Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Nadroparin

Proprietary Product Name: Fraxiparine

Sponsor: Aspen Pharmacare Australia Pty Ltd

September 2018

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 AusPARs

- An Australian Public Assessment Report (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations and extensions of indications.
- An AusPAR is a static document; it provides information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

Common abbreviations

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

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

I. Introduction to product submission

Submission details

Type of submission:	Extension of indications
Decision:	Approved
Date of decision:	28 August 2017
Date of entry onto ARTG:	31 August 2017
ARTG numbers:	51308 (1,900 IU anti-Xa/0.3 mL) 51309 (2,850 IU anti-Xa/0.3 mL) 51310 (3,800 IU anti-Xa/0.4 mL) 51311 (5,700 IU anti-Xa/0.6 mL) 51312 (7,600 IU anti-Xa/0.6 mL) 51313 (9,500 IU anti-Xa/0.6 mL)
Active ingredient:	Nadroparin
Product name:	Fraxiparine
Sponsor's name and address:	Aspen Pharmacare Australia Pty Ltd 34-36 Chandos Street St Leonards NSW 2065
Strengths / dose forms:	Disposable glass pre-filled single use syringes containing nadroparin calcium 9,500 IU anti-Xa/mL. The following strengths are applicable to this submission: · 2,850 IU anti-Xa/0.3 mL · 3,800 IU anti-Xa/0.4 mL · 5,700 IU anti-Xa/0.6 mL
Container:	Disposable glass pre-filled single-use syringes
Pack sizes:	2 and 10 syringes
Approved therapeutic use:	Prophylaxis of venous thromboembolism in high-risk medical patients who are immobilised due to acute illness or hospitalised in an intensive care unit
Route of administration:	Subcutaneous

Product background

This AusPAR describes a literature-based submission (LBS) by the sponsor to extend the indications for nadroparin (tradename: Fraxiparine). The current indications are:

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

The proposed new indications are:

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

Nadroparin is a low molecular weight heparin (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), leading to an accelerated inhibition of factor Xa and to a lesser extent factor IIa.

Fraxiparine is a sterile, clear, preservative-free solution supplied in disposable glass pre-filled single-use syringes containing nadroparin calcium 9,500 IU anti-Xa/mL in water for injection 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

The Product Information (PI) states that all volumes and pack sizes may not be available in Australia.

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.

Table 2: Proposed dosing

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 0.3 mL (2,850 IU anti-Xa) may be appropriate.

Following initial consultation with TGA, the sponsor prepared a literature based submission to support the proposed new indication. Fraxiparine injections have been approved in a number of countries (including Australia) for the treatment and prophylaxis of thromboembolic disorders for greater than 10 years, in line with guidance for literature based submissions.

The dossier included six published reports evaluating the efficacy and safety of nadroparin as a thromboprophylactic agent in hospitalised, acutely ill medical patients. Two were

randomised controlled trials (Fraisse, 2000;[1] Harenberg, 1992, 1996), two were systematic meta-analyses (Alikhan, 2014; Dooley, 2014) and two were open label studies (Luba, 2007; Pottier, 2000). Two additional publications reported on the safety of prophylactic nadroparin in hospitalised, acutely ill medical patients (Forette, 1995; Pessina, 2003).

The TGA-adopted CHMP 2006'Guideline on clinical investigation of medicinal products for the prophylaxis of venous thromboembolic risk in non-surgical patients' was considered during evaluation of this submission.[2] This provides guidance on adequate representation of medical subgroups:

> *If a 'general indication' is intended, 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 first included in the Australian Register of Therapeutic Goods (ARTG) on 14 August 1995.

Nadroparin was considered by the Australian Drug Evaluation Committee (ADEC) in 1998.[3] ADEC supported the application to register a new formulation, Fraxiparine Forte, to be administered daily for the treatment of DVT, compared to twice daily for the existing formulation of Fraxiparine which was half the strength.

Regulatory status

At the time of this submission to TGA, nadroparin had been approved in some European countries for the prevention of thromboembolic disease in medical patients. There are variations in the wording of the indications because they were assessed as separate national submissions (translations may also account for some of the minor differences). Of the 13 countries:

- 7 have an indication for high risk medical patients (respiratory failure and/or respiratory infection and/or cardiac failure) hospitalised in an ICU (Belgium, Croatia, Lithuania, Luxembourg, Romania, Slovakia, Slovenia)
- 2 have an indication for high risk patients immobilised/bedridden due to acute illness or hospitalised in an ICU (Austria, Czech)
- 4 have an indication for medical patients at high, or medium to high, risk of VTE (Hungary, Poland, Portugal, Spain)

At the time of this submission to TGA, nadroparin was not approved in USA or UK. It was approved in Canada, but not for the proposed indication. The proposed indication for medically ill patients was under review by the Swiss and Canadian regulatory agencies.

[1] Fraisse F, et al. Nadroparin in the prevention of deep vein thrombosis in acute decompensated COPD. The Association of Non-University Affiliated Intensive Care Specialist Physicians of France. *Am J Respir Crit Care Med.* 161(4 Pt 1): 1109-14 (2000).
[2] Guideline on clinical investigation of medicinal products for prevention of venous thromboembolism (VTE) in nonsurgical patients (formerly CPMP/EWP/6235/04)
[3] ADEC, the Australian Drug Evaluation Committee, was formed in 1963 and given the role of providing independent, scientific advice on new drugs, within the policy framework of the time, to the Federal Government. In 2010, ADEC was replaced by the Advisory Committee on Prescription Medicines (ACPM), and subsequently replaced by the Advisory Committee on Medicines (ACM).

Product Information

The Product Information (PI) approved with the submission which is described in this AusPAR can be found as Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

II. Registration timeline

The following table captures the key steps and dates for this application and which are detailed and discussed in this AusPAR.

Table 3: Registration timeline

Description	Date
Submission dossier accepted and first round evaluation commenced	30 September 2016
First round evaluation completed	28 February 2017
Sponsor provides responses on questions raised in first round evaluation	1 May 2017
Second round evaluation completed	24 May 2017
Delegate's Overall benefit-risk assessment and request for Advisory Committee advice	4 July 2017
Sponsor's pre-Advisory Committee response	13 July 2017
Advisory Committee meeting	4 August 2017
Registration decision (Outcome)	28 August 2017
Completion of administrative activities and registration on ARTG	31 August 2017
Number of working days from submission dossier acceptance to registration decision*	188

* Legislative timeframe is 255 working days

III. Quality findings

Introduction

There was no requirement for a quality evaluation in a submission of this type.

IV. Nonclinical findings

There was no requirement for a nonclinical evaluation in a submission of this type.

V. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

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 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.

Contents 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 (LBS).

Following initial consultation with and endorsement by TGA, the sponsor 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 (randomised control trials (RCT) 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 aIU anti-Xa.
- 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:[4]

- 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); and

[4] These studies are outlined in the Delegate's Overview in this AusPAR.

· 2 studies which only evaluated safety (Forette, 1995; Pessina, 2003).

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.

Good clinical practice

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

Pharmacokinetics

Studies providing pharmacokinetic data

No new pharmacokinetic information was provided.

Evaluator's conclusions on pharmacokinetics

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

Pharmacodynamics

Studies providing pharmacodynamic data

No new pharmacodynamic information was provided.

Evaluator's conclusions on pharmacodynamics

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

Dosage selection for the pivotal studies

Pharmacokinetics and pharmacodynamics: dose finding studies

Not applicable.

Phase II dose finding studies

No data provided.

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 IU anti-Xa, that is, 0.4 mL for 45 to 70 kg; 5,700 anti-Xa, that is, 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 to 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 three times daily or 3100 IU (anti-Xa)/0.3 mL LMWH (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 immobilisation was observed in the open-label study but interpretation was limited by open-label study design and low occurrence of events.

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.

Efficacy

Studies providing 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.

Evaluator's conclusions on efficacy

A total of 6 published reports evaluating the safety and efficacy of nadroparin as a thromboprophylactic agent in hospitalised, acutely ill medical patients were 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 IU anti-Xa and > 70 kg, 5700 IU anti-Xa). 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 immobilisation time will result in larger clinical benefits than prophylaxis limited to the immobilisation time.

The studies by Forette 1995, Pottier 2000 and Harenberg 1996, administered a lower dose of nadroparin (3100 or 3075 IU IU anti-Xa), consistent with the proposed recommendation in this application for elderly patients (2850 IU IU anti-Xa). 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 IU aIU anti-Xa) 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, for example,stroke, cardiac disease, cancer and infection/ inflammation, due to the heterogeneous nature of predisposing factors (CHMP guidelines).[5] 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 immobilisation (100%), respiratory disease (100%), bronchial superinfection (74%), congestive heart failure (29%), age > 65 years (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, acute myocardial infarction (AMI) and admission to intensive care units (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.[6] Dalteparin is not approved for thromboprophylaxis in medical patients bedridden due to acute illness although it is approved for treatment of unstable angina.[7] 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 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 to 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.

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

[6] 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).

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

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

Safety

Studies providing safety data

Pivotal studies that assessed safety as the sole primary outcome

None.

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

The 2 pivotal meta-analyses 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 versuss 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 thrombocytopaenia 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.

Other 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.

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.

Patient exposure

The 8 published studies provided safety data following treatment with nadroparin doses from 3075 to 5700 IU IU anti-Xa, 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 IU IU anti-Xa, 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 IU IU anti-Xa in patients < 70 kg and 5700 IU anti-Xa in patients > 70kg.) The remaining two RCTs (Harenberg, 1996; Forette, 1995) used doses (3075, 3100 IU anti-Xa) similar to the proposed reduced dosage for elderly patients (2850 IU IU anti-Xa); 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 IU IU anti-Xa.

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.

Safety issues with the potential for major regulatory impact

Liver function and liver toxicity

Integrated safety analyses

Not applicable.

Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

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.

Other studies

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

Renal function and renal toxicity

Integrated safety analyses

Not applicable.

Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

Pivotal and/or main efficacy studies

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

Other studies

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

Other clinical chemistry

Integrated safety analyses

Not applicable.

Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

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)

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.

Haematology and haematological toxicity

Integrated safety analyses

Not applicable.

Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

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 (that is, ≤ 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.

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.

Other laboratory tests

Integrated safety analyses

Not applicable.

Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

Pivotal and/or main efficacy studies

Not applicable.

Other studies

Not applicable.

Electrocardiograph findings and cardiovascular safety

Integrated safety analyses

Not applicable.

Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

Pivotal and/or main efficacy studies

ECG assessments were not done in the 2 pivotal controlled studies or the meta-analyses.

Other studies

ECG assessments were not done in the other studies.

Vital signs and clinical examination findings

Integrated safety analyses

Not applicable.

Pivotal studies that assessed safety as the sole primary outcome

Not applicable.

Pivotal and/or main efficacy studies

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

Other studies

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

Immunogenicity and immunological events

Integrated safety analyses

Not applicable.

Main/pivotal studies that assessed safety as the sole primary outcome

Not applicable.

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.

Other studies

None.

Serious skin reactions

Integrated safety analyses

Not applicable.

Pivotal studies that assessed safety as the sole primary outcome

Not applicable.

Pivotal and/or main efficacy studies

None.

Other studies

None.

Post-marketing data

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.

Evaluator's conclusions on 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 IU anti-Xa, 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 IU anti-Xa in patients < 70 kg and 5700 IU anti-Xa in patients > 70kg.) The remaining two RCTs (Harenberg, 1996; Forette, 1995) used doses consistent with the proposed reduced dosage for elderly patients (2850 IU anti-Xa); 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 IU anti-Xa. 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;[8] 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 IU anti-Xa of nadroparin as prophylaxis for VTE, which is higher than the proposed dose (2850 IU anti-Xa) in elderly patients in this submission.

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 IU anti-Xa 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 IU anti-Xa) versus 'low dose' (3100 IU anti-Xa) 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 IU anti-Xa) of nadroparin for the new indication of thromboprophylaxis of *elderly* bedridden patients with acute medical illness.

[8] 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.

First round benefit-risk assessment

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%;	Reduction in DVT was modest; the difference in incidence of total DVT was barely statistically significant (nadroparin versus placebo: 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. No PE was reported in this pivotal study mainly due to lack of objective testing.
Nadroparin showed comparable efficacy to UFH in preventing DVT and PE (Harenberg, 1996).	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..
Requires once daily administration compared to thrice daily with UFH. 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. Similar or better safety profile in terms of haemorrhagic side effects compared to UFH	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 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. Compared to UFH, significantly lower rate of withdrawals, thrombocytopenia, haematomas and local reactions (Forette, 1995).

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. Metanalyses contained very few studies specifically evaluating nadroparin. 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. 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. 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. 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. 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.

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 (discussed in detail in Section 7) 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 0.3mL (2850 IU anti-Xa) of nadroparin in elderly patients.

The submitted data provides evidence to suggest that nadroparin, when administered in the doses recommended (3800 to 5700 IU anti-Xa) 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 to 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 years (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).

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, and so on, 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 IU anti-Xa) 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.

Second round evaluation

For details of the second round evaluation including the issues raised by the evaluator (Clinical questions), the sponsor's responses and the evaluation of these responses please see Attachment 2.

Second round benefit-risk assessment

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.

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.

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.

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 IU anti-Xa) 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.

VI. Pharmacovigilance findings

The TGA granted a waiver from the requirement for a Risk Management Plan (RMP) for this application.

VII. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

There was no requirement for a quality evaluation in a submission of this type.

Nonclinical

There was no requirement for a nonclinical evaluation in a submission of this type.

Clinical

The clinical evaluators recommend rejection for the initial proposed indication:

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

The main reason is the submitted studies lacked adequate representation of some medical subgroups, including unstable angina, AMI and stroke, and therefore did not support a broad indication for medical patients. The evaluator also noted that nadroparin is not indicated for the treatment of unstable angina and myocardial infarction, so there is potential that a broad indication for medical patients could mislead prescribers regarding the approved indications.

In the second round evaluation, the clinical evaluator advised that the studies in the submission indicated a modest reduction in the risk of a thromboembolic event while generally reducing the risks of bleeding events, thrombocytopaenia and local reactions compared to UFH, so approval could be considered for a more restricted indication:

> *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.*

The sponsor agreed to this proposed indication in its response to the final evaluation report but requested consideration of including cancer patients in the category of hospitalised patients.

The sponsor submitted the following request to TGA on 22 June 2017:

[The sponsor has] just re-read the translation of the Czech PI (given below) and would appreciate the TGA giving consideration to the Australian PI having the exact wording as the Czech indication:

- *Prophylaxis of thromboembolic disease in high-risk patients (e.g. respiratory failure and/or respiratory infections and/or heart failure) confined to bed due to acute disease or hospitalized at the intensive care unit.*

The main changes from the wording proposed by the evaluators are the removal of ''medical'' from the description of ''high-risk patients'', the inclusion of 'e.g.' (which could create some uncertainty around the definition of 'high-risk patients' by implying that the three conditions are examples of high-risk patients), the use of 'confined to bed' rather than 'immobilised' and the use of 'acute disease' rather than 'acute illness'. The translation of the Czech indication submitted by the sponsor uses the words 'bedridden for acute illness'.

Pharmacology

Pharmacokinetics

No new pharmacokinetic information was provided in this submission. The pharmacokinetic properties of nadroparin are documented in the approved PI. Following subcutaneous administration, the peak anti-Xa activity (Cmax) is reached after approximately 3 to 6 hours (Tmax). Bioavailability is almost complete (around 88%). The elimination half-life is approximately 3.5 hours. Moderate and severe renal impairment is associated with increased exposure to nadroparin, so dosage adjustment or cessation may be required.

Pharmacodynamics

No new pharmacodynamic information was provided in this submission. The pharmacodynamic properties of nadroparin are documented in the approved PI. Nadroparin has both immediate and prolonged antithrombotic action. It 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. Compared with unfractionated heparin, nadroparin has less effect on thrombocyte function and aggregation in vitro and only a slight effect on primary haemostasis.

Dosage

Two of the individual RCTs (Fraisse, 2000; Luba, 2007) used a nadroparin dosage consistent with the generally recommended dosage in this application (3800 IU anti-Xa in patients < 70kg, 5700 IU anti-Xa in patients > 70kg). The other two RCTs (Harenberg, 1996; Forette, 1995) used dosages (3075 & 3100 IU anti-Xa) equivalent to the proposed reduced dosage for elderly patients (2850 IU anti-Xa); the lower dosages used in these studies, particularly Forette, could be justified by the older cohort of patients recruited into these studies (mean age 70.5 and 82.8 years respectively). The uncontrolled study by Pottier also used a dosage of 3075 IU anti-Xa.

There were some inconsistencies in the strengths of formulations reported in the various clinical papers, but the sponsor has explained that these differences were due to changes in the international standards for expression of anti-Xa activity from Institut Choay Units (25,000 anti-Xa ICU/ml) to the WHO classification in 1991 (10,250 IU anti-Xa/ml) and the European Pharmacopeia standard in 1996 (9,500 IU anti-Xa/ml).

Efficacy

Fraisse (2000) was a prospective, randomised, double-blind, placebo-controlled trial to evaluate the therapeutic benefits of Fraxiparine in patients with acute, decompensated

chronic obstructive pulmonary disease (COPD) who required mechanical ventilation. The study was conducted in 34 intensive care units in France between 1992 and 1995. A placebo-controlled study was considered ethical because there was no consensus regarding the efficacy of VTE prophylaxis in critically ill patients.

The main inclusion criteria were patients with acute, decompensated COPD requiring mechanical ventilation, aged 40 to 80 years, weight 45 to 110kg, with written informed consent. The main exclusion[9] criteria were history of DVT in the previous 6 months, signs of a DVT on Doppler ultrasonography at inclusion, an organic lesion that could bleed, severe liver failure, severe renal impairment, uncontrolled hypertension, coagulation disorder, history of thrombocytopaenia to heparin or current treatment with aspirin, ticlodipine or oral anticoagulants.

Dosage was determined by the patient's body weight (3,800 IU anti-Xa/0.4ml for 45 to 70kg, 5,700 IU anti-Xa/0.6ml for 71 to 110kg), the same dosage as proposed in this submission. Nadroparin, or matching placebo, was given once daily by subcutaneous injection. Duration of treatment could not exceed 21 days. The mean duration of treatment was 11-12 days.

Patients had a history of COPD for an average of 10 years. Other risk factors for DVT included immobilization (100%), respiratory disease (100%), bronchial superinfection (74%), congestive heart failure (29%), age > 65 years (50%), obesity (23%), venous insufficiency (13%), neoplastic disease (5%) and previous thromboembolic disorders (4%). DVT risk factors were similar in both groups.

Patients were assessed daily for symptoms or signs of DVT, haemorrhage or other adverse event. Doppler ultrasonography was performed before inclusion, weekly during the study and in all cases of suspected DVT. Venography was performed at completion and for positive, doubtful or uninterpretable Doppler examinations. Clinical assessment for pulmonary embolism was performed daily but there was a lack of detail about the clinical criteria for pulmonary embolism.

For the primary efficacy outcome, there was a lower incidence of DVT in patients receiving nadroparin (15.5%, 13/84) than in those receiving placebo (28.2%, 24/85) and the difference between treatment groups just reached statistical significance (p=0.045). Proximal DVT occurred in three patients in the nadroparin group versus seven patients in the placebo group suggesting a trend in favour of nadroparin although the difference from placebo was not statistically significant due to the small number of events.

Harenberg (1992, 1996) was a randomised active-controlled study in 1,590 elderly inpatients with a high risk of thromboembolism. The study compared Fraxiparine 3100 IU/0.3ml once daily (plus 2 placebo injections daily) with Calciparine (UFH) 5000 IU three times daily. The primary endpoint was the incidence of proximal DVT and PE. The study was performed across 10 centres in Germany.

The Harenberg 1992 paper describes that the hypothesis was changed during the course of the study, after 800 patients had been included, due to the low incidence (1%) of thromboembolic events. Based on this rate of thromboembolic events, the sample sizes would need to be two to three times larger than initially calculated to demonstrate superiority, so the Steering Committee changed the aim of the study from superiority to equivalence. This change in strategy is not described in the 1996 paper.

The inclusion criteria were medical inpatients with an increased risk of thromboembolism, aged 50-80 years and expected bed rest of 10 or more days. Patients were to have one or more of the following risk factors for DVT: obesity, varicosis, chronic venous insufficiency, post-thrombotic syndrome, oral contraceptives or oestrogen,

[9] The publication appears to have erroneously labelled these conditions as inclusions rather than exclusions.

thrombocytosis >450,000/µl or hyperviscosity syndrome, previous myocardial infarction, thrombotic cerebral infarction or peripheral arterial ischemia. Exclusion criteria included known intolerance to heparin, thrombocytopenia, coagulation disorder, acute DVT, pre-treatment with heparin, medication influencing blood coagulation, diseases with unfavourable short-term prognosis, septicaemia, hypertension, history of any bleeding and severe renal impairment.

Table 6: Main diagnosis of the Harenberg study patients on admission to hospital.

Disease	UF heparin n (%)	LMW heparin n (%)	Total
Cardiac insufficiency	143 (18.33)	150 (18.52)	293
Cerebrovascular diseases	134 (17.18)	149 (18.40)	283
Coronary heart disease	131 (16.79)	139 (17.16)	270
Cancer	63 (8.08)	57 (7.04)	120
Diabetes	57 (7.31)	47 (5.80)	104
Gastro. or neph. disease	45 (5.77)	35 (4.32)	80
COLD	46 (5.90)	41 (5.06)	87
Pneumonia or infections	16 (2.05)	26 (3.21)	42
Wrong classification	1	0	1
Other diseases	144 (18.46)	166 (20.49)	310
Total	780 (100.0)	810 (100.0)	1,590

Figures in parentheses are percentages. Gastro. = Gastrointestinal; neph. = nephrological; COLD = chronic obstructive lung disease.

Table 7: Clinical characteristics of the Harenberg study patients (n=1,590)

Variable	UF heparin n = 780	LMW heparin n = 810	p
Body weight, kg	69.9 ± 14.5	69.7 ± 14.5	0.66
Height, cm	166.3 ± 9.4	166.0 ± 9.0	0.38
Age, years	70.4 ± 7.9	70.5 ± 8.3	0.37
Bed rest, days (median 5–95%)	0–20	0–20	0.57
Female/male (n)	408/372	466/344	0.04
Smoker (no/ex/yes), n	482/185/113	504/173/103	0.31
Risk factors			
Adiposity	250	254	0.79
Previous DVT	33	50	0.09
Previous PE	13	18	0.47
Varicosis	135	179	0.02
Ulcus cruris	35	33	0.71
Thrombocytosis	33	38	0.72
Peripheral AD	160	167	1.00
Previous MI	113	123	0.72
Previous stroke	121	119	0.67
Cardiac insufficiency	343	348	0.69
Hyperviscosity	118	112	0.48
Estrogen	2	4	0.69

DVT = Deep-vein thrombosis; PE = pulmonary embolism; AD = arterial disease; MI = myocardial infarction.

The dose of Fraxiparine used in this study (3100 IU/0.3ml) could be explained by the older patient population (mean age 70 years, 55% aged 70-80 years). Duration of treatment was 10 days. Treatment was commenced within 12 hours of admission to hospital. Patients were examined at days 1, 4, 6, 8 and 10 for clinical symptoms and signs

of DVT and PE. Compression sonography to detect DVT was performed on day 1 and between days 8 and 11. If PE was clinically suspected, perfusion scintigraphy was performed.

The primary endpoint, proximal DVT and/or PE, was observed in 4/710 (0.6%) for UFH and 6/726 (0.8%) for nadroparin at the interim analysis. Equivalence of the two treatments was demonstrated (p=0.012) and the trial was terminated.

The incidence of thromboembolism in the stratification groups were: 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).

Limitations of this study include the low incidence of the primary endpoint, lack of detail regarding the degree of immobility of patients, lack of detail regarding the use of other preventive strategies such as early mobilisation, physiotherapy and compression stockings and lack of detail regarding randomisation and blinding methods.

The low incidence of the primary endpoint was partly attributable to the exclusion of 21 patients at entry into the study due to detection of clinically unapparent DVT by the initial compression sonography. This lends support to the concept that venous thromboembolism in medical illness, in contrast to post-operative scenarios, may have a less clearly defined onset and may occur prior to admission to hospital. Other factors that may have contributed to the low incidence of the primary endpoint include the short follow-up period, lack of definition around the degree of patient immobility and the lower sensitivity of compression sonography in asymptomatic compared to symptomatic patients.

Alikhan (2014) was a meta-analysis performed 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.

Randomised controlled trials comparing UFH or LMWH with placebo or no treatment, or comparing UFH with LMWH, were identified from searches of the Specialised Register and Cochrane Central Register of Controlled Trials and were assessed for inclusion in the review.

The 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).

Only 3 of these studies evaluated nadroparin (Bergmann 1996; Fraisse 2000; Forette 1995). One of these (Forette 1995) was primarily a tolerance/safety study. The Bergmann study lacks relevance to this submission as it involved a high dose of nadroparin (7,500 IU anti-Xa).

Subjects in this review included: 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 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.

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.

Statistical analysis was performed separately on two groups: heparin (UFH or LMWH) versus placebo (or no treatment); LMWH versus UFH.

The meta-analysis demonstrated that UFH and LMWH resulted in a reduction in DVT (OR=0.41; 95% CI: 0.25 to 0.67; P = 0.0004) and a non-significant reduction in combined non-fatal and fatal PE (OR 0.66; 95% CI 0.43 to 1.02; P = 0.06) when compared with placebo or no treatment. There was a significant reduction in DVT in the LMWH treatment group compared to the UFH group (OR 0.77; 95% CI: 0.62 to 0.96; P = 0.02). The meta-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 (OR 0.97; 95% CI: 0.87 to 1.08; P = 0.57).

This meta-analysis provides only supportive evidence for nadroparin due to the following limitations:

- Only 3 individual studies included in the meta-analysis evaluated nadroparin: one compared nadroparin to UFH (Forette, 1995) and the others to placebo (Fraisse, 2000; Bergmann, 1996). The Forette (1995) study was primarily a safety/tolerance study with limited efficacy data. Bergmann used a higher dose (7,500 IU anti-Xa) than proposed in this submission.
- The meta-analysis did not specify that all studies included only patients who were bedridden. Studies involving cancer patients and patients with AMI or 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 the proposed new indication.

Dooley (2014) was a systematic review and mixed-treatment comparison (MTC) meta-analysis to compare the efficacy and safety of LWMHs for venous thromboembolism prophylaxis in hospitalised medically ill patients.

20 trials enrolling 37,284 patients met the inclusion criteria for this analysis. Only 4 of these trials involved nadroparin, 2 comparing nadroparin to placebo (Fraisse, 2000; Mahe, 2000) and 2 comparing nadroparin to UFH (Harenberg, 1996; Forette, 1995). The Fraisse, Harenberg and Forette studies have been considered individually in this submission. Forette was primarily a safety/tolerance study with limited efficacy data. The Mahe study lacks relevance to this submission as it involved a high dose of nadroparin (7,500 IU anti-Xa) for hospitalised patients immobilised for <24 hours.

The primary objective was to evaluate LMWHs compared to each other. The results are based on indirect evidence as none of the 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. The odds of PE or DVT did not vary significantly among the three LMWHs evaluated (nadroparin, enoxaparin and certoparin). Dalteparin was not included in the network for PE or DVT due to lack of reported outcomes. Major and minor bleeding was evaluated for all four LMWHs with no statistically significant findings. These results suggest that the four LMWHs (enoxaparin, nadroparin, dalteparin and certoparin) 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 compelling data suggesting one LMWH over another for VTE prophylaxis in hospitalised medically ill patients.

This mixed treatment comparison meta-analysis provides only supportive evidence as interpretation is 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.
- Only 4 of the 20 trials involved nadroparin. Of these, the Mahe study lacks relevance to this submission due to the high dosage. The Forette study was mainly a safety/tolerance study and provided limited efficacy data. The other two studies (Fraisse, 2000; Harenberg, 1996) have been evaluated individually in this submission.
- Hospitalised medical patients are often a heterogeneous population. Definitions used by individual trials for outcomes such as VTE varied and diagnostic strategies (including mandatory screening for DVT) also varied across trials. These characteristics may have contributed to the observed heterogeneity in the outcomes for DVT and PE. Furthermore, rarity of events, particularly in mortality and PE, contributed to imprecise estimates demonstrated by the wide confidence intervals reported.

Luba (2007) was a randomised, open-label study of 300 medical patients hospitalised in Poland for acute illnesses to evaluate the efficacy and safety of thromboprophylaxis with nadroparin over different durations. Group I received nadroparin only during the period of immobilisation and Group II received nadroparin during the period of immobilisation and for the following 10 days.

Inclusion criteria were hospitalisation for at least 6 days, immobilisation for 3-14 days, age >40 years and absence of clinical and ultrasound features of DVT. Exclusion criteria were current requirement for anticoagulant therapy, immobilising disease in the past 6 months, contraindication to LMWH, cancer, mental disorder and alcoholism. Cancer patients were excluded due to follow-up in specialist centres. The main reasons for immobilisation were severe respiratory diseases (55%), heart failure (24.3%) and ischaemic stroke (12.3%). The most common thrombotic risk factors were age > 70 years (62.7%), heart failure (51.3%), cigarette smoking (10% and obesity (9%).

Dosage of nadroparin was 3,800 IU/0.4ml for ≤70kg and 5,700 IU/0.6ml for >70kg (same dosage as proposed in this submission). The mean duration of nadroparin treatment in Group I was 5.1 days and Group II 14.5 days. Four-point compression sonography was performed on the day of admission, on completion of prophylactic treatment and at 3-month follow-up.

The endpoints (lower limb DVT and death) occurred in 17 patients (5.7%), all during the 3-month follow up period. There were 15 (5%) cases of DVT during the follow-up period, 10 (6.7%) in Group I and 5 (3.3%) in Group II. Two sudden deaths of unknown cause occurred during the 3-month follow-up, both in Group I. The difference in endpoints between Group I and II was not statistically significant (p=0.08). Larger, controlled studies would be required to confirm this trend of a decrease in thromboembolic events in patients receiving prophylaxis beyond the period of immobilisation.

Pottier (2000) was an open-label epidemiological study which aimed to create streamlined groupings of indications for VTE prevention in a variety of medical environments and assess the clinical incidence of VTE.

In-patients across five medical departments (dermatology, endocrinology, hepato-gastroenterology, internal medicine, rheumatology) were eligible. All patients were included except those who were expected to stay fewer than 3 days, had surgery within

one month, were on anti-coagulant treatment on admission or received different preventative measures to the trial protocol.

24,497 patients were admitted during the study period and 10,534 patients met the criteria for inclusion. Patients were stratified to different risk levels based on pre-defined risk factors. The primary endpoint was the occurrence, during the hospital stay, of a deep or superficial venous thrombosis of the lower limbs, a pulmonary embolism or unexplained sudden death. Screening was based on clinical features double-checked by venous Doppler ultrasonography and/or ventilation/perfusion lung scan.

Patients classified as high or intermediate risk were eligible to receive nadroparin 3,075 IU/0.3ml daily by subcutaneous injection. The dosage was not weight-based. This dosage is different to the proposed dosage in this submission.

Overall, 53 VTE were reported. The incidence of VTE in each risk group was:

- 28 in 3,730 (0.75%) patients classified as high risk or intermediate risk who were treated with nadroparin in accordance with the study criteria
- 18 in 1,022 (1.7%) patients classified as high risk or intermediate risk who were not treated, in contravention of the study criteria ('prevention overlooked')
- 5 in 3,602 (0.14%) patients classified as low risk and not treated, in accordance with the study criteria
- 2 in 495 (0.4%) patients classified as high risk or intermediate risk and not treated due to contraindications
- 0 in 1,264 patients with no risk factors and were not treated.

The study report does not provide reasons why treatment was not provided to intermediate or high risk patients in the 'prevention overlooked' group.

The study used risk factor analysis to identify a population with a VTE risk of 1.7%. The risk of VTE was 55% lower in intermediate and high risk patients who received nadroparin prophylaxis compared to those who did not receive nadroparin even though they qualified for treatment based on identified risk factors.

Interpretation of the results of this study is limited because it was a non-randomised, open-label study which derived its main efficacy finding from a group which was not treated in accordance with the study criteria (the 'prevention overlooked' group). The study report does not identify why treatment was not provided to a group of intermediate and high risk patients who qualified for treatment. In addition, the study report lacks detail regarding loss of mobility and the use of other preventive measures such as early mobilisation, physiotherapy and compression stockings. The overall incidence of VTE was low. The dosage used in this study was not consistent with the proposed dosage for this submission.

Safety

Six individual clinical reports provided safety data for 4,945 hospitalised medical patients treated with nadroparin doses from 3075 to 5700 IU anti-Xa administered subcutaneously daily for a duration up to 28 days (mean duration 5.1 days). Two studies (Fraisse, 2000; Luba, 2007) used nadroparin in a dosage equivalent to the generally recommended dosage in this submission. Two other RCTs (Harenberg, 1992, 1996; Forette, 1995) used a dosage equivalent to the proposed reduced dosage for elderly patients. All four of the RCTs included pre-defined major and minor haemorrhage as safety outcomes. All but Forette pre-defined thrombocytopaenia as a safety outcome.

- In Fraisse (2000), safety criteria included the incidence of major and minor haemorrhage, thrombocytopaenia and any other treatment-related adverse event.

Although the incidence of adverse events was high in both groups (46.3% for nadroparin, 39.3% for placebo), reflective of the severity of illness in this patient cohort, no significant difference in thrombocytopaenia or major or minor haemorrhage was reported following nadroparin treatment compared to placebo.

- Harenberg (1992, 1996) reported that major haemorrhage occurred rarely, with no difference between the nadroparin and UFH treatment groups (n=4 for UFH, n=5 for nadroparin, p=1.0). Minor haemorrhage was observed more frequently with UFH, but the difference from nadroparin was not statistically significant. The incidence of injection site haematoma and erythema were lower in the nadroparin group than UFH. Thrombocytopenia occurred more frequently in patients treated with UFH (n=4) than nadroparin (n=0, p=0.05).
- Forette (1995) was an open-label, randomised study to compare the tolerance of nadroparin (3,075 IU anti-Xa SC daily) versus UFH (5000 IU if <70kg or 7500 IU if ≥70kg, SC twice daily) for 28 days in 295 hospitalised medical patients aged >70 years (mean age 82.8 years). The frequency of premature discontinuation of treatment was lower for nadroparin compared with UFH (0.7% versus 6.7%, p = 0.01).
- In the Alikhan (2014) meta-analysis, the primary safety outcome was major haemorrhage; the secondary safety outcomes were minor haemorrhage and thrombocytopenia. There was no standardised definition of major haemorrhage across the studies. Only one of the studies in the heparin versus placebo analysis (Fraisse 2000) and one of the studies in the UFH versus LMWH analysis (Forette 1995) evaluated nadroparin. Heparin (UFH and LMWH) 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). The analysis of LMWH versus UFH showed a significantly reduced risk of major haemorrhage with LMWH compared to UFH (OR =0.43; 95% CI 0.22 to 0.83; p=0.01), borderline reduced risk of minor haemorrhage (OR= 0.70; 95% CI: 0.48 to 1.00; p = 0.05) and similar risk of developing thrombocytopenia.
- Dooley (2014) was a mixed-treatment comparison meta-analysis which concluded that the LMWHs enoxaparin, dalteparin, nadroparin and certoparin were associated with similar rates of major and minor bleeding. None of the studies in this meta-analysis directly compared LMWHs.
- Pottier (2000) was an open-label epidemiological study which did not include safety endpoints and did not report on adverse events, other than noting that no serious haemorrhagic strokes or cases of thrombocytopenia due to nadroparin were reported.
- Luba (2007) was an open label study which reported an unexpected absence of serious haemorrhage in the study group and no thrombocytopaenia (defined as 50% decrease in platelets from initial level).
- Pessina (2003) was a single case report involving a large rectus abdominis haematoma.

Mortality

In Harenberg (1992, 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 were more common causes of death in the LMWH treatment group. There was a difference in the number of deaths at centres depending on whether or not primary endpoints were observed at those centres. No differences were reported between treatment groups at centres with primary endpoints (UFH versus LMWH: 1.09% versus 1.6%, p=0.6). In contrast, the incidence of death was 3.5 fold higher in the LMWH

group at centres where no primary endpoints were observed (1.25% versus 4.49%, p=0.02). A blind analysis by the critical-event committee found that pulmonary embolism was regarded as doubtful or excluded in patients at centres which did not observe primary endpoints. Further analysis pointed to the difference in death rates being explained by poor prognosis, longer duration of preclinical bed rest and higher clinical risk. However, this was a randomised study and the baseline characteristics and risk factors, including previous bed rest, were described in the published report as similar in both groups.

Sixteen patients died during the Fraisse (2000) study with no significant difference between the nadroparin and placebo groups (8 in each group). Most deaths were due to cardiovascular complications associated with infection.

In Alikhan (2014), all-cause mortality was assessed in seven of the trials comparing heparin (UFH and LMWH) versus placebo/no treatment, with no clear evidence of a difference in mortality (OR=0.97; 95% CI: 0.87 to 1.08; p = 0.57). All-cause mortality was assessed in five studies which compared LMWH versus UFH, with no clear evidence of a difference in mortality (OR=0.79; 95% CI: 0.54 to 1.16; p = 0.23). Dooley (2014) reported no statistically significant difference in mortality among all four LMWHs (dalteparin, certoparin, enoxaparin and nadroparin). This was based on indirect evidence as no trials directly compared one LMWH to another. Luba (2007) reported two sudden deaths of unknown cause at day 30 and 52 after completion of prophylactic treatment (reasons for death not verified at autopsy).

Risk management plan

A Risk Management Plan (RMP) was not provided because Fraxiparine has been in use for many years and the safety aspects of the product are well characterised. The sponsor has confirmed that routine pharmacovigilance will be overseen by the pharmacovigilance manager in Australia.

Risk-benefit analysis

Delegate's considerations

Efficacy

Fraisse (2000) reported a lower incidence of DVT in patients with acute decompensated COPD requiring mechanical ventilation who were treated with nadroparin compared to placebo. Treatment with nadroparin resulted in a 45% reduction in incidence of DVT compared with placebo. This study provides evidence for the efficacy of nadroparin in patients with acute decompensated COPD requiring mechanical ventilation. Patients in this study did have other medical co-morbidities and DVT risk factors (bronchial superinfection 74%, congestive heart failure 29%, obesity 23%, venous insufficiency 13%, neoplasia 5%, previous venous thrombosis 4%) but there are limitations in extrapolating the results of this study to hospitalised medical patients generally.

Harenberg (1992, 1996) reported equivalent efficacy of 10 days of prophylaxis with nadroparin or UFH in hospitalised medical patients who were expected to require bed rest of 10 or more days. This study had a reasonably broad representation of medical subgroups. The study provides support for the efficacy of nadroparin in hospitalised medical patients, but interpretation of the outcome of this study is limited by the low incidence of the primary endpoint and the lack of definition around the degree of patient immobility. The low overall incidence of venous thromboembolic events may indicate that the patient population was not well defined and may not accurately reflect the target population for the proposed indication.

The Alikhan meta-analysis demonstrated a decreased risk of DVT in patients treated with LMWH compared to placebo or UFH. However, only 3 of the 16 studies included in the Alikhan meta-analysis involved nadroparin. One of these was primarily a safety/tolerance study with limited efficacy data and one involved a higher dosage than proposed in this submission. LMWHs are not clinically interchangeable and so the general evidence provided for other LMWHs and UFH should not be extrapolated as evidence for the efficacy of nadroparin for the proposed new indication. The Alikhan meta-analysis excluded patients admitted to hospital with acute myocardial infarction or stroke and cancer patients not in an acute medical setting. The exclusion of these medical subgroups does not support the initial indication for medical patients bedridden due to acute illness.

The Dooley (2014) meta-analysis reported that enoxaparin, nadroparin and certoparin were similar in preventing PE and DVT in hospitalised medical patients, with similar rates of major and minor bleeding. This finding was based on indirect comparisons because none of the studies directly compared any of the LMWHs. One of these LMWHs (certoparin) is not approved in Australia. No comparative data for DVT and PE were available for dalteparin. Only 4 of the 20 studies included in Dooley involved nadroparin. One of these studies (Mahe) lacked relevance because of the high dosage and one (Forette) was primarily a safety/tolerance study with limited efficacy data.

Luba (2007) was a randomised, open-label study which did not demonstrate a significant difference in endpoints for the two groups treated with nadroparin for different durations.

Pottier (2000) was a large, open-label epidemiological study which created streamlined risk groupings for VTE prevention and evaluated the incidence of VTE. I have a number of concerns about the quality of the findings from this study, including the potential for bias arising from the use of the 'prevention overlooked' group as a comparator to the treated intermediate/high risk group, the lack of definition regarding loss of mobility and other preventive strategies that may modify VTE risk, the low overall incidence of VTE and the lower dosage used in this study.

Some of the studies used a lower dose of nadroparin. Harenberg 1992, 1996 (3,100 IU anti-Xa) and Forette 1995 (3,075 IU anti-Xa) had an older cohort of patients. These studies provide support for the proposed lower dosage of 2,850 IU anti-Xa/0.3ml for elderly patients. Pottier 2000 also used a dosage of 3,075 IU anti-Xa (mean age 72 years, range 18 – 95).

Safety

Nadroparin has an established safety record, having been approved in Australia for other indications since 1995. The studies in this submission provide safety data for nadroparin VTE prophylaxis in medical patients. The studies generally involved elderly patients, many with serious medical comorbidities. The range and frequency of AEs reported in the publications submitted in this application are generally consistent with the information provided in the Fraxiparine PI.

Harenberg reported a higher incidence of deaths in the nadroparin group, particularly in centres which did not observe primary endpoints (DVT or PE). A detailed analysis by the critical-event committee attributed this difference to poor prognosis, longer duration of preclinical bed rest and higher clinical risk. However, this was a randomised study and the baseline characteristics and risk factors, including previous bed rest, were described as similar in both groups.

Data deficiencies

The two pivotal randomised controlled trials (Fraisse, 2000; Harenberg 1992, 1996) were published 17 and 21 years ago respectively. These studies compared nadroparin to placebo and UFH respectively. No studies in the submission directly compared nadroparin with another LMWH. The Alikhan meta-analysis reported a decreased risk of DVT in patients treated with LMWH compared to UFH, with a reduced risk of major bleeding,

raising a question regarding the need for a trial comparing nadroparin to another LMWH, such as enoxaparin which is approved in Australia for prophylaxis in medical patients bedridden due to acute illness.

The pivotal studies lack data on the use of other thrombo-preventive strategies such as early mobilisation, physiotherapy and compression stockings. The CHMP guidelines state that the potential for site-specific standards of care to affect the efficacy and safety should be prospectively identified. The study reports also lack details regarding randomisation methods.

The submitted studies lack adequate representation of some medical subgroups, in particular unstable angina, acute myocardial infarction and stroke, and therefore do not support a broad indication for the treatment of immobilised medical patients.

Summary

The Delegate agrees with the clinical evaluator that the initial proposed indication:

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

is not adequately supported by the studies in this submission. The studies lack adequate representation of medical subgroups, including unstable angina, acute myocardial infarction and stroke. Nadroparin is not indicated for the treatment of unstable angina or myocardial infarction so there is the potential that an indication for the treatment of immobilised medical patients could result in broader use than justified by the evidence provided in this submission.

The clinical evaluator suggested consideration of a more restricted indication:

> *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.*

This addresses the concern about the subgroups of unstable angina, myocardial infarction and stroke which were not adequately represented in the clinical studies. A remaining issue is whether the evidence provided in this literature-based submission is sufficient to support the proposed extension of indication. There is some concern that the patient population was not well defined in the Harenberg study and may not accurately reflect the target population for the proposed indication. The meta-analyses include only a small number of studies involving nadroparin. In addition, although the safety profile of nadroparin presented in this submission is generally consistent with its established safety profile, the Harenberg study reported a higher incidence of deaths in the nadroparin group. The advice of ACM is sought regarding the proposed indication and the efficacy and safety data provided in this submission.

Following the Round 2 evaluation, the sponsor requested consideration of including cancer patients in the proposed category of hospitalised patients. No proposed wording has been submitted. Fraisse involved patients with acute decompensated COPD requiring mechanical ventilation; 5% of patients (11/223) were reported as having neoplastic disease, 3/109 in the nadroparin treatment group and 8/114 in the placebo group. Harenberg reported 2 cases of VTE in the malignant stratification group (2/189, 1.06%). 120 (7.5%) of the study patients were classified as having a main diagnosis of cancer on admission, 63 (8.1%) in the UFH group and 57 (7.0%) in the nadroparin group. Alikhan excluded studies that primarily involved cancer patients not in an acute medical setting, such as receiving chemotherapy. The Alikhan meta-analysis did not perform subgroup analysis based on medical diagnosis as there were insufficient data on outcomes within subgroups in the published studies. Dooley did not evaluate cancer subgroups. Luba excluded cancer patients. At this stage, my view is that the submission has not provided sufficient evidence for the use of nadroparin in the prevention of VTE in cancer patients to

support this proposal, but the Delegate seeks the advice of ACM on this matter before making my decision. In addition to insufficient representation of cancer patients in this submission, the Delegate is concerned that including hospitalised cancer patients in the indication could encourage the use of nadroparin in hospitalised cancer patients receiving chemotherapy, when this clinical scenario has not been evaluated in this submission.

On 22 June 2017, the sponsor requested consideration of the Australian indication having the same wording as the translated Czech indication:

> *Prophylaxis of thromboembolic disease in high-risk patients (e.g. respiratory failure and/or respiratory infections and/or heart failure) confined to bed due to acute disease or hospitalized at the intensive care unit.*

The removal of 'medical' from the description of high-risk patients may have the effect of broadening the eligible treatment group beyond the scope of patient groups considered in this submission. The inclusion of 'e.g.' could create uncertainty around the definition of high-risk patients by implying that the listed conditions are just three examples of high-risk patients. Overall, the Delegate is not convinced that these proposed changes are justified based on the evidence presented in the submission.

During the evaluation process, in response to concern about the broad indication for medical patients, the sponsor included the statement 'Nadroparin is not approved for unstable angina' in the Precautions section of the draft PI. With the proposed change to the indication restricting treatment to high-risk medical patients with respiratory failure and/or respiratory infection and/or cardiac failure, the sponsor has questioned the necessity of this statement. At this stage, my view is that this statement would not need to be included in the PI provided the indication clearly defines the types of medical patients eligible for treatment. The advice of ACM is sought on this issue.

Questions for sponsor

- The 'Presentation and Storage Conditions' section of the PI states that 'All volumes and pack sizes may not be available in Australia.' Please confirm which volumes and pack sizes are available in Australia.
- The Alikhan meta-analysis excluded patients requiring admission to an intensive care unit, yet the Fraisse study, which included patients with acute decompensated COPD requiring mechanical ventilation, was conducted in 34 ICUs in France. Can you clarify this anomaly?
- Could you please outline your reasons for wanting to change the proposed indication to align with the wording of the Czech indication?

Summary of issues

Indication

The initial proposed indication is not considered acceptable, primarily because the studies lack adequate representation of medical subgroups, in particular unstable angina, myocardial infarction and stroke. A broad indication for medical patients is not considered appropriate in this context, particularly given that nadroparin is not indicated for the treatment of unstable angina or myocardial infarction. The evaluators recommend consideration of a more restricted indication. The sponsor agreed to adopt the proposed indication but requested consideration of inclusion of hospitalised cancer patients in the revised indication. The sponsor has subsequently requested further wording changes to align with the Czech indication.

Efficacy

Fraisse (2000) provides evidence for the efficacy of nadroparin in patients with acute decompensated COPD requiring mechanical ventilation. Harenberg (1992, 1996) reported equivalence of nadroparin and UFH for a broader cohort of hospitalised medical patients, though there are some limitations in the interpretation of this study. The evidence provided by the two meta-analyses (Alikhan, 2014; Dooley, 2014) is constrained by the small number of efficacy studies involving nadroparin in a dosage relevant to this submission. sNone of the studies directly compare nadroparin with another LMWH.

Safety

Harenberg reported a higher incidence of deaths in the nadroparin group, particularly in centres which did not observe primary endpoints (DVT or PE). Further analysis attributed the difference to poor prognosis, longer duration of pre-clinical bed rest and higher clinical risk. However, this was a randomised study and the baseline characteristics and risk factors, including previous bed rest, were described as similar in both groups.

Proposed action

The Delegate is not in a position to say, at this time, that the application for extension of indication for nadroparin should be approved.

Request for ACM advice

The committee is requested to provide advice on the following specific issues:

1. What is the committee's view on the indication proposed by the evaluator in the Round 2 evaluation?
2. Is the committee satisfied that the submission has provided sufficient evidence of efficacy for both categories of high risk medical patients: those immobilised due to acute illness and those hospitalised in an intensive care unit?
3. Is the committee satisfied that the study populations adequately represent the target population for the proposed indication?
4. What is the committee's view on the safety implications of the higher incidence of deaths in the nadroparin group in the Harenberg study?
5. What is the committee's view on the sponsor's proposal to align the wording to the Czech indication?
6. Does the committee consider that the submission has provided sufficient evidence to support the sponsor's request for the indication to include cancer patients in the category of hospitalised patients?
7. What is the committee's view regarding the PI containing a statement in the Precautions section that nadroparin is not indicated for the treatment of unstable angina?
8. Could the committee comment on the Pottier (2000) study, with particular regard to the potential for bias in the design and implementation of the study and the strength of the evidence for efficacy? What is the committee's view with regard to inclusion of the outcomes of this study in the Clinical Trials section of the PI?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Aspen accepts the TGA's recommendation for the indication:

> *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, Aspen retracts the Czech indication (as outlined in the Delegate's overview). However, Aspen seeks the ACM's advice on Aspen's proposal to include cancer patients in the indication, based on the rationale given below. Should ACM consider that cancer patients could be included in the proposed indication, then the following indication is proposed:

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

Rationale for including cancer patients

Aspen believes the evidence included in the literature based submission (LBS) supports the inclusion of cancer patients as a group likely to benefit from the prophylactic use of nadroparin in these high risk patients. Both the pivotal prospective, randomised, double blind, controlled trials submitted in support of the extension of indication recruited patients diagnosed with cancer at admission to hospital. It should be further noted that Harenberg stratified randomization 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. They also analysed the incidence of thromboembolism by stratification.

While the study by Fraisse 2000 enrolled only 11 of the 223 patients with this diagnosis, Harenberg (1992 and 1996) enrolled a substantially larger number (120) patients of patients with established malignancy, with a further 69 included in the final stratified analysis.

Harenberg found no significant difference ($p = 0.86$) in the incidence of thromboembolism in the stratified groups with 4 recorded in the 516 cardiovascular group, 2 out of 189 malignancies, 1 out of 319 neurological cases and 1 out of 157 pulmonary patients.

It is also worth noting that a total of 230 patients recruited into the Harenberg study demonstrated hyperviscosity. It is common for hyperviscosity to be associated with malignant disease, particularly advanced stage cancers.[10] High fibrinogen turnover is considered an important determinant of hyperviscosity in malignancy, making anticoagulants suitable therapy to prevent thrombosis. In addition, two of the supportive studies conducted by Forette 1995 (open label RCT) and Pottier 2000 (cohort study) recruited patients diagnosed with cancer. Of the 295 patients recruited by Forette, 15 were admitted with a cancer. Of the 3730 patients treated with nadroparin in the Pottier study, 634 were admitted with progressive cancer.

Consequently, the number of patients diagnosed with cancer in the individual studies submitted in this application approached 800, with the majority (at least 81%) exposed to nadroparin. In addition, it may reasonably be assumed that some of the 230 patients displaying symptoms of hyperviscosity may also have had underlying cancers, increasing the number contributing to the total patient pool analysed by Harenberg.

[10] von Templehof GF, Heilmann L, Hommel G, Pollow K. Impact of rheological variables in cancer. Seminars in Thrombosis and Hemostasis 2003; 29: 499-513.

Issues raised in the overview

- *2. Is the committee satisfied that the submission has provided sufficient evidence of efficacy for both categories of high risk medical patients: those immobilised due to acute illness and those hospitalised in an intensive care unit?*

The application submitted in support of the extension of indication for nadroparin was based solely on published clinical study data, known as a literature based submission (LBS). The aim of a LBS is to identify published articles through a structured and objective systematic review of scientific data bases, which are relevant to establishing the safety and/or efficacy of the proposed PI amendments in the appropriate clinical settings. In this case, the specific research statement used to frame the systematic literature search strategy was:

> *Efficacy in adult patients, receiving nadroparin in non-surgical settings and who are immobilized, for prevention of thromboembolic disorders*

The subsequent search strategy was developed in conjunction with an experienced Medical Librarian and agreed with the TGA, prior to running a computerised search to identify relevant data.

Table 8 summarises the relevant inclusion criteria used to identify patients eligible for recruitment into the individual clinical studies submitted in this application. The total number of patients enrolled, and percentage meeting these relevant criteria are provided, as well as relevant explanatory notes. While Forette is primarily a tolerability and safety study, it is relevant to efficacy evaluation as it compared the frequency of premature discontinuations in patients receiving nadroparin and unfractionated heparin, as premature withdrawal can impact efficacy. Aspen consider that the studies provided in this application are adequate to support the use of prophylactic nadroparin treatment in both immobile medical patients, as well as those admitted to intensive care environments.

Table 8: Inclusion criteria used to recruit patients to studies submitted in the extension of indication application, relevant to both categories of high risk medical patients application, relevant to both categories of high risk medical patients

STUDY	IMMOBILSED DUE TO ACUTE ILLNESS N (%)	ADMITTED TO INTENSIVE CARE N (%)	OTHER RELEVANT INCLUSION CRITERIA N (%)
Fraisse 2000		223 (100) respiratory decompensated and ventilated COPD patients	
Harenberg 1992 and 1996	1,590 (100) medical inpatients Bed rest for ≥10 days		
Forette 1995			Temporary decline in locomotor autonomy, expected hospitalisation ≥4 weeks, requiring VTE prophylaxis 295 (100)
Luba 2007	300 (100) medical inpatients Immobilised ≥3 days		
Pottier 2000			Medical inpatients with loss of mobility 1194 (32) Or lower limb paralysis 375 (12)

- *3. Is the committee satisfied that the study populations adequately represent the target population for the proposed indication?*

Aspen believe that the studies submitted with this application include sufficient numbers of patients with a range of concomitant conditions and characteristics to support the following indication: '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.' Our rationale for this conclusion is presented in the response above.

- *4. What is the committee's view on the safety implications of the higher incidence of deaths in the nadroparin group in the Harenberg study?*

Apart from Harenberg, reports of deaths were included in the studies by Forette 1995, Fraisse 2000 and Luba 2007. The incidence of reported deaths associated with nadroparin administration were similar to that reported for patients treated with placebo, heparin or longer courses of nadroparin treatment in these three studies.

The study by Forette was specifically designed to evaluate the safety of nadroparin compared to heparin in 295 elderly patients hospitalised for a minimum of 4 weeks. Death was reported in 6 patients (4.1%) of patients (mean age 82.8 ± 0.5 years) randomised to nadroparin treatment and 7 (4.7%) receiving heparin treatment (mean age 83.8 ± 0.6 years). There was no difference in the incidence of death in patients receiving either anticoagulant.

Fraisse evaluated the safety and efficacy of nadroparin compared to placebo in 223 COPD patients mechanically ventilated in hospital based intensive care. There were 8 deaths in each group. The percentage of patients who died in the nadroparin arm was 7.4% and in

the placebo arm 7.1%. Most deaths were due to cardiovascular complications or nosocomial pneumonias.

Luba evaluated the safety and efficacy of shorter or longer courses of nadroparin therapy in 300 elderly hospitalised medical patients. No deaths were reported in either group.

Harenberg compared the safety and efficacy of nadroparin to heparin in 1590 medical patients at high risk of developing thromboembolism. Death was a pre-defined secondary end point.

The sample size calculation for this study was based on the primary end point of the combined rate of occurrence of DVT and pulmonary embolism. While a Bonferroni adjustment was performed, this was to allow for multiple analysis of the primary end point. The level of statistical significance used in the analysis of results appears not to be adjusted to account for the multiple (5) primary and secondary end points analysed in this study. This can increase the chance of a false positive result occurring.

The overall incidence of reported deaths in this study was also very low (32 (2%) out of 1590 treated patients). This was reflected in the individual percentages reported in the group receiving nadroparin (1.44%) and heparin (0.57%), compared to the other studies. While that difference was significant at 0.02, a firm conclusion may be compromised by the application of the statistical analysis as discussed above.

Haemorrhage (primary safety endpoint) as the cause of death was excluded in both treatment groups by the clinical endpoint adjudication committee. Cause of death related to pulmonary embolism was assigned as probable in 3 UFH patients and one confirmed LMWH patient. The analysis of risk factors for the occurrence of death showed a prevalence of thrombocytosis ($p = 0.052$), history of pulmonary embolism ($p = 0.022$), higher age ($p = 0.009$), lower weight ($p = 0.016$) and longer previous bed rest ($p = 0.0001$).

Furthermore, the authors concluded that the difference in death rates between treatments was explained by poor prognosis, longer pre-treatment bed rest and higher overall clinical risk characterising the patients recruited in each arm.

Aspen concludes, on the basis of the data provided, that there are no safety implications to the reported higher incidence of death in the Harenberg study. The result is inconsistent with other data presented, may lack statistical robustness and is more likely to be associated with differences in patient characteristics rather than the medicines themselves.

- *8. Could the committee comment on the Pottier (2000) study, with particular regard to the potential for bias in the design and implementation of the study and the strength of the evidence for efficacy? What is the committee's view with regard to inclusion of the outcomes of this study in the Clinical Trials section of the PI?*

The proposed PI contains the statement that prophylactic nadroparin is estimated to reduce the risk of VTE by 2.5 times as part of the 7 summary points at the end of the Clinical Trials section. This statement is based on the study by Pottier 2000. The study was a prospective observational study, and therefore not randomised or adequately controlled, so Aspen agrees with the Delegate that it may not provide an ideal level of quality for decision making.

However there are also strengths associated with the design, which provide some useful insight into the potential benefits of prophylactic nadroparin in a routine practice environment.

The study indirectly measures safety and efficacy via the primary endpoint and measurement for adverse events. 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 and safety was measured via the assessment of adverse events including haemorrhagic complications.

The study evaluated all patients admitted to 5 medical departments over a 2 year period, assigning them to three risk categories according to the likelihood of them developing a venous thromboembolism. At the time of this study, best practice indicated that the high risk patients should receive prophylactic anticoagulation treatment. The incidence of thromboembolism in those who received nadroparin, and those who did not, despite best practice recommendations, were prospectively tracked, compared and reported. In this way the study has design elements and scientific rigor similar to a case controlled cohort study.

The incidence of venous thromboembolism was 28 in the 3,730 high risk patients receiving nadroparin (0.75%) and 18 in the 1,022 high risk patients who did not receive this treatment (1.7%).

Thus the incidence of VTE in high risk medical patients was reduced by around 2.5 times in patients appropriately receiving prophylactic nadroparin.

Aspen believes that this study provides a sufficiently sound basis on which to base this summary claim.

Questions for the sponsor

- *1. The following volumes and pack sizes are available in Australia:*

Volume	Pack size	Volume	Pack size	Volume	Pack size
0.2 mL	2	0.3 mL	2	0.4 mL	2
0.6 mL	2	0.8 mL	2	1.0 mL	2

- *2. The Alikhan meta-analysis excluded patients requiring admission to an intensive care unit, yet the Fraisse study, which included patients with acute decompensated COPD requiring mechanical ventilation, was conducted in 34 ICUs in France. Can you clarify this anomaly?*

Aspen is not aware of why this discrepancy is here. Also, it appears that they included a study performed by Gallus, 1973 which explicitly states that they included patients in an ICU setting (Inclusion criteria: > 40 years old; admitted for elective surgery, emergency surgery after fracture of the femoral neck, and medical patients suspected of having myocardial infarction admitted to a coronary and intensive medical-care ward). Please note that Aspen is currently awaiting a response from the Cochrane library to try and resolve this anomaly.

Other issues raised by delegate

The Delegate noted that the pivotal RCT (Fraisse 2000 and Harenberg 1992 & 1996) submitted in support of this application compared nadroparin to placebo or heparin rather than an alternative LMWH, and were conducted some time ago.

These facts reflect both the time at which nadroparin was under clinical development, the regulatory requirements associated with the development of an objective and systematic LBS, and the time at which nadroparin was introduced to market compared to other LMWH such as enoxaparin, and best practice.

Nadroparin was first entered onto the ARTG in 1995. Enoxaparin was first entered onto the ARTG in November 1996. The majority of clinical trial activity associated with the developed and registration of nadroparin would be expected to be conducted through the 1990s as exemplified by the two pivotal trials submitted with this application. As enoxaparin was marketed later than nadroparin, comparators such as heparin or placebo are more likely to be used in these clinical trials.

In fact at the time that the Fraisse study was published in France, the authors stated that:

> *There is no consensus regarding the efficacy of thromboembolism prophylaxis in critically ill patients. Further, no clear guidelines as to drug dose and regimen can yet be derived from clinical studies. As a consequence, it was thought to be ethical to include a placebo group in this study…*

A similar justification for using heparin was provided by Harenberg in the study published in Germany in 1996.

It is also relevant to note that the TGA LBS guidelines generally require a product to be marketed for at least 10 years, prior to a LBS being considered appropriate as the basis of a regulatory submission.

Both Fraisse and Harenberg were well designed studies with clearly defined hypotheses, sample size calculations, blinding of treatment, statistical plans and follow up. While both studies were randomised, the methods used to generate the sequence and concealment of codes were not provided.

The delegate also noted that the pivotal studies did not provide details of other non-pharmacological thromboembolism prevention strategies. As both studies had the study protocol approved by the relevant human ethics committee prior to commencement, it is reason to accept that existing standards of care were provided to all patients recruited to each study.

Finally, the Delegate noted that the submitted studies lacked adequate numbers of patients with unstable angina, acute myocardial infarction and stroke to support the original broader indication requested. While both Fraisse and Harenberg treated a substantial percentage of patients with concomitant cardiovascular conditions (Fraisse included 14% patients with venous insufficiency and 32% with heart failure, Harenberg included 15% patients who had experienced stroke, 15% previous MI and 43% who had a degree of cardiac insufficiency), Aspen support an indication which does not specifically mention these conditions, and have included a precautionary statement in the PI stating that nadroparin is not indicated for the treatment of unstable angina.

Conclusion

Aspen requests that our application for extension of indication for nadroparin be approved, as Aspen has:

- agreed to the TGA's proposed indication,
- agreed to all revisions proposed for the PI (including those in the Delegate's overview) and, and
- adequately addressed the Delegate's concerns in this response.

Furthermore, the evaluator has stated in the final evaluation report:

> *However, nadroparin, when administered in the recommended doses (3800 to 5700 IU anti-Xa) 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.*

Advisory Committee Considerations[11]

The ACM, taking into account the submitted evidence of efficacy, safety and quality, did not agree with the Delegate and considered Fraxiparine disposable glass pre-filled single use syringes containing:

- 1,900 IU anti-Xa/0.2ml
- 2,850 IU anti-Xa/0.3ml
- 3,800 IU anti-Xa/0.4ml
- 5,700 IU anti-Xa/0.6ml
- 7,600 IU anti-Xa/0.8ml
- 9,500 IU anti-Xa/1.0ml

of nadroparin calcium to have an **overall positive benefit-risk profile**, with some amendment to the proposed therapeutic indication and the precautions section.

Revised indication proposed after Round 2 evaluation:

> *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*

Initially proposed indication:

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

ACM resolved to recommend the following indication:

> *Prophylaxis of venous thromboembolism in high-risk medical patients who are immobilised due to acute illness or hospitalised in an intensive care unit*

ACM advised that specific comment should be included in the PI that nadroparin is not indicated for the treatment of unstable angina or myocardial infarction.

In making this recommendation, ACM noted the evidence regarding use in the proposed indication.

Proposed conditions of registration

ACM agreed with the Delegate on the proposed conditions of registration.

Proposed PI/CMI amendments

The ACM agreed with the delegate to the proposed amendments to the PI and CMI and specifically advised on the amendment of the therapeutic indication which has been proposed by the committee.

[11] The ACM provides independent medical and scientific advice to the Minister for Health and TGA on issues relating to the safety, quality and efficacy of medicines supplied in Australia including issues relating to pre-market and post-market functions for medicines. The Committee is established under Regulation 35 of the *Therapeutic Goods Regulations 1990*. Members are appointed by the Minister. The ACM was established in January 2017 replacing Advisory Committee on Prescription Medicines (ACPM) which was formed in 2010. ACM encompasses pre and post-market advice for medicines, following the consolidation of the previous functions of the Advisory Committee on Prescription Medicines (ACPM), the Advisory Committee on the Safety of Medicines (ACSOM) and the Advisory Committee on Non-Prescription Medicines (ACNM). Membership comprises of professionals with specific scientific, medical or clinical expertise, as well as appropriate consumer health issues relating to medicines.

Specific advice

The ACM advised the following in response to the delegate's specific questions on the submission:

1. *What is the committee's view on the indication proposed by the evaluator in the Round 2 evaluation?*

ACM considered that the evidence supports the prophylactic use of nadroparin in high-risk medical patients immobilised in hospital or ICU due to acute illness, without the need to restrict use to patients with respiratory failure and/or respiratory infection and/or heart failure. ACM also considered the term 'illness' to be more appropriate that 'disease'.

2. *Is the committee satisfied that the submission has provided sufficient evidence of efficacy for both categories of high risk medical patients: those immobilised due to acute illness and those hospitalised in an intensive care unit?*

ACM was satisfied that evidence of efficacy for both categories of high risk patients, those immobilised due to acute illness and those hospitalised in an intensive care unit has been provided in the submission.

3. *Is the committee satisfied that the study populations adequately represent the target population for the proposed indication?*

ACM considered that the study populations adequately represent the target population for the proposed indication.

4. *What is the committee's view on the safety implications of the higher incidence of deaths in the nadroparin group in the Harenberg study?*

ACM advised that though the study groups were matched initially, the deaths seen did not fit the pattern consistent with medication related factors. The committee noted that an increased risk of mortality was not seen in other studies. The committee was satisfied with the safety profile of nadroparin.

5. *What is the committee's view on the sponsor's proposal to align the wording to the Czech indication?*

ACM proposed alternative wording for the indication because it considered that the indication should not restrict usage to high-risk medical patients with respiratory failure and/or respiratory infection and/or heart failure. ACM preferred the term 'illness' over 'disease'.

6. *Does the committee consider that the submission has provided sufficient evidence to support the sponsor's request for the indication to include cancer patients in the category of hospitalised patients?*

Though patients with cancer were included in studies, there has not been a specific study of the use of nadroparin in cancer patients. As cancer is recognised to increase thrombotic risk, the committee did not consider that there was enough evidence provided to include cancer patients as a category of hospitalised patients. ACM considered that its proposed indication did not require specific reference to cancer patients.

7. *What is the committee's view regarding the PI containing a statement in the Precautions section that nadroparin is not indicated for the treatment of unstable angina?*

ACM considered that since other LMWHs are indicated in the treatment of unstable angina, unless health practitioners are advised that there is insufficient evidence associated with nadroparin, it may be used in clinical practice in patients with unstable angina. The committee supported the addition of a statement in the 'Precautions' section of the PI document that nadroparin is not indicated for the treatment of unstable angina.

8. *Could the committee comment on the Pottier (2000) study, with particular regard to the potential for bias in the design and implementation of the study and the strength of the evidence for efficacy? What is the committee's view with regard to inclusion of the outcomes of this study in the Clinical Trials section of the PI?*

ACM noted that though the Pottier (2000) study was changed from a superiority study to an equivalence study, they did not consider that the study was biased in a practical or clinical sense. The committee considered that the study demonstrated efficacy of nadroparin. The committee was satisfied with the wording regarding the Pottier study in the revised PI document.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration of Fraxiparine containing nadroparin calcium.

The new indications are:

> *Prophylaxis of venous thromboembolism in high-risk medical patients who are immobilised due to acute illness or hospitalised in an intensive care unit*

The full indications are:

- *Prophylaxis against deep vein thrombosis (DVT) associated with general or orthopaedic surgery*
- *Treatment of DVT*
- *Prevention of clotting during haemodialysis*
- *Prophylaxis of venous thromboembolism in high-risk medical patients who are immobilised due to acute illness or hospitalised in an intensive care unit*

Attachment 1. Product Information

The PI for Fraxiparine approved with the submission which is described in this AusPAR is at Attachment 1. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>.

Attachment 2. Extract from the Clinical Evaluation Report

Therapeutic Goods Administration

PO Box 100 Woden ACT 2606 Australia
Email: info@tga.gov.au Phone: 1800 020 653 Fax: 02 6232 8605
https://www.tga.gov.au