 27.75 for mortality, 24.04 for DVT, 25.63 for minor bleeding and 32.14 for major bleeding.

There were no significant findings for the outcomes of mortality and PE. In the evaluation of DVT, there were several significant findings. The odds of DVT was increased with fondaparinux

[18] The traditional meta-analysis was conducted using StatsDirect, version 2.7.8.

compared with enoxaparin (OR=3.86, 95% CI:1.13 to 13.66), placebo compared with enoxaparin (OR=6.21, 95% CI: 2.76 to 14.51), placebo compared with certoparin (OR= 5.86, 95% CI:2.30 to 16.75) and placebo compared with UFH (OR= 4.84, 95% CI: 2.31 to 10.730). Major bleeding was significantly increased with UFH compared with control (OR= 3.40, 95% CI: 0.090 to 0.8800) while no other comparisons were found to significantly influence this outcome. There were no significant differences among therapies in the odds of minor bleeding.

Traditional meta-analyses: Mortality was evaluated in the comparison of enoxaparin to control, enoxaparin to UFH and certoparin to UFH with no statistically significant findings for any comparison. VTE and PE were evaluated in the comparison of enoxaparin to control and enoxaparin to UFH and again there were no statistically significant findings. DVT was assessed in the comparison of enoxaparin to UFH, certoparin to UFH and UFH to control. There was a statistically significant decrease in the risk of DVT with UFH compared to control (RR= 0.13, 95% CI: 0.05 to 0.35) and no other significant findings. Major bleeding was assessed in all pairwise comparisons and UFH was found to significantly increase the risk of major bleeding compared to control (RR=2.77, 95% CI: 1.12 to 6.86). Minor bleeding was evaluated in the comparisons of enoxaparin to control, certoparin to UFH and nadroparin to control with no statistically significant differences. Publication bias was not evaluated given the small number of studies included.

There is a lack of adequate direct comparative data of different LMWHs for VTE prophylaxis in medically ill patients. This systematic literature search confirmed that LMWHs have not been directly compared for this indication in RCTs and therefore the results of the MTC are based solely on indirect evidence obtained from trials comparing a LMWH to UFH or control. Both LMWHs with FDA approval for VTE prophylaxis (enoxaparin and dalteparin) were included in this analysis, as were nadroparin and certoparin since trials met inclusion criteria. However, it is important to note that only enoxaparin, dalteparin and nadroparin are available in Australia (certoparin is not approved in Australia).

Only one observational study (Carson et al, 2012) has attempted to compare within the class of LMWHs for VTE prophylaxis in hospitalised medically ill patients. This was a retrospective cohort study comparing dalteparin to enoxaparin for VTE prophylaxis in medically ill patients. Although the event rate of VTE was higher in the dalteparin group (1.77%) compared to the enoxaparin group (1.66%), the difference was not statistically significant. However, interpretation of results from this study were limited by small sample size with low event rates (which could have led to type II error) and lack of attempts to control for confounding factors.

Comments: Overall, the results of the MTC suggest that these four LMWHs are similar to each other in terms of relative effects on VTE, mortality, major bleeding and minor bleeding. Enoxaparin, nadroparin and certoparin were found to be similar in relative effects on DVT and PE. There was no data on DVT or PE to compare dalteparin. There was no compelling data suggesting one LMWH over another for VTE prophylaxis in hospitalised medically ill patients. The sponsors claim that this meta-analysis provided Level I (NHMRC) evidence to support nadroparin for proposed indication, but the evaluators feel that this meta-analysis only provided supportive evidence as interpretation was limited by the following factors:

- Traditional meta-analysis was not possible for many drug comparisons made within the MTC, which limited ability to evaluate consistency. Dalteparin was not included in the network for DVT or PE since the one trial evaluating dalteparin did not report these outcomes. Given the availability of dalteparin in Australia, this limits the applicability of this analysis. Furthermore, certoparin which was included in the meta-analysis is not available in Australia.
- Four of these trials involved nadroparin and compared nadroparin to placebo (Fraisse, 2000 and Mahe, 2000) or to UFH (Harenberg, 1996; Forette, 1995). It is

important to note that the Mahe study is not relevant to this submission as it involved a very high dose of nadroparin and only enrolled patients hospitalised and immobilised for <24hrs due to an acute medical illness. The Forette study was mainly a safety/tolerance study and provided limited efficacy data. The other 2 RCTs (Fraisse, 2000 and Hareneberg, 1996) have already been discussed in detail.

§ Hospitalised medical patients are often a heterogeneous population. Furthermore, definitions used by individual trials for outcomes such as VTE varied and diagnostics strategies (including mandatory screening for DVT) also varied across trials. These characteristics may also have contributed to the observed heterogeneity in the outcomes of VTE, DVT and minor bleeding. Furthermore, rarity of events, particularly in mortality and PE, contributed to imprecise estimates demonstrated by the wide confidence intervals reported.

## 7.5. Evaluator's conclusions on clinical efficacy

A total of 6 published reports evaluating the safety and efficacy of nadroparin as a thromboprophylactic agent in hospitalised, acutely ill medical patients was included in this submission. Two additional publications focussed on the safety of prophylactic nadroparin in hospitalised, acutely ill medical patients.

In the first meta-analysis (Alikhan, 2014), 16 studies were used to compile evidence, 10 comparing heparin prophylaxis with no treatment or placebo and six which compared LMWH to UFH, with a total of 34,369 participants. However, only 3 of the 16 included studies evaluated prophylactic nadroparin, one compared nadroparin to UFH (Forette, 1995) and the other to placebo (Fraisse, 2000). The second meta-analysis (Dooley, 2014) included 20 trials involving 37284 patients and compared the safety and efficacy of various LMWHs to either UFH or placebo. No individual study included in the analysis directly compared one LMWH to another, however an indirect analysis using common comparators was performed. The overall conclusion from both meta-analyses was that patients treated with prophylactic LMWH generally were at a significantly lower risk of DVT, compared to those treated with UFH (OR= 0.77; 95% CI 0.62 to 0.96; p = 0.02), with no clear difference between LWMH and UFH with regards to the incidence of PE or death. In addition, patients treated with LMWH have a significantly lower risk of major bleeding (OR =0.43; 95% CI 0.22 to 0.83; p = 0.01) and similar risk of developing thrombocytopenia. In the MTC comparing individual LMWHs,, enoxaparin, nadroparin and certoparin were found to be similar in preventing PE and DVT in hospitalised medical patients, with similar rates of major and minor bleeding. However, it is important to note that results are based on indirect evidence as no LMWHs were directly compared t6o each other in any of these trials. Certoparin is not available in Australia and there is no comparative data with dalteparin which is available in Australia. LMWHs are not clinically interchangeable and so the general evidence provided for heparin (UFH and LMWH) and for all LMWHs cannot be extrapolated as evidence for efficacy/ safety of nadroparin for proposed new indication of thromboprophylaxis of bedridden patients with acute medical illness.

In addition to the two meta-analyses, 4 individual clinical trial publications are included in this application to support efficacy of nadroparin. Three of these are RCTs (Fraisse, 2000, Harenberg, 1996, Luba, 2007), while the remaining safety and efficacy study (Pottier, 2000) was an uncontrolled prospective study of acutely ill medical patients admitted to hospital, classified as low, immediate or high risk of developing a VTE and provided only supportive evidence of efficacy due to the large number of patients recruited to the study and objective monitoring of efficacy and safety outcomes. The comparators used in the RCTs were either placebo (Fraisse, 2000), UFH (Harenberg, 1996) or short versus longer duration nadroparin treatment (Luba, 2007). All were reviewed by a relevant ethics research committee and written informed participant consent obtained prior to commencement. All participants were randomly allocated to treatments, however the methods of randomisation were not clearly summarised. In

addition, the study by Luba 2007 indicated that the assessment of the primary outcome was blinded to treatment allocation. However, only the two pivotal studies (Fraisse, 2000; Harenberg, 1996) estimated the sample size necessary to provide a statistically meaningful comparison of efficacy, based on the primary outcome measure. The RCT by Fraisse was included in both the Alikhan and Dooley meta-analyses, while the RCT by Harenberg was included in the Dooley meta-analysis. The pre-determined primary efficacy outcome of all studies included DVT. Other co-primary outcomes included PE and mortality. The presence of DVT was confirmed using objective measures including venography, sonography ± phlebography. Both Fraisse and Harenberg specified that the comparisons were based on the intention to treat populations. The methods used to statistically analyse the comparisons undertaken in the studies were generally well described and appropriate to the analyses. Secondary efficacy endpoints included VTE, in other locations besides the lower limbs, arterial embolism and myocardial infarction. Overall, the methodology applied to the design and analysis of these studies was considered adequate and the outcome measures evaluated relevant to the proposed extension of indication for nadroparin in this application. However, there was lack of data on patient care such as early mobilisation, physiotherapy and use of mechanical prophylaxis measures (such as elastic compression stockings, intermittent pneumatic compression) for the submitted studies. As mentioned in the CHMP guidelines, these specific standards of care in hospitalised patients along with concomitant illness and/ or treatment may confound interpretation of efficacy/safety of nadroparin for the new indication of thromboprophylaxis in medical patients bedridden due to acute illness.

A total of 4,774 patients were administered nadroparin during these trials. The patients recruited into these trials were all over 40 years of age. Two of the RCTs (Fraisse 2000 and Luba 2007) administered prophylactic nadroparin according to patient weight, consistent with the dosage recommendations in this application (< 70 kg, 3800 anti-Xa IU and > 70 kg, 5700 anti-Xa IU). Both studies recruited patients hospitalised and bedridden due to an acute medical illness. The possible pre-existence of a DVT was assessed for each patient prior to study entry.

Despite some limitations, Fraisse (2000) was a reasonably well-conducted, randomised, double-blind, placebo-controlled study which provided evidence for efficacy of Fraxiparine (nadroparin) in 221 patients with acute, decompensated COPD requiring mechanical ventilation. Compared with placebo, nadroparin (dose-adjusted to body weight with mean duration of 11 days) showed a 45% reduction in incidence of DVT, which was not associated with a high incidence of serious bleeding or thrombocytopenia. No proven pulmonary embolism was observed during the study although it was not systematically investigated by objective tests.

The other pivotal, active-controlled study (Harenberg, 1996) demonstrated equivalence of LMWH-nadroparin and UFH for prophylaxis of thromboembolism in hospitalised, bedridden patients with medical diseases. The incidence of primary endpoint of DVT or PE was about 1% in both treatment groups. The main advantage of nadroparin over UFH was the equal efficacy with only one daily SC injection and a lower incidence of AEs. However, interpretation was limited by low incidence of primary endpoint, lack of details (95% intervals not provided for efficacy results), study population not well-defined and increased incidence of deaths in the nadroparin treatment group.

The open-label study (Luba, 2007) confirmed the safety and efficacy of thromboprophylaxis with proposed dose of nadroparin in medical patients hospitalised for acute illness. A tendency for a reduced occurrence of endpoints in patients receiving LMWH (nadroparin) for longer than only during immobilisation, was also observed. However, larger, controlled medical inpatient studies need to be conducted in order to assess if prophylactic treatment prolongation beyond the immobilization time will result in larger clinical benefits than prophylaxis limited to the immobilization time.

The studies by Forette 1995, Pottier 2000 and Harenberg 1996, administered a lower dose of nadroparin (3100 or 3075 anti-Xa IU), consistent with the proposed recommendation in this application for elderly patients (2850 anti-Xa IU). While no formal comparison of the incidence of DVT across the five individual studies evaluated in this overview can be reliably made, due to differences in study population, study hypothesis, intrinsic risk of DVT and treatment duration, the incidence reported 'low dose' studies [Harenberg 1996 (0.74%) Pottier 2000 (0.75%) and Forette 1995 (2%)] were consistent with the incidence reported in the 'usual dose' studies [Fraisse 2000 (15.48%) and Luba 2007 (0.05%)]. Hence, there was adequate evidence to support a dose reduction to 0.3 mL (2,850 Anti-Xa IU) of nadroparin in elderly patients for the proposed indication.

The sponsors state that 5 of the 6 safety and efficacy publications meet the NHMRC 1999 criteria of level I or level II evidence, providing sufficient details of study design, outcomes and statistical analysis for an independent assessment of the safety and efficacy of nadroparin in the proposed indication (Alikhan, 2014, Dooley, 2014, Fraisse, 2000, Harenberg, 1996, Luba, 2007). However, the evaluators do not agree with the sponsor's statement that the two meta-analyses provide Level I evidence.

The main evidence to support efficacy of nadroparin was provided by the Fraisee (2000) and Hareneberg (1992, 1996) studies (Level II evidence). Supportive evidence for efficacy was provided by the open-label study (Luba 2007) and the 2 meta-analyses (Alikhan, 2014; Dooley, 2014).

Since a 'general indication' of 'thromboprophylaxis for bedridden patients with acute medical illness' is intended for this submission, it is important that the trial population has adequate representation of several applicable subgroups e.g., stroke, cardiac disease, cancer and infection/ inflammation, due to the heterogeneous nature of predisposing factors (CHMP guidelines).[19] Specifically, Fraisse (2000) which was the only placebo-controlled, randomised study evaluated patients with acute respiratory decompensated COPD who required mechanical ventilation. Although patients in this study did present with serious risk factors for DVT such as immobilization (100%), respiratory disease (100%), bronchial superinfection (74%), congestive heart failure (29%), age > 65 yr (50%), obesity (23%), venous insufficiency (13%), neoplastic disease (5%) and previous thromboembolic disorders (4%), it appears that patients with stroke and acute myocardial infarction were excluded from this study. Furthermore, the Alikhan (2014) meta-analysis excluded patients with stroke, AMI and admission to ICU.

Enoxaparin is approved for thromboprophylaxis in medical patients bedridden due to acute illness. However, enoxaparin has separate approved indications for unstable angina (with aspirin) and treatment of acute STEMI.[20] Dalteparin is not approved for thromboprophylaxis in medical patients bedridden due to acute illness although it is approved for treatment of unstable angina.[21] Nadroparin is not approved separately for unstable angina and hence it is

[19] The CHMP guidelines on clinical investigation of medicinal products for the prophylaxis of venous thromboembolic risk in non-surgical patients (June 2006)

[20] Enoxaparin sodium (Levenox) is currently approved in Australia for the following indications and it includes the proposed indication for nadroparin:

- Prevention of thrombo-embolic disorders of venous origin in patients undergoing orthopaedic and general surgery.
- Prophylaxis of venous thromboembolism in medical patients bedridden due to acute illness.
- Prevention of thrombosis in extra-corporeal circulation during haemodialysis.
- Treatment of established deep vein thrombosis.
- Treatment of unstable angina and non-Q-wave myocardial infarction, administered concurrently with aspirin.
- Treatment of acute ST-segment Elevation Myocardial Infarction (STEMI) as an adjunctive to thrombolytic treatment, including patients to be managed medically or with subsequent Percutaneous Coronary Intervention (PCI).

[21] Dalteparin (Fragmin) is approved for the following:

- Prophylaxis against thrombotic complications during haemodialysis and treatment of acute deep vein thrombosis (DVT).

very important to specify this fact as the 'general' indication proposed in this submission may be misleading. The risk of VTE and the need for thromboprophylaxis differs in patients with stroke and AMI (Collins 1996 and Geerts 2001). Further, the proposed indication does not clarify that only patients with minimum expected duration of immobilisation of 2-3 days could be treated with nadroparin and that efficacy/ safety of nadroparin in proposed indication was only evaluated for maximum treatment duration of 28 days.

# 8. Clinical safety

## 8.1. Studies providing evaluable safety data

### 8.1.1. Pivotal studies that assessed safety as the sole primary outcome

None.

### 8.1.2. Pivotal and/or main efficacy studies

In the pivotal placebo-controlled study (Fraisse, 2000), safety criteria included the incidence of major or minor haemorrhage. Haemorrhage was considered major when it was overt and was associated with a decrease in haemoglobin concentration of ≥ 2 g/dl compared with the baseline value, when it necessitated a transfusion of two or more units of packed red cells, when it was retroperitoneal or intracranial, or when the investigator decided to end the treatment with heparin because of his judgment on the benefit/risk ratio. Minor haemorrhages were those not considered major. Other safety criteria included severe thrombocytopenia (i.e., platelet count< 50,000 cells/$mm^3$ with or without clinical signs, platelet count between 50,000 and 100,000 cells/$mm^3$ with clinical signs, or a 50% decrease compared with the baseline reference count); and any other treatment-related adverse events. AEs were defined as serious if they caused death, were life threatening, or prolonged hospital stay. The Committee on Critical Events (members were independent of the study and unaware of the nature of the treatment administered) assessed whether serious adverse events (SAEs) were treatment-related. Standard laboratory tests were performed at enrolment and the day after the final treatment (end of study) and in the event of early permanent discontinuation. Laboratory tests included: complete blood count with leukocyte differential, haemoglobin, haematocrit, activated partial thromboplastin time (APTT), PT, serum electrolytes and creatinine. Platelets were counted twice per week.

In the pivotal non-inferiority study of UFH vs LMWH (nadroparin) (Harenberg, 1992, 1996), all adverse reactions were classified according to their severity as slight, moderate or severe. The relationship between the adverse reaction and the study medication was classified by the investigators as: not related, uncertain, possibly related, probably related or definitely related. The size of hematomas at injection sites was measured, every other day (i.e. day 4, 6, 8, 10) and the number of hematomas with a diameter above 2.5 cm were recorded. Patients were also examined for haematuria and hematomas at others than the injection sites and side effects such as alopecia, pruritus, or allergic reactions. Clinical chemistry analyses were performed on days 1 and 10 of the study: asparagine aminotransferase, alanine aminotransferase, gamma-glutamyltranspeptidase, cholesterol, triglycerides, lactate dehydrogenase, alkaline phosphatase, urea and serum creatinine. Haematological evaluation included haematocrit, erythrocyte,

- Extended treatment of symptomatic venous thromboembolism (VTE) (proximal deep vein thrombosis and/or pulmonary embolism) to reduce the recurrence of VTE in patients with solid tumour cancers.
- Treatment of unstable coronary artery disease, i.e. unstable angina and non-ST-elevation myocardial infarction (also known as non-Q-wave myocardial infarction).
- Prophylaxis against thromboembolic complications in the peri- or postoperative period of surgery.

leucocyte and thrombocyte count, prothrombin time, antithrombin III and fibrinogen. All clinical chemistry parameters were measured using commercially available test systems.

The 2 pivotal metanalyses included limited safety evaluations mainly related to bleeding complications. Alikhan (2014) was Cochrane review was conducted to determine the effectiveness and safety of heparin (UFH or LMWH) thromboprophylaxis in acutely ill medical patients admitted to hospital, excluding those admitted to hospital with an acute myocardial infarction or stroke (ischaemic or haemorrhagic) or those requiring admission to an intensive care unit. Sixteen studies were included and individual data used to perform the following comparisons: 1. Heparin (LMWH and UFH) versus placebo or no treatment, 2. LMWH vs UFH. Three nadroparin studies were included in this meta-analysis, including Bergmann 1996, Forette 1995 and Fraisse 2000. Major haemorrhage was the primary safety outcome and minor haemorrhage and thrombocytopenia the secondary safety outcomes analysed in the systematic review. Dooley (2014) was a systemic review and mixed treatment comparison (MTC) meta-analysis with the primary objective of comparing the efficacy and safety of LMWHs (enoxaparin, dalteparin, nadroparin and certoparin) for prophylaxis of VTE in hospitalised medically ill patients; 15 of the 20 trials included in the meta-analysis reported major bleeding and only 13 trials reported minor bleeding.

### 8.1.3. Other studies

#### *8.1.3.1. Other efficacy studies*

- Luba, 2007: This is a randomised, open label study assessing the efficacy and safety of 2 models of thromboprophylaxis with nadroparin in medical patients hospitalised for acute illnesses. The safety profile of nadroparin was assessed based on observation of the bleeding complications and frequency, as well as thrombocytopenia and local skin reactions. The bleeding was recognised as the endpoint if overt and requiring transfusion of at least 2 units of packed red cells, or correlating with a fall in haemoglobin concentration of 2.0 g/dl. A drop in the thrombocyte count of 50% compared to initial value was regarded as thrombocytopenia. A rash at the injection site was recognised as a local skin reaction.
- Pottier, 2000: This was an open-label, prospective epidemiological study to evaluate groupings of indications for thromboprophylaxis in a variety of medical environments and to assess the clinical incidence of VTE. This study did not include safety endpoints and specific AEs were not documented. However, the authors noted that no serious haemorrhagic strokes or cases of thrombocytopenia due to nadroparin were reported.

#### *8.1.3.2. Studies with evaluable safety data: dose finding and pharmacology*

None.

#### *8.1.3.3. Studies evaluable for safety only*

Two of the 8 publications submitted in this application only provided data on safety of nadroparin and these are discussed below.

## 8.2. Studies that assessed safety as the sole primary outcome

Forette (1995) was an open-label, randomised study to evaluate the tolerance of calcium nadroparin vs calcium heparin[22] in 295 elderly patients (aged >70 years), hospitalised for a minimum duration of 4 weeks, for recent and presumably temporary decline in locomotor autonomy, justifying a prophylactic treatment of venous thromboembolic disease.

[22] Nadroparin 0.3 ml (3075 anti-Xa IU) daily or subcutaneous calcium heparin twice a day (0.2ml·5000 UI if bodyweight was <70 kg or 0.3 ml·7500 IU if it was ≥ 70 kg).

The overall incidence of premature withdrawals (related and unrelated to study treatments) was non-significantly (p = 0.2) lower in the nadroparin group (16/146, 11%) compared with the calcium heparin group (24/149, 16.1%,). In total 11 premature discontinuations of treatment were considered as related to calcium nadroparin or calcium heparin administration. The frequency of premature discontinuation related to treatments was statistically significantly lower in the calcium nadroparin group compared with the calcium heparin group (0.7% vs 6.7%, p = 0.01). In the calcium heparin group, the 10 treatment-related withdrawals were due to allergies, intolerances, major haemorrhages, thromboembolic complications and thrombocytopenia; there was only one treatment-related withdrawal (due to allergy) in the calcium nadroparin group.

There was no statistically significant difference between treatment groups in incidence of thromboembolic complication: 4 DVT and one PE occurred in the calcium heparin group and 3 DVT in the calcium nadroparin group.

Comment: Overall, results from this study were consistent with those reported earlier (Aquino, 1991 and Manciet, 1991). There was a higher incidence of serious haemorrhage in patients treated with UFH compared with calcium nadroparin, but this difference was not statistically significant. Furthermore, the frequency of minor bleeding was lower in the calcium nadroparin group compared to the UFH group, likely due to the single injection administered in the nadroparin group compared to twice daily injections in the UFH group.

Pessina (2003) was a single case report of a large rectus abdominalis haematoma in patient affected by COPD, complicated by respiratory insufficiency, treated with LMWH. This case report highlights the fact that in case of signs of anaemia associated with abdominal pain during treatment with heparin, the appearance of retroperitoneal hematomas or of the abdominal wall muscles should be considered not only in subjects undergoing anticoagulant therapy but also in those receiving prophylactic treatment with LWMH for thromboembolic disease. A haemorrhagic event with involvement of the rectus abdominis muscle can appear in the course of prophylaxis with LMWH for DVT in hospitalised patients, suffering from acute medical conditions, without any obvious predisposing conditions such as renal failure, severe hypertension, trauma, changes in blood counts, physical exercise, coughing. The administration of LWMH should be carefully considered also in relation with conditions that can cause bleeding (age, renal insufficiency, previous gastroduodenal ulcers) and associated side effects (thrombocytopenia); also, the monitoring of the treatment should be considered in order to suspend it as soon as the thromboembolic risks appear.

## 8.3. Patient exposure

The 8 published studies provided safety data following treatment with nadroparin doses from 3075 to 5700 anti-Xa IU, administered subcutaneously daily for a duration up to 28 days (mean = 5.1 days). Majority of these studies included hospitalised medical patients, who were immobilised or on bed rest, with or without an increased risk of VTE. It is important to note that Fraisse (2000) which was the only placebo-controlled, randomised study only evaluated patients with acute respiratory decompensated COPD who required mechanical ventilation. Patients with stroke and acute myocardial infarction were also excluded from the pivotal Alikhan (2014) meta-analysis. Dooley (2014) did not specify if stroke patients were excluded from the meta-analysis although patients with recent myocardial infarction were included.

The patient population exposed to nadroparin in the individual clinical reports submitted in the safety evaluation of this application includes 4945 hospitalised medical patients. All patients were older than 40 years of age. Nadroparin was administered subcutaneously in daily doses ranging from 3075 to 5700 anti-Xa IU, for a duration up to 28 days (mean duration 5.1 days). Two of the individual RCTs (Fraisse, 2000; Luba, 2007) administered nadroparin in a dose

consistent with the generally recommended dosage in this application (3800 anti-Xa IU in patients < 70kg and 5700 anti- Xa IU in patients > 70kg.) The remaining two RCTs (Harenberg, 1996; Forette, 1995) used doses (3075, 3100 anti-Xa IU) similar to the proposed reduced dosage for elderly patients (2850 anti-Xa IU); the lower dose used in these studies reflected the older cohort of patients recruited into these studies, particularly the latter (70.5 ±8.3 and 82.8 ±0.5 years respectively). The uncontrolled study by Pottier also used a dose of 3075 anti-Xa IU.

Comment: The study design, patient population and dosage of nadroparin used in these studies were generally appropriate for the safety evaluation of nadroparin in the extension of indication proposed in this application and the suggested dose reduction in elderly patients.

## 8.4. Adverse events

### 8.4.1. All adverse events (irrespective of relationship to study treatment)

#### *8.4.1.1. Integrated safety analyses*

Not applicable.

#### *8.4.1.2. Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

#### *8.4.1.3. Pivotal and/or main efficacy studies*

Fraisse, 2000: Of the 221 patients evaluated for safety, one or more AEs (regardless of severity or causal relationship to treatment) were experienced by 46.3% and 39.3% of patients receiving nadroparin and placebo, respectively; the difference in AE incidence was not significant. The most commonly reported AEs were haemorrhage (nadroparin vs placebo: 25 vs 18, p = 0.18) and thrombocytopenia (10 vs 7, p = 0.39). The incidence of reported AEs was high in both groups, which can be expected since all patients had chronic lung disorders requiring hospitalization and most were elderly. There were no significant differences between the two groups for total AEs, SAEs, or discontinuations due to AEs. The most common AEs were haemorrhage often associated with septic shock (n = 25 for patients receiving nadroparin, six serious; and n = 18 for those receiving placebo, three serious).

**Table 3: Fraisse, 2000: Clinical safety: Adverse events**

| | Nadroparin (*n* = 108) | Placebo (*n* = 113) | p Value |
|---|---|---|---|
| Total adverse events | | | |
| Patients, n (%) | 50 (46.3) | 45 (39.8) | 0.33 |
| Adverse events of which, n | 84 | 79 | |
| Hemorrhage | 25 | 18 | 0.18 |
| Major hemorrhage | 6 | 3 | 0.28 |
| Minor bleeding | 19 | 15 | |
| Thrombocytopenia | 10 | 7 | 0.39 |
| Serious adverse events† | | | |
| Patients, n (%) | 27 (25) | 22 (19.5) | 0.32 |
| Adverse events of which, n | 34 | 28 | |
| Hemorrhage | 6 | 3 | |
| Thrombocytopenia | 3 | 2 | |
| Adverse events resulting in early permanent discontinuation of therapy | | | |
| Patients, (%) | 13 (12) | 10 (8.8) | 0.44 |
| Adverse events of which, n | 18 | 11 | |
| Hemorrhage, n | 5 | 2 | 0.41 |
| Thrombocytopenia, n | 7 | 3 | 0.40 |
| Serious adverse events (considered to be related to treatment by the Committee on Critical events), n | 7 | 3 | |
| Hemorrhage, n | 5 | 2 | |
| Thrombocytopenia, n | 1 | 1 | |

* Some patients experienced several adverse events.
† *See* Assessment of Outcome in Methods.

Harenberg, 1996: This is a multi-centre, double-blind, randomised-controlled study comparing the efficacy and safety of a LMWH (nadroparin) with low dose UFH in hospitalised bedridden patients with a high risk of thromboembolism. Major bleeding complications were rare and were not different between the two groups. Minor bleeding was observed more frequently with UFH, but the difference from LMWH was not statistically significant. Thrombocytopenia occurred more frequently in patients treated with UFH (p = 0.05). No patients with thrombocytopenia developed thrombosis and no patient with thromboembolism presented with thrombocytopenia. In addition, the incidence of subcutaneous haematomas (diameter >2.5cm) was significantly higher in the UFH group (p = 0.0001).

Alikhan, 2014: Heparin (UFH and LMWH) vs placebo: Major bleeding was evaluated in eight studies (Belch 1981; Dahan 1986; Fraisse 2000; Gardlund 1996; Ibarra-Perez 1988; LIFENOX 2011; MEDENOX 1999; PREVENT 2004) but meta-analysis was conducted using only seven trials, excluding Gardlund 1996[23]. Heparin was associated with a borderline statistically significant increase in major bleeding compared to placebo/ no treatment (OR= 1.65; 95% CI:1.01 to 2.71; P = 0.05). When sensitivity analysis was performed by removing studies with inadequate definitions of the major bleeding (Belch 1981 and Dahan 1986), the association became statistically significant (OR=1.83; 95% CI: 1.09 to 3.07; P = 0.02). Minor bleeding was evaluated in five studies (Fraisse 2000; Ibarra-Perez 1988; LIFENOX 2011; MEDENOX 1999; PREVENT 2004) and heparin was associated with significantly increased odds of 1.61 (95% CI: 1.26 to 2.08; P = 0.0002). Thrombocytopenia was measured in four studies (Fraisse 2000;

[23] This was for the same reason as for the outcome of non-fatal PE: major bleeding was only evaluated through necropsy data and was not evaluated in all patients.

LIFENOX 2011; MEDENOX 1999; PREVENT 2004). There was no clear evidence of a difference between the two groups for thrombocytopenia (OR=1.05; 95% CI: 0.64 to 1.74; P = 0.85).

UFH vs LMWH: Six studies measured major bleeding as an outcome (CERTAIN 2010;CERTIFY 2010; EMSG1996; Forette 1995; PRIME 1996; THE-PRINCE 2003).There was a statistically significant reduced odds found in the LMWH group compared with the UFH group (OR=0.43; 95% CI: 0.22 to 0.83; P = 0.01). Minor bleeding was assessed in three studies (CERTAIN 2010; CERTIFY 2010; Forette 1995) and was associated with a decreased odds with LMWH (OR= 0.70; 95% CI: 0.48 to 1.00; P = 0.05), possibly a chance effect. When the CERTAIN 2010 study was removed for sensitivity analysis to assess the effect of the longer follow-up time period, there was little change for major bleeding (OR=0.43; 95% CI: 0.22 to 0.87; P = 0.02) and minor bleeding moved from a possible chance effect to statistically significant (OR= 0.66; 95% CI: 0.45 to 0.96; P = 0.03). Thrombocytopenia was evaluated in three studies (CERTAIN 2010; CERTIFY 2010; Forette 1995). There was no difference between LMWH and UFH (OR=0.41; 95% CI: 0.08 to 2.11; P = 0.28). When sensitivity analysis was performed by removing the CERTAIN 2010 study to assess the effects of the longer follow-up period, there was very little change (OR=0.43; 95% CI: 0.06 to 2.92; P = 0.39).

Dooley, 2014: During MTC, differences in the incidence of major and minor bleeding were evaluated for all four LMWHs with no statistically significant differences noted. The MTC comparison for individual LMWH for the individual outcomes of major and minor bleeding and PE are presented; results suggested that enoxaparin, dalteparin, nadroparin and certoparin are associated with similar rates of major or minor bleeding.

#### *8.4.1.4. Other studies*

- Luba, 2007: During the thromboprophylaxis period (stage 1), there were no drop-outs, deaths or heparin induced thrombocytopenia. On the day of completion of thromboprophylaxis the ultrasound compression test was negative in all patients. Safety assessment was not discussed for stage 2 and there was no indication whether any other AEs were monitored or reported during the study.
- Pottier 2000: This open-label, prospective epidemiological study did not include safety endpoints and specific AEs were not documented. However, the authors noted that no serious haemorrhagic strokes or cases of thrombocytopenia due to nadroparin were reported.

### 8.4.2. Treatment related adverse events (adverse drug reactions)

#### *8.4.2.1. Integrated safety analyses*

Not applicable.

#### *8.4.2.2. Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

#### *8.4.2.3. Pivotal and/or main efficacy studies*

Specific results for treatment related AEs were not presented for any of the 4 published pivotal studies.

#### *8.4.2.4. Other studies*

- Luba (2007): No data
- Pottier (2000): Not evaluated

### 8.4.3. Deaths and other serious adverse events

#### *8.4.3.1. Integrated safety analyses*

Not applicable.

#### *8.4.3.2. Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

#### *8.4.3.3. Pivotal and/or main efficacy studies*

Fraisse (2000): Sixteen patients died during the study with no significant difference between the nadroparin (32%, 8/108) and placebo (27.6%, 8/113) groups. Most deaths were due to cardiovascular complications or nosocomial pneumopathies.

Overall, 49 patients experienced one or more serious adverse events. The most commonly reported SAE was cardiovascular (nadroparin vs placebo: 14 vs 9), mainly heart failure after septic shock. SAEs were considered (Committee on Critical Events) "possibly" or "likely" to be related to nadroparin in five cases of haemorrhage, one case of thrombocytopenia and one case of "pneumonia"; and to placebo in two cases of bleeding and one case of thrombocytopenia.

Harenberg (1996): The incidence of deaths was significantly higher in the nadroparin group (n = 23) compared to the UFH group (n = 9) (p = 0.02); pneumonia, stroke and cardiac insufficiency as clinical causes of death were more common in the LMWH treatment group. There was a difference in number of deaths at centres depending on whether or not primary endpoints were observed as the primary endpoints were only observed in 4 of the 10 centres. No differences were observed between treatment groups at centres with primary endpoints (UFH vs LMWH: 1.09% vs 1.6%, p = 0.6). In contrast, the incidence of death was 3.5 fold higher in the LMWH group at centres without endpoint observation (1.25% vs 4.49%, p = 0.02).

Alikhan (2014): All cause mortality was assessed in 7 of the trials comparing heparin (UFH and LMWH) vs placebo/no treatment; there was no clear evidence of a difference in mortality between the heparin (UFH and LMWH) and placebo/ no treatment groups with an OR of 0.97 (95% CI: 0.87 to 1.08; P = 0.57). All-cause mortality was assessed in five studies (CERTIFY 2010; EMSG1996; Forette 1995; PRIME 1996; THE-PRINCE 2003) which compared LMWH vs UFH; there was no clear evidence for a difference in mortality (OR= 0.79; 95% CI:0.54 to 1.16; P = 0.23).

Dooley (2014): In the MTC analysis, there was no statistically significant difference in mortality among all four LMWHs (dalteparin, certoparin, enoxaparin and nadroparin). It is important to note that the results are based on indirect evidence as no trials directly compared one LMWH to another.

Comment: SAEs were not reported for the Harenberg (1996) study and both the meta-analyses.

#### *8.4.3.4. Other studies*

- Luba (2007): Two sudden deaths were observed on day 30 and 52 after completion of prophylactic treatment (its reasons not being verified at autopsy). However, both the deaths occurred in the short prophylaxis duration group.
- Pottier (2000): No data provided.

### 8.4.4. Discontinuations due to adverse events

#### *8.4.4.1. Integrated safety analyses*

Not applicable.

#### *8.4.4.2. Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

#### *8.4.4.3. Pivotal and/or main efficacy studies*

Fraisse (2000): Early permanent discontinuation of treatment because of an AE occurred in 13 (12%) patients receiving nadroparin and in 10 (8.8%) patients receiving placebo; the difference was not significant.

Information on incidence of discontinuations due to AEs was not provided in the Harenberg (1996), Alikhan (2014) and Dooley (2014) publications.

#### *8.4.4.4. Other studies*

- Luba (2007): No data provided.
- Pottier (2000): No data provided.

## 8.5. Evaluation of issues with possible regulatory impact

### 8.5.1. Liver function and liver toxicity

#### *8.5.1.1. Integrated safety analyses*

Not applicable.

#### *8.5.1.2. Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

#### *8.5.1.3. Pivotal and/or main efficacy studies*

Specific results related to liver function tests were only provided in the Harenberg (1996) study. The well-established heparin-induced increase in ALAT, ASAT and GGT, decrease in AT-III and increase in cholesterol and triglycerides were not observed in patients treated with LMWH (nadroparin). Significant and favourable differences in many of these parameters were observed in patients treated with nadroparin and UFH.

#### *8.5.1.4. Other studies*

#### *8.5.1.5. Specific results related to liver function tests were not provided for the other studies.*

### 8.5.2. Renal function and renal toxicity

#### *8.5.2.1. Integrated safety analyses*

Not applicable.

#### *8.5.2.2. Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

#### *8.5.2.3. Pivotal and/or main efficacy studies*

Specific renal function test results were not provided for any of the pivotal studies or meta-analysis.

#### *8.5.2.4. Other studies*

Specific renal function test results were not provided for any of the other studies.

### 8.5.3. Other clinical chemistry

#### *8.5.3.1. Integrated safety analyses*

Not applicable.

#### *8.5.3.2. Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

#### *8.5.3.3. Pivotal and/or main efficacy studies*

Clinical chemistry results were not provided for any of the pivotal meta-analysis.

- Fraisse (2000): Only haematology results were provided in the published study report.
- Harenberg (1996)

#### *8.5.3.4. Other studies*

- Luba (2007): In most patients, results of the standard laboratory tests and complete blood count were within the normal range.
- Pottier (2000): No data provided.

### 8.5.4. Haematology and haematological toxicity

#### *8.5.4.1. Integrated safety analyses*

Not applicable.

#### *8.5.4.2. Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

#### *8.5.4.3. Pivotal and/or main efficacy studies*

- Fraisse (2000): No significant differences were observed in the hematologic or coagulation factors measured. Clinically significant abnormal haemoglobin levels (i.e. ≤ 8 g/dl or a decrease of 3 g/dl versus baseline) were found in 17 (15.7%) patients receiving nadroparin compared with 14 (12.4%) receiving placebo. Ten (9.3%) patients receiving nadroparin and seven (6.2%) receiving placebo had platelet counts <100,000/mm$^3$ or a 50% decrease compared with their baseline value; however, the difference was not significant. In patients receiving nadroparin, thrombocytopenia occurred concomitantly with septic shock (n = 5); an ischemic vascular event (n = 1); or with haematuria (n = 1). In the other three cases, treatment was continued and platelet count returned to normal in the following days. The Critical Events Committee considered three of these cases to be serious and only one to be possibly related to nadroparin. Thrombocytopenia in the seven patients receiving placebo was associated with septic shock (n = 3), DVT (n = 1), a bleeding event (n = 1) and fatal cardiogenic shock (n = 1). It was asymptomatic in one patient and did not worsen during the following days, despite continued treatment. The Critical Events Committee considered two of these cases to be serious and only one to be possibly related to placebo.
- Harenberg (1996): No haematology results were provided in the published study report.
- Alikhan (2014): There was no detailed analysis of haematological laboratory parameters in the meta-analysis. Major and minor haemorrhage and thrombocytopenia was discussed.
- Dooley (2014): There was no detailed analysis of haematological laboratory parameters in the meta-analysis. Major and minor bleeding was discussed.

#### *8.5.4.4. Other studies*

- Luba (2007): In most patients, results of the standard laboratory tests and complete blood count were within the normal range. Haemorrhagic ecchymosis occurred in injection sites in all patients, however no important haemorrhagic complications were found.
- Pottier (2000): No data provided.

### 8.5.5. Other laboratory tests

#### *8.5.5.1. Integrated safety analyses*

Not applicable.

#### *8.5.5.2. Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

#### *8.5.5.3. Pivotal and/or main efficacy studies*

Not applicable.

#### *8.5.5.4. Other studies*

Not applicable.

### 8.5.6. Electrocardiograph findings and cardiovascular safety

#### *8.5.6.1. Integrated safety analyses*

Not applicable.

#### *8.5.6.2. Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

#### *8.5.6.3. Pivotal and/or main efficacy studies*

ECG assessments were not done in the 2 pivotal controlled studies or the metanalyses.

#### *8.5.6.4. Other studies*

#### *8.5.6.5. ECG assessments were not done in the other studies.*

### 8.5.7. Vital signs and clinical examination findings

#### *8.5.7.1. Integrated safety analyses*

Not applicable.

#### *8.5.7.2. Pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

#### *8.5.7.3. Pivotal and/or main efficacy studies*

Results regarding vital signs and clinical examination findings were not provided for any of the pivotal studies.

#### *8.5.7.4. Other studies*

Results regarding vital signs and clinical examination findings were not provided for the other studies.

### 8.5.8. Immunogenicity and immunological events

#### *8.5.8.1. Integrated safety analyses*

Not applicable.

#### *8.5.8.2. Main/pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

#### *8.5.8.3. Pivotal and/or main efficacy studies*

In the pivotal non-inferiority study (Harenberg, 1996), allergy was reported in 1% (8/810) and 2.1% (16/780) of the patients treated with nadroparin and UFH, respectively. No allergic reactions were reported in the placebo-controlled Fraisse (2000) study.

In the open-label, controlled study (Luba, 2007), one patient experienced an itching, macropapular rash at the nadroparin injection site and it presented as an allergic reaction on the last day (day 6) of administration; the rash cleared after the administration of topical 1% hydrocortisone.

#### *8.5.8.4. Other studies*

None.

### 8.5.9. Serious skin reactions

#### *8.5.9.1. Integrated safety analyses*

Not applicable.

#### *8.5.9.2. Pivotal studies that assessed safety as the sole primary outcome*

Not applicable.

#### *8.5.9.3. Pivotal and/or main efficacy studies*

None.

#### *8.5.9.4. Other studies*

None.

## 8.6. Other safety issues

### 8.6.1. Safety in special populations

Safety in elderly patients: The rationale for proposing a reduced dosage of nadroparin in elderly patients was supported by the study by Forette 1995, which demonstrated that a dose of 3075 anti-Xa IU nadroparin was as effective as twice daily UFH in reducing VTE but resulted in fewer bleeding events. Furthermore, a comparison of the incidence of major and minor bleeding and thrombocytopenia, in elderly patients (mean 69.4 ±7.7 years versus 70.5 ±8.3 years), receiving 'usual dose (3800 or 5700 anti-Xa IU) versus 'low dose' (3100 anti-Xa IU) nadroparin showed a higher incidence of AEs in the 'usual dose' study (Fraisse, 2000) compared with the 'reduced dose' study (Harenberg, 1996). Major bleeding was reported in 5.6% and 0.4% of patients in Fraisse and Harenberg studies, respectively; the incidence of thrombocytopenia was 9.3% and 0% respectively.

Safety of nadroparin in patients with renal or hepatic impairment was not evaluated.

### 8.6.2. Safety related to drug-drug interactions and other interactions

No data provided.

## 8.7. Post marketing experience

Fraxiparine is already marketed for the proposed new indication and dosage in Austria, Belgium, Luxembourg, Portugal and Spain (all under a different sponsor and/ or trade name). The sponsors state that PSURs/PBRERs from the previous 10 years are available. It is mentioned that these PSURs incorporate safety data for all indications registered for Fraxiparine, including the proposed extension to indication in this application. However, the PSURs did not categorise safety data according to the indications and hence, it would not be possible to evaluate post-marketing safety experience for nadroparin when used for the specific proposed indication of thromboprophylaxis in patients with acute medical illnesses.

## 8.8. Evaluator's overall conclusions on clinical safety

Of the 8 publications submitted in this application, 2 studies provided only safety data for nadroparin: an open-label, randomised study compared tolerability of nadroparin with calcium heparin (UFH) in 295 elderly patients hospitalised for minimum of 4 weeks (Forette, 1995) and a case report of a rectus abdominalis haematoma during nadroparin treatment (Pessina, 2003). Forette was primarily a safety study comparing the overall incidence of premature discontinuation of treatment, the incidence of haemorrhage, adverse events and VTE in elderly hospitalised, medical patients. All RCT studies (Fraisse, 2000; Harenberg, 1996; Luba, 2007) were undertaken in hospitalised medical patients in which nadroparin or an active or placebo comparator were administered as a prophylactic treatment for potential VTE. The patient population exposed to nadroparin in the individual clinical reports submitted in the safety evaluation of this application includes 4945 hospitalised medical patients. All patients were older than 40 years of age. Nadroparin was administered subcutaneously in daily doses ranging from 3075 to 5700 anti-Xa IU, for a duration up to 28 days (mean duration 5.1 days).

Two of the individual RCTs (Fraisse, 2000; Luba, 2007) administered nadroparin in a dose consistent with the generally recommended dosage in this application (3800 anti-Xa IU in patients < 70kg and 5700 anti- Xa IU in patients > 70kg.) The remaining two RCTs (Harenberg, 1996; Forette, 1995) used doses consistent with the proposed reduced dosage for elderly patients (2850 anti-Xa IU); the lower dose used in these studies reflected the older cohort of patients recruited into these studies, particularly the latter (70.5 ±8.3 and 82.8 ±0.5 years respectively). The uncontrolled study by Pottier also used a dose of 3075 anti-Xa IU. The study design, patient population and dosage of nadroparin used in these studies were appropriate for the safety evaluation of nadroparin in the extension of indication proposed in this application and the suggested dose reduction in elderly patients.

All four individual RCTs included in the safety analysis pre-defined major and minor haemorrhage/bleeding as a safety outcome of interest. All but Forette 1995 also pre-defined thrombocytopenia as another important outcome to the evaluation of safety. Luba 2007 and Harenberg 1996 monitored local skin reactions and haematoma as part of the safety monitoring of the trial participants. While Luba noted that all subjects treated with nadroparin experienced haemorrhagic ecchymosis,[24] they were not classified by the authors as important haemorrhagic complications. Forette 1995 and Fraisse 2000 recorded treatment-emergent AEs which were mainly events related to bleeding and platelet decrease.

When compared to placebo, no significant difference in thrombocytopenia or bleeding was noted following nadroparin treatment (Fraisse 2000). In the randomised, non-inferiority pivotal study (Harenberg, 1996), subcutaneous LMWH showed slightly better safety profile compared with UFH for prophylaxis of thromboembolic diseases in bedridden hospitalised medical patients, in particular, the incidence of injection site haematoma and local erythema were reduced and results of laboratory tests showed no change in liver enzymes, total cholesterol, triglycerides and AT-III.

In the Alikhan (2014) meta-analysis, there was a reduced risk of major and minor haemorrhage with LMWH compared with UFH**.** However, there was no clear evidence of differences between LMWH and UFH for thrombocytopenia**.** Dooley (2014) concluded that the LMWHs enoxaparin, nadroparin and certoparin were associated with similar rates of major and minor bleeding. Pottier 2000 noted that no serious haemorrhagic strokes or cases of thrombocytopenia due to nadroparin were reported in their study. The case report by Pessina 2003 summarised an adverse bleeding outcome in a patient suffering from acute exacerbation of COPD. He was treated with 3800 anti-Xa IU of nadroparin as prophylaxis for VTE, which is higher than the proposed dose (2850 anti-Xa IU) in elderly patients in this submission.

[24] It should be noted that the MedDRA definition of ecchymosis is distinct from both haematoma and haemorrhage and therefore by definition less clinically concerning in an overall assessment of safety.

The rationale for proposing a reduced dosage of nadroparin in elderly patients was supported by the Forette (1995) study, which demonstrated that a dose of 3075 anti-Xa IU nadroparin was as effective as twice daily UFH in reducing VTE but resulted in fewer bleeding events. Furthermore, a comparison of the incidence of major and minor bleeding and thrombocytopenia, in elderly patients (mean 69.4 ±7.7 years versus 70.5 ±8.3 years), receiving 'usual dose (3800 or 5700 anti-Xa IU) versus 'low dose' (3100 anti-Xa IU) nadroparin showed a higher incidence of adverse events in the 'usual dose' study (Fraisse, 2000) compared with the 'reduced dose' study (Harenberg, 1996). Major bleeding was reported in 5.6% and 0.4% of patients in Fraisse and Harenberg studies, respectively; the incidence of thrombocytopenia was 9.3% and 0% respectively.

Overall, the safety profile of nadroparin when administered in the doses recommended in this application as a thromboprophylactic agent to medical patients bedridden due to an acute illness is predictable and consistent with its mode of action and its pharmacology. Furthermore, the range and frequency of AEs reported in the publications submitted in this application are consistent with the information already provided in the Fraxiparine PI, with no new safety concerns identified. Furthermore, there is adequate evidence to support a dose reduction to 0.3 mL (2850 anti-Xa IU) of nadroparin for the new indication of thromboprophylaxis of **elderly** bedridden patients with acute medical illness.

# 9. First round benefit-risk assessment

## 9.1. First round assessment of benefits

See Table 4.

**Table 4: First round assessment of benefits.**

| Indication | |
|---|---|
| Benefits | Strengths and Uncertainties |
| Compared with placebo, weight based dosing with nadroparin at recommended doses significantly lowers incidence of DVT by 45%;<br>Nadroparin showed comparable efficacy to UFH in preventing DVT and PE (Harenberg, 1996).<br>Requires once daily administration compared to thrice daily with UFH.<br>Enoxaparin, nadroparin and certoparin were found to be similar in preventing PE and DVT in hospitalised medical patients, with similar rates of major and minor bleeding.<br>Similar or better safety profile in terms of haemorrhagic side effects compared to UFH | Reduction in DVT was modest; the difference in incidence of total DVT was barely statistically significant (nadroparin vs placebo: 13 vs 23, p = 0.045). The distribution of proximal (3 vs 7, p = 1.00) and distal (10 vs 17, p>0.05) thrombi was not statistically different between groups. No PE was reported in this pivotal study mainly due to lack of objective testing.<br>Interpretation was limited by low incidence of primary endpoint and lack of details (95% CI not presented). Furthermore, incidence of deaths was higher in the nadroparin treatment group..<br>This was based on indirect evidence from a MTC (Dooley, 2014) and there is lack of studies which directly compare one LMWH against another. LMWHs |

| Indication | |
|---|---|
| Benefits | Strengths and Uncertainties |
| | are not clinically interchangeable and so the general evidence provided for heparin (UFH and LMWH) and for all LMWHs cannot be extrapolated as evidence for efficacy/ safety of nadroparin for proposed new indication of thromboprophylaxis of medical patients bedridden due to acute illness.<br><br>Compared to UFH, significantly lower rate of withdrawals, thrombocytopenia, haematomas and local reactions (Forette, 1995). |

## 9.2. First round assessment of risks

See Table 5.

**Table 5: First round assessment of risks.**

| Risks | Strengths and Uncertainties |
|---|---|
| Risk of major and minor bleeding.<br><br>Metanalyses contained very few studies specifically evaluating nadroparin.<br><br>Patients with AMI and stroke were excluded from most of the studies and metanalyses. Hence, the proposed PI for nadroparin should specify lack of evidence of efficacy/ safety in these patient populations.<br><br>There was lack of data on patient care such as early mobilisation, physiotherapy and use of mechanical prophylaxis measures (such as elastic compression stockings, intermittent pneumatic compression) for the submitted studies. | Risks associated with nadroparin lower than with UFH.<br><br>Data provided was generalised for LMWHs- only some studies specifically evaluated nadroparin. Alikhan (2014) only 3/16 studies evaluated nadroparin; Dooley (2014) only 4/20 studies evaluated nadroparin.<br><br>This is especially relevant as nadroparin is not currently approved for treatment of unstable angina, STEMI, etc. while the other LMWHs dalteparin and enoxaparin are. Hence the general indication in acute medical illness proposed for nadroparin may be misleading.<br><br>As mentioned in the CHMP guidelines, specific standards of care in hospitalised patients along with concomitant illness and/ or treatment may confound interpretation of efficacy/ safety of nadroparin for the new indication of thromboprophylaxis in medical patients bedridden due to acute illness. |

## 9.3. First round assessment of benefit-risk balance

This was a LBS which included 6 published reports evaluating the safety and efficacy of nadroparin as a thromboprophylactic agent in hospitalised, acutely ill medical patients. Two additional publications focussed on the safety of prophylactic nadroparin in hospitalised, acutely ill medical patients and therefore primarily provided only safety data.

Most of the submitted publications complied with the TGA guidelines which state that a LBS must consist of reports of clinical trials that are conducted using the same active ingredients, with the same dosage concentration, a similar dosage regimen, dosage form, route of administration and indications to the product proposed for registration and are reported in sufficient detail to allow an independent assessment of the results in relation to the safety and efficacy of the product proposed for registration. The relevant published articles were identified through a structured and systematic review of scientific databases and selected using screening criteria designed to select those studies which met the objectives of the application. However, there were some limitations which precluded definitive conclusions from the submitted studies.

Compared with placebo, nadroparin at recommended doses (mean duration of treatment 11 days) significantly lowers incidence of DVT by 45% in COPD patients requiring mechanical ventilation (Fraisse, 2000). Nadroparin showed comparable efficacy to UFH in preventing DVT and PE (Harenberg, 1996). The main evidence for efficacy of nadroparin was provided by these two RCTs with supportive evidence provided by the 2 metanalyses (Alikhan, 2014; Dooley, 2014). There was a trend suggesting that additional benefits in preventing VTE are seen by extending the time of administration of nadroparin (Luba, 2007) although this requires confirmation in larger, randomised, controlled trials.

Nadroparin requires once daily administration compared to thrice (or twice) daily dosing with UFH. Nadroparin was also associated with significantly lower rate of withdrawals, thrombocytopenia, haematomas and local reactions compared with UFH (Forette, 1995).

The safety profile of nadroparin when administered in the doses recommended in this application as a thromboprophylactic agent to medical patients bedridden due to an acute illness is predictable and consistent with the information already provided in the approved Fraxiparine PI, with no new safety concerns identified. Furthermore, there is adequate evidence to support a dose reduction to 0.3 mL (2850 anti-Xa IU) of nadroparin in elderly patients.

The submitted data provides evidence to suggest that nadroparin, when administered in the doses recommended (3800 to 5700 anti-Xa IU) in this application as a thromboprophylactic agent to medical patients bedridden due to an acute illness, reduces the risk of a thromboembolic event, while generally reducing the risks of bleeding events, thrombocytopenia and local reactions compared to UFH. The efficacy/ safety of nadroparin in the recommended doses was evaluated in medical patients bedridden/immobilised for a minimum of 2-3 days with maximum duration of treatment up to 28 days.

The benefit of a reduction in venous thromboembolic events has to be balanced against a potential increase in the risk of bleeding. The risks of DVT and major bleeding are reduced with LMWH compared with UFH, indicating LMWH to be superior to UFH (Alikhan, 2014). Dooley (2014) concluded that enoxaparin, nadroparin and certoparin were found to be similar in preventing PE and DVT in hospitalised medical patients, with similar rates of major and minor bleeding. However, certoparin is not available in Australia and there is no comparative data with dalteparin, which is available in Australia. Furthermore, it is important to note that LMWHs are not clinically interchangeable and so the general evidence provided for heparin (UFH and LMWH) and for other LMWHs cannot be extrapolated as evidence for efficacy/ safety of nadroparin for proposed new indication of thromboprophylaxis of medical patients bedridden due to acute illness.

Since a 'general indication' of 'thromboprophylaxis for bedridden patients with acute medical illness' is intended for this submission, it is important that the trial population has adequate representation of several applicable subgroups e.g., stroke, cardiac disease, cancer and infection/inflammation, due to the heterogeneous nature of predisposing factors (CHMP guidelines). However, the pivotal RCTs did not evaluate all of above subgroups. Specifically, Fraisse (2000) which was the only placebo-controlled, randomised study evaluated patients with acute respiratory decompensated COPD who required mechanical ventilation. Although patients in this study did present with serious risk factors for DVT such as immobilization (100%), respiratory disease (100%), bronchial superinfection (74%), congestive heart failure (29%), age > 65 yr (50%), obesity (23%), venous insufficiency (13%), neoplastic disease (5%) and previous thromboembolic disorders (4%), it appears that patients with stroke and acute myocardial infarction were excluded from this study. Furthermore, the Alikhan (2014) meta-analysis excluded patients with stroke, AMI and admission to ICU. Although the Harenberg (1996) pivotal non-inferiority study included a much wider patient population, interpretation from this study was limited by low incidence of primary endpoints (DVT and PE) as well as lack of details in the study report to confirm that all patients enrolled in this study were actually bedridden (the inclusion criteria only stated expected duration of hospitalisation/ immobilisation >10 days and the actual duration of immobilisation was not provided in the study report). Furthermore, the incidence of deaths was higher in the nadroparin group.

There are 3 LMWHs available in Australia: nadroparin, enoxaparin and dalteparin. Enoxaparin is approved for thromboprophylaxis in medical patients bedridden due to acute illness. However, enoxaparin has separate approved indications for unstable angina (with aspirin) and treatment of acute STEMI. Dalteparin is not approved for thromboprophylaxis in medical patients bedridden due to acute illness although it is approved for treatment of unstable angina. It is important to note that the risk of VTE and the need for thromboprophylaxis differs in patients with stroke and AMI. Nadroparin is not approved separately for unstable angina and hence it is very important to specify this fact as the 'general' indication proposed in this submission may be misleading.

The benefit-risk balance for nadroparin for proposed indication of thromboprophylaxis in medical patients bedridden with acute illness is unfavourable, but may become favourable if specific changes are made to proposed PI (especially indications, dosing and clinical trials).

# 10. First round recommendation regarding authorisation

It is recommended that submission for registration of Fraxiparine (nadroparin) for extended indication of:

*Prophylaxis of venous thromboembolism in medical patients bedridden due to acute illness*

be rejected at this stage.

The main reasons for rejection at this stage are:

- CHMP guidelines clearly state that it is important that the trial population has adequate representation of several applicable subgroups e.g., stroke, cardiac disease, cancer and infection/ inflammation, due to the heterogeneous nature of predisposing factors. Nadroparin was not evaluated in patients with unstable angina, AMI and stroke and hence the proposed generalised indication for "medical patients with acute illness' may be misleading. This is especially relevant as nadroparin is not currently approved for treatment of unstable angina, STEMI, etc. while the other LMWHs dalteparin and enoxaparin are.
- The pivotal placebo-controlled study (Fraisse, 2000) excluded patients with stroke and AMI. The Alikhan meta-analysis excluded patients with stroke, AMI and admission to intensive care unit. Although equivalence between nadroparin and UFH was demonstrated in the

other pivotal controlled study (Harenberg, 1996) which enrolled patients from many subgroups, interpretation was limited by low incidence of primary endpoints (DVT and PE), lack of adequate details for efficacy results and increased incidence of deaths in the nadroparin group.

- Furthermore, it is important to note that LMWHs are not clinically interchangeable and so the general evidence provided for heparin (UFH and LMWH) and for other LMWHs in the two meta-analysis cannot be extrapolated as evidence for efficacy/safety of nadroparin for proposed new indication of thromboprophylaxis of medical patients bedridden due to acute illness.
- However, nadroparin, when administered in the recommended doses (3,800 to 5,700 anti-Xa IU) to medical patients bedridden due to an acute illness may lead to modest reduction in the risk of a thromboembolic event, while generally reducing the risks of bleeding events, thrombocytopenia and local reactions compared to UFH. Hence, approval could be considered following incorporation of suggested changes to the proposed PI and satisfactory response to clinical questions.

# 11. Clinical questions

## 11.1. Clinical questions

### 11.1.1. Pharmacokinetics

Not applicable.

### 11.1.2. Pharmacodynamics

Not applicable.

### 11.1.3. Efficacy

1. Fraisse, 2000: The published study mentions the following:

   *From March 1992 through April 1995, consecutive patients admitted with acute, respiratory-decompensated COPD, who required mechanical ventilation, were enrolled if they were 40 to 80 yr of age and weighed 45 to 110 kg. Patients were **included** if they had: a history of a confirmed DVT within the previous 6 mo or presence of signs of a DVT on the Doppler ultrasonography at inclusion, an organic lesion that could bleed, i.e., an active gastroduodenal ulcer or a recent hemorrhagic cerebrovascular accident; severe liver failure leading to a decrease of the prothrombin time (PT) to less than 50% (normal values between 70 and 100%); severe renal impairment (serum creatinine > 300 mmol/L); confirmed or uncontrolled hypertension (diastolic blood pressure . 120 mm Hg); a congenital or acquired coagulation disorder; a history of hypersensitivity or thrombocytopenia to heparins of any type; were contraindicated to anticoagulant therapy, venography, or angiography; or were receiving any form of acetylsalicylic acid, ticlopidine, or oral anticoagulants.*

   There appears to be an error as the authors seem to imply that these patients were **excluded** from the study. Could the sponsor provide clarification regarding this apparent typographical error?

2. Harenberg (1992, 1996): The dose of nadroparin used in this study was not weight-based. The reduced dose of 0.3 mL was justified as the patient population enrolled in this study was elderly (with mean age of 70 years and 55% aged 70-80 years). However, it is not clear why 0.3 mL of Fraxiparine used in this study had 3100 anti-Xa IU while the proposed PI

mentions 0.3 mL as 2850 anti-Xa IU. Could the sponsor provide clarification regarding this apparent discrepancy in anti-Xa activity?

3. Harenberg (1992, 1996): The published study did not specify if all patients were actually bedridden as the inclusion criteria: 'expected duration of bed rest and hospital stay ≥ 10 days' was too generalised. The only information regarding actual duration of bed rest mentions that the median duration of bed rest ranged from 0-20 days in both treatment groups. Furthermore, details regarding patient care such as early mobilisation and physiotherapy were not provided or considered in the analysis and may limit interpretation. Could the sponsor provide clarification on these issues?
4. Luba, 2007: The paper provided in the submission mentions the following: "The immobilization duration was **37 days** (mean 4.8 days; in group I – 5.1 days and in group II – 4.5 days)." However, there appears to be a typographical error as table mentions duration of immobilisation was 3-11 days with mean of 4.8 days (group I=5.1 days and group II=4.5 days). Could the sponsor clarify this issue?
5. Pottier, 2000: The dose of nadroparin used in this open-label, epidemiological study was not weight-based. Patients included in this study were not only elderly to the reason for fixed reduced dose is not clear. Furthermore, it is important to note that 0.3 mL of Nadroparin used in this study had 3075 anti-Xa IU while the proposed PI mentions 0.3 mL as 2850 anti-Xa IU. Could the sponsors clarify this issue?
6. Forette, 1995: The 0.3 mL dose of Nadroparin used in this study had 3075 anti-Xa IU while the proposed PI mentions 0.3 mL as 2850 anti-Xa. IU. Could the sponsor clarify this issue?

#### 11.1.4. Safety

None.

# 12. Second round evaluation

The initial questions by the evaluators are mentioned first followed by a summary of the sponsor's response and the evaluator's comments on this response.

**Question 1**

· Fraisse, 2000: The published study mentions the following:

> *From March 1992 through April 1995, consecutive patients admitted with acute, respiratory-decompensated COPD, who required mechanical ventilation, were enrolled if they were 40 to 80 yr of age and weighed 45 to 110 kg. Patients were **included** if they had: a history of a confirmed DVT within the previous 6 mo or presence of signs of a DVT on the Doppler ultrasonography at inclusion, an organic lesion that could bleed, i.e., an active gastroduodenal ulcer or a recent hemorrhagic cerebrovascular accident; severe liver failure leading to a decrease of the prothrombin time (PT) to less than 50% (normal values between 70 and 100%); severe renal impairment (serum creatinine > 300 mmol/L); confirmed or uncontrolled hypertension (diastolic blood pressure . 120 mm Hg); a congenital or acquired coagulation disorder; a history of hypersensitivity or thrombocytopenia to heparins of any type; were contraindicated to anticoagulant therapy, venography, or angiography; or were receiving any form of acetylsalicylic acid, ticlopidine, or oral anticoagulants.*

There appears to be an error as the authors seem to imply that these patients were **excluded** from the study. Could the sponsor provide clarification regarding this apparent typographical error?

**Sponsor's response**

The applicant reviewed the paper and agree with the assessor that it is more likely that these patients were excluded from the study and that the word "included" in the source article is in fact a typographical error. Review of the criteria show that many are in fact contraindicated for use of nadroparin (an active gastroduodenal ulcer, recent haemorrhagic cerebrovascular accident, severe renal impairment and history of hypersensitivity or thrombocytopenia to heparins of any type) due to an unacceptable risk of bleeding or hypersensitivity reaction. Others are documented to be used with caution (confirmed or uncontrolled hypertension, severe liver failure) as the patients are at an increased risk of bleeding. The other exclusion criteria are likely to bias assessment of the efficacy outcomes (recent history of DVT, use of acetylsalicylic acid, ticlopidine, or oral anticoagulants).

**Evaluator's comments**

The sponsor's response is satisfactory.

**Question 2, 5 and 6**

- Harenberg (1992, 1996): The dose of nadroparin used in this study was not weight-based. The reduced dose of 0.3 mL was justified as the patient population enrolled in this study was elderly (with mean age of 70 years and 55% aged 70-80 years). However, it is not clear why 0.3 mL of Fraxiparine used in this study had 3100 anti-Xa IU while the proposed PI mentions 0.3 mL as 2850 anti-Xa IU. Could the sponsor provide clarification regarding this apparent discrepancy in anti-Xa activity?
- Pottier, 2000: The dose of nadroparin used in this open-label, epidemiological study was not weight-based. Patients included in this study were not only elderly to the reason for fixed reduced dose is not clear. Furthermore, it is important to note that 0.3 mL of Nadroparin used in this study had 3075 anti-Xa IU while the proposed PI mentions 0.3 mL as 2850 anti-Xa IU. Could the sponsors clarify the issue of dose raised in the evaluation report?
- Forette, 1995: The 0.3 mL dose of Nadroparin used in this study had 3075 anti-Xa IU while the proposed PI mentions 0.3 mL as 2850 anti-Xa.IU. Could the sponsors clarify this issue?

**Sponsor's response**

The potency of nadroparin calcium was initially expressed in Institut Choay Units (ICU) (25,000 anti-Xa ICU/ mL). In 1991, according to the World Health Organization (WHO), the potency of nadroparin calcium was expressed in International Units (IU WHO) (10,250 anti-Xa IU/ mL). One anti-Xa ICU is equivalent to 0.41 anti-Xa IU WHO (Leyvraz, 1991). Therefore 0.3 mL is equivalent to 3075 anti Xa IU WHO.

Since 1996, nadroparin calcium has been expressed in new IUs according to directives from the European Pharmacopoeia (9,500 anti-Xa IU. Eur.Ph/ mL). One anti-Xa ICU is equivalent to 0.38 anti-Xa IU. Therefore 0.3 mL is equivalent to 2850 IU Eur.Ph. In this module, the units in the published citation may vary depending on the standards for expressing anti-Xa activity at the time the study was conducted.

As an additional measure, the sponsor has written directly to the publication authors requesting further clarification. Aspen will provide the TGA with a copy of any response received from the publication authors.

**Evaluator's comment**

The sponsor's response is satisfactory.

**Question 3**

- Harenberg (1992, 1996): The published study did not specify if all patients were actually bedridden as the inclusion criteria: 'expected duration of bed rest and hospital stay ≥ 10

days' was too generalised. The only information regarding actual duration of bed rest mentions that the median duration of bed rest ranged from 0-20 days in both treatment groups. Furthermore, details regarding patient care such as early mobilisation and physiotherapy were not provided or considered in the analysis and may limit interpretation. Could the sponsor provide clarification on these issues?

**Sponsor's response**

The patient characteristics of those included in the study were elderly patients aged between 50 and 80 years due to cardiac insufficiency, cerebrovascular disease, coronary heart disease, cancer, diabetes, gastro or nephrology disease, COPD, infection and other diseases. The eligible patients also had additional risk factors for VTE of excess weight, varicosis, history of thrombosis or pulmonary embolism, intake of oestrogens, thrombocytosis, previous myocardial infarction, thrombotic or cerebral infarction, or peripheral arterial ischemia. It is also noted in the publication that patients were excluded from further evaluation after randomisation due to early discharge and transfer to a different ward. Although lacking specificity in the actual publication, it is expected that the majority of these patients would be immobilised as a result of their admission to hospital, underlying disease with additional risk factors for VTE and age. In addition, the patient characteristics describe acutely ill patients who were assessed at days 1, 4, 6, 8 and 10 for clinical symptoms of deep vein thrombosis and pulmonary embolism, it is unlikely that within 10 days hospitalisation for their underlying illness that they underwent early mobilisation or physiotherapy. Although the follow-up observation period was from 1-94 days, the mean duration of follow-up was 7.5 (nadroparin) to 8 (UFH) days indicating that the majority of patients were followed up for less than 10 days.

**Evaluator's comments**

The sponsor's response is satisfactory.

**Question 4**

- Luba, 2007: The paper provided in the submission mentions the following: "The immobilization duration was **37 days** (mean 4.8 days; in group I – 5.1 days and in group II – 4.5 days)."However, there appears to be a typographical error as table mentions duration of immobilisation was 3-11 days with mean of 4.8 days (group I=5.1 days and group II=4.5 days). Could the sponsor clarify this issue?

**Sponsor's response**

The applicant reviewed the paper and agrees with the assessor that it is likely that the immobilisation period of 37 days was a typographical error in the article. One of the inclusion criteria is specified as immobilization period of 3-14 days and it also specified an immobilisation period of 3-14 days. It is also documented that "the immobilization time in the confirmed deep vein thromboembolism group (n = 15) was 8 days on the average and was nearly twice as long as the mean immobilization time in the rest of the patients." In the context of above and the mean days in both groups it is more probable that that this should read 3-14 days.

With regard to questions 1, 3 and 4, while Aspen agrees that it is likely there are typographical errors in the papers, it is not possible to confirm this from the publications itself. The sponsor has therefore written directly to the publication authors requesting clarification of these apparent errors.

**Evaluator's comments**

The sponsor's response is satisfactory.

**General question**

- A statement in "Foreign regulatory status" suggests that nadroparin has received approval for proposed new indication in only Austria and the Czech Republic. However, the "Clinical summary" mentions the following:
    - § This extension to indication has already been approved in Austria (2001), Belgium (2000), Luxembourg (2000), Portugal (2004) and Spain (1998).

  Could the sponsors please provide clarification on this? Furthermore, the approved product information for these countries was not provided. Could the sponsors please provide these for review?

**Sponsor's response**

The sponsors have provided a table summarising current approval status in EU countries which was already provided earlier. The sponsors also state that these were all national submissions and approved at different times so the wording is slightly different depending on how the national assessor evaluated the data, also these are all translations from local language so may account for some of the minor differences. There is no EU DCP for nadroparin that has this indication approved. Due to the long timelines for translation, Aspen was only able to get the Austrian and Czech PI translated into English.

**Evaluator's comment**

Review of the English translations of the approved PIs in the Czech Republic and Austria reveal that wording of the approved indication in these countries was as follows:

- In the Czech Republic:

  *Prophylaxis of thrombotic complications in high-risk patients (respiratory insufficiency and/or respiratory tract infection and/or heart failure) confined to bed due to acute disease or hospitalised at the intensive care unit.*

- In Austria:

  *Prophylaxis of thrombotic complications in high-risk patients (respiratory insufficiency and/or respiratory tract infection and/or heart failure) who are immobilized or in intensive care unit because of acute illness.*

It is important to note that the above wording is similar to the wording proposed by the evaluators in Australia.

# 13. Second round benefit-risk assessment

## 13.1. Second round assessment of benefits

After consideration of the responses to clinical questions, the benefits of nadroparin in the proposed usage are unchanged from those identified in the first round.

## 13.2. Second round assessment of risks

After consideration of the responses to clinical questions, the risks of nadroparin in the proposed usage are unchanged from those identified in the first round.

### 13.3. Second round assessment of benefit-risk balance

The benefit risk balance of nadroparin is unfavourable given the proposed usage, but would become favourable if the changes recommended are adopted.

# 14. Second round recommendation regarding authorisation

It is recommended that submission for registration of Fraxiparine (nadroparin) for extended indication of:

> *Prophylaxis of venous thromboembolism in medical patients immobilised due to acute illness*

be rejected.

The main reason for rejection is the submitted studies lacked adequate representation of several applicable subgroups as nadroparin was not evaluated in patients with unstable angina, AMI and stroke and hence the proposed generalised indication is too broad. This is especially relevant as nadroparin is not currently approved for treatment of unstable angina, STEMI, etc. while the other LMWHs dalteparin and enoxaparin are. The pivotal placebo-controlled study (Fraisse, 2000) excluded patients with stroke and AMI. The Alikhan meta-analysis excluded patients with stroke, AMI and admission to intensive care unit. Although equivalence between nadroparin and UFH was demonstrated in the other pivotal controlled study (Harenberg, 1996) which enrolled patients from many subgroups, interpretation was limited by low incidence of primary endpoints (DVT and PE), lack of adequate details for efficacy results and increased incidence of deaths in the nadroparin group.

However, nadroparin, when administered in the recommended doses (3,800 to 5,700 anti-Xa IU) to medical patients immobilised due to an acute illness may lead to modest reduction in the risk of a thromboembolic event, while generally reducing the risks of bleeding events, thrombocytopenia and local reactions compared to UFH. Hence, approval could be considered for a more restricted indication as follows:

> *Prophylaxis of venous thromboembolism in high risk medical patients (respiratory failure and/or respiratory infection and/or cardiac failure), immobilised due to acute illness or hospitalised in an intensive care unit.*

Further, approval for the above restricted indication is also subject to incorporation of all suggested changes to the proposed PI.

# 15. References


- Aquino JP, Gambier A, Ducros JJ. Prevention des accidents thrombo-emboliques par nadroparine calcique chez les sujets ages. Fraxiparin -2e Symposium International – Ed. Bounameaux H. Samama Ten Cate 1991;51-4.
- Barnes, RW, Lavender RC and Ernest JF. Perioperative asymptomatic veft;;; thrombosis. Role of duplex scanning versus venography. J. Vast. Surg, 2,25 l-260,
- Barrelier MT. Echo Doppler veineux; future examen de reference dans le diagnostic des thrombosis des membres inferieurs? Ann Fr Anesth Reanim 1992; 11:370-6.
- Bergmann JF and Neuhart E. 1996. A multicenter randomised double- blind study of enoxaparin compared with unfractionated heparin in the prevention of venous

thromboembolic disease in elderly inpatients bedridden for an acute medical illness. *Schattauer Verlagsgesellschaft mbH*. 76:529–534.

- Borris, LC, Christiansen HM, Lassen MR, Olson AD and Schott P. Real-time B-mode ultrasonography in the diagnosis of postoperative deep vein thrombosis in non-symptomatic high-risk patients. Eur. J. Vast. Sure. 4, 473-475, 1990.
- Carson W, Schilling B, Simons R, et al. Comparative effectiveness of dalteparin and enoxaparin in the hospital setting. J Pharm Pract 2012;25:180-9.
- Cohen AT, Davidson BL, Gallus AS, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. Br Med J. 2006; 332: 325-329.
- Cohen AT, Davidson BL, Gallus AS, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. BMJ 2006;332:325-9.
- Cohen AT, Edmondson RA, Phillips MJ, Ward VP, Kakkar VV. The changing pattern of venous thromboembolic disease. *Haemostasis* 1996;**26**(2):65–71.
- Collins R, MacMahon S, Flather M, Baigent C, Remvig L, Mortensen S, et al. Clinical effects of anticoagulant therapy in suspected acute myocardial infarction: systematic overview of randomised trials. *BMJ* 1996;**313**(7058): 652–9.
- Cronan JJ, Dorfman GS and Grusmark, J. Lower extremity deep venous thrombosis: further experience and refinement of US-assessment. Radiology 168, lOl- 107, 1988.
- Dahan, R, Houlbert D, Caulin C, Cuzin E, Viltart C, Woler M and Segrestaa JM. 1986. Prevention of deep vein thrombosis in elderly medical in-patients by a low molecular weight heparin: a randomised double-blind trial. *Haemostasis* 16:159–164.
- Dahlback B. Advances in understanding pathogenic mechanisms of thrombophilic disorders. *Blood* 2008;**112** (1):19–27.
- Diener HC, Ringelstein EB, von Kummer R, et al. Prophylaxis of thrombotic and embolic events in acute ischemic stroke with the low-molecular-weight heparin certoparin: results of the PROTECT trial. Stroke. 2006; 37: 139-144
- Elias A, Boccalon H. Methodes d'investigation des thrombosis veineuses. Interets respectifs et strategie du diagnostic. Sang Thrombose Vaisseaux 1991;3:109-16.
- Elias, A. Lecroff, G. Bouvier, JL. Benichou, M. Serradimigni, A. Diagnosis of deep venous thrombosis: value of real time B mode ultrasound imaging and continuous wave doppler (echography-doppler) compared to venography. H Anpio.6, 175-182, 1987.
- Forette B. and Wolmark, Y. 1995. Nadroparine calcique dans la prevention de la maladie thrombo-embolique chez le sujet âgé. *Presse Med.* 24:567–571.
- Gardlund B; for the Heparin Prophylaxis Group. Randomised, controlled trial of low-dose heparin for prevention of fatal pulmonary embolism in patients with infectious disease. Lancet 1996;347:1357-61.
- Geerts WH, Bergqvist D, Pineo GF, Heit JA, Samama CM, Lassen MR, et al. Prevention of venous thromboembolism. *Chest* 2008;**133**(6 Suppl):381S–453S.
- Gubitz G, Sandercock P, Counsell C. Anticoagulants for acute ischaemic stroke (Review). *Cochrane Database of Systematic Reviews* 2004, Issue 3. [DOI: 10.1002/ 14651858.CD000024.pub2]
- Habscheid W and Wilhelm T. Diagnostik der tiefen Beinvenenthrombose durch Real-time-Sonographie. Dtsch. Med. Wschr,m, 586-591, 1988.

- Habscheid W, Hghmann M, Wilhelm T and Epping J. Real-time ultrasound in the diagnosis of acute deep venous thrombosis of the lower extremity. Angiology 41, 599-608, 1990.
- Higgins JPT, Green S (eds). Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available at: www.cochrane-handbook.org [Last accessed 1 November 2012
- Hillbom M, Erila T, Sotaniemi K, et al. Enoxaparin vs heparin for prevention of deepvein thrombosis in acute ischemic stroke: a randomised, double-blind study. Acta Neurol Scand. 2002; 106: 84-92.
- International Consensus Statement. 1997. Prevention of Thromboembolism. Med-Orion Publishing Company, London. 19. 21. Rubenstein, I., D. Murray and V. Hoffstein. 1988. Fatal pulmonary emboli in hospitalised patients: an autopsy study. *Arch. Intern. Med.* 148:1425–1426.
- Jongbloets LMM, Lensing AWA, Buller HR and Ten Cate JW. The value of real-time compression ultrasonography in detecting deep-vein thrombosis in asymptomatic high-risk patients. Thromb. Res,& Suppl. 1, C 88, 1992.
- Kakkar AK, Ciminniello C, Goldhaber SZ, et al. Low-molecular-weight heparin and mortality in acutely ill medical patients. N Engl J Med. 2011;365:2463-72.
- Kamphuisen PW, Agnelli G, Sebastianelli M. Prevention of venous thromboembolism after acute ischemic stroke. J Thromb Haemost. 2005; 3: 1187-1194.
- Kay R, Wong KS, Yu YL, Chan YW, Tsoi TH, Ahuja AT, Chan FL, Fong KY, Law CB and Wong A. 1995. Low-molecular- weight heparin for the treatment of acute ischemic stroke. *N. Engl. J. Med.* 333:1588–1593.
- Kelly J, Rudd A, Levis RR, et al. Screening for proximal deep vein thrombosis after acute ischemic stroke: a prospective study using clinical factors and plasma D-dimers. J Thromb Haemost. 2004; 2: 1321-1326.
- Lederle FA, Sacks JM, Fiore L, et al. The prophylaxis of medical patients for thromboembolism pilot study. Am J Med 2006;119:54-9.
- Lederle, F. A. 1998. Heparin prophylaxis for medical patients? *Ann. Intern. Med.* 118:768–770.
- Leizorovicz A, Cohen AT, Turpie AG, et al. Randomised, placebo-controlled trial of dalteparin for the prevention for venous thromboembolism in acutely ill medical patients. Circulation 2004;110:874-9.
- Lensing AWA, Prandoni P, Brandjes D, Huisman PM, Vigo M, Tomasella G, Krekt J, Ten Cate, J.W., HIUSMAN, M.V. and BULLER, H.R. Detection of deep-vein thrombosis by real-time B-mode ultrasonography. N. Frtgl& Els;d m, 342-345, 1989.
- Mahe I, Bergmann JF, d'Azemar P, et al. Lack of effect of a low-molecular weight heparin (nadroparin) on mortality in bedridden medical in-patients: a prospective randomised double blind study. Eur J Clin Pharmacol 2005;61:347-51.
- Manciet G. Vergnes C. Boisseau MR. Etude de l'efficacite et de la tolerance de nadroparine calcique administree au long cours chex le sujet age. Fraxiparine – 2e Symposium International. Ed. Bounameaux. H. Samama, Ten Cate 1991;51-4.
- Manciet G, Richard S, Albert D, Vergnes C, Emeriau JP and Boisseau MR. 1996. Indications of low-molecular-weight heparins in elderly patients. *Rev. Gériatr.* 21:460–468.

- Millewich LA, Bedford GR, Beach KW and Strandes DE. Diagnosis of deep venous thrombosis, a prospective study comparing duplex scanning to contrast venography. Circulatiou29,810-814, 1989.
- Planes A, Vochelle N, Darmon JY, Fagola M, Bellaud M and Huet Y. 1996. Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: double-blind randomised comparison of enoxaparin versus placebo. *Lancet* 348:224– 228.
- Prescott SM, Richards KL, Tikoff G, Armstrong JD Jr and Shigeoka JW. 1981. Venous thromboembolism in decompensated chronic obstructive pulmonary disease: a prospective study. *Am. Rev. Respir. Dis.* 123:32–36.
- Rubenstein I, Murray D and Hoffstein V. 1988. Fatal pulmonary emboli in hospitalised patients: an autopsy study. *Arch. Intern. Med.* 148: 1425–1426.
- Samama MM, Cohen AT, Darmon JY, et al. Prophylaxis for medical patients with enoxaparin study group. A comparison of enoxaparin with placebo for the prevention of venous thromboembolism in acutely ill medical patients. N Engl J Med 1999;341:793-800
- Sandset PM, Dahl T, Stiris M, Rostad B, Scheel B and Abildgaard U. 1990. A double-blind and randomised placebo controlled trial of low molecular weight heparin once daily to prevent deep vein thrombosis in acute ischemic stroke. *Semin. Thromb. Hemost.* 16(Suppl.): 25–33. Thromboembolic Risk Factors (Thrift) Consensus Group. 1992. Risk of and prophylaxis for venous thromboembolism in hospital patients. *B.M.J.* 305:567–574.
- Turpie AGG, Levine MN, Hirsch J, Carter CJ, Jay RM, Powers PJ, Andrew M, Magnani HN, Hull RD and Gent M. 1987. Double-blind randomised trial of ORG 10172 low-molecular-weight heparinoid in prevention of deep-vein thrombosis in thrombosis stroke. *Lancet* I 8532:523–526.
- Vesconi, S, Rossi GP, Pesenti A, Fumagalli R and Gattinoni L. 1988. Pulmonary microthrombosis in severe adult respiratory distress syndrome. *Crit. Care Med.* 16:111–113.
- Winter JH, Buckler PW, Bautista AP, Smith FW, Sharp PF, Bennett B and Douglas AS. 1983. Frequency of venous thrombosis in patients with an exacerbation of chronic obstructive lung disease. *Thorax* 38:605–608.
- Woolson ST, Crory DW, Walter JF, Malney WJ, Wait JM and Cahill PD. B-mode ultrasound scanning in the detection of proximal venous thrombosis after total hip replacement. *J. Bone Joint Surg*, m, 983-987,1990.

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