

5.09 Nadroparin calcium, pre-filled syringe, 1900, 2850, 3800, 5700, 7600, 9500, 11400, 15200, 19,000 IU anti-Xa/mL, Fraxiparine® and Fraxiparine Forte®, Aspen Pharmacare Australia Pty Ltd.

1 Purpose of Application

1.1 Unrestricted listing for nadroparin (Fraxiparine® and Fraxiparine Forte®) and Restricted Benefit listing for nadroparin (Fraxiparine®) for haemodialysis.

2 Requested listing

2.1 Suggestions and additions proposed by the Secretariat to the requested listing are added in italics and suggested deletions are crossed out with strikethrough.

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer
NADROPARIN CALCIUM				
injection 1,900 IU anti-Xa in 0.2 mL, 10 2 x 0.2 mL single use pre-filled syringe	2	0	\$ [REDACTED]	
injection 2,850 IU anti-Xa in 0.3 mL, 10 2 x 0.3 mL single use pre-filled syringe	2	0	\$ [REDACTED]	
injection 3,800 IU anti-Xa in 0.4 mL, 10 2 x 0.4 mL single use pre-filled syringe	2	0	\$ [REDACTED]	Fraxiparine® Aspen
injection 5,700 IU anti-Xa in 0.6mL, 10 2 x 0.6 mL single use pre-filled syringe	2	0	\$ [REDACTED]	
injection 7,600 IU anti-Xa in 0.8 mL, 10 2 x 0.8 mL single use pre-filled syringe	1	1	\$ [REDACTED]	
injection 9,500 IU anti-Xa in 1mL, 10 2 x 1 mL single use pre-filled syringe	1	1	\$ [REDACTED]	
NADROPARIN CALCIUM				
injection 11,400 IU anti-Xa in 0.6mL, 10 2 x 0.6 mL single use pre-filled syringe	1	1	\$ [REDACTED]	
injection 15,200 IU anti-Xa in 0.8mL, 10 2 x 0.8 mL single use pre-filled syringe	1	1	\$ [REDACTED]	Fraxiparine Forte® Aspen
injection 19,000 IU anti-Xa in 1 mL, 10 2 x 1 mL single use pre-filled syringe	1	1	\$ [REDACTED]	
Restriction	General Benefit			

	Max. Qty	No. of Rpts	Dispensed Price for Max. Qty	Proprietary Name and Manufacturer	
NADROPARIN CALCIUM					
injection 1,900 IU anti-Xa in 0.2 mL, 10 2 x 0.2 mL single use pre-filled syringe	2	3	\$ [REDACTED]	Fraxiparine® Aspen	
injection 2,850 IU anti-Xa in 0.3 mL, 10 2 x 0.3 mL single use pre-filled syringe	2	3	\$ [REDACTED]		
injection 3,800 IU anti-Xa in 0.4 mL, 10 2 x 0.4 mL single use pre-filled syringe	2	3	\$ [REDACTED]		
injection 5,700 IU anti-Xa in 0.6mL, 10 2 x 0.6 mL single use pre-filled syringe	2	3	\$ [REDACTED]		
injection 7,600 IU anti-Xa in 0.8 mL, 10 2 x 0.8 mL single use pre-filled syringe	2	3	\$ [REDACTED]		
injection 9,500 IU anti-Xa in 1mL, 10 2 x 1 mL single use pre-filled syringe	2	3	\$ [REDACTED]		
Condition	Haemodialysis				
Restriction	Restricted Benefit				

- 2.2 Listing was requested on a cost-minimisation basis compared to enoxaparin.
- 2.3 There is potential for more wastage associated with nadroparin compared to enoxaparin, due to the requirement for a dose increase from Day 4 onwards post-orthopaedic surgery, the availability of the Fraxiparine Forte® formulations requesting the same quantity and repeats as the Fraxiparine® formulations despite requiring half the dosing frequency for the treatment of deep vein thrombosis (DVT), and the requested quantities defaulting to those for the prevention of DVT despite the overlap between the doses used in prevention of DVT and the treatment of DVT.

For more detail on PBAC's view, see section 7 "PBAC outcome"

3 Background

- 3.1 Nadroparin was first TGA registered on 14 August 1995, with the higher concentration formulation registered on 3 December 1998. The TGA-approved indications for the lower concentration formulation (Fraxiparine®) are prophylaxis against DVT associated with general or orthopaedic surgery, treatment of DVT and prevention of clotting during haemodialysis. The higher concentration formulation (Fraxiparine Forte®) is TGA-approved for the treatment of DVT.
- 3.2 Nadroparin was previously listed on the PBS between February 1997 and August 2001 under a different sponsor. At the time of withdrawal from the PBS, Fraxiparine® had Authority Required listings for prophylaxis following major hip surgery and Fraxiparine Forte® had Authority Required listings for the treatment of DVT.
- 3.3 The sponsorship of the nadroparin has been transferred twice since its withdrawal from the PBS.

4 Clinical place for the proposed therapy

- 4.1 DVT is a blood clot that forms in the deep veins of the leg. The thrombus (blood clot) may dislodge from the original site and travel to the lung, resulting in a life-threatening complication called pulmonary embolism (PE). The risk of developing DVT after surgery depends on the procedure and other predisposing factors. 'Blood-thinning drugs', such as nadroparin, are used to prevent and treat DVT. These drugs also given to prevent thrombosis (clotting) during haemodialysis.
- 4.2 The submission stated that the PBS-listing of nadroparin is not expected to alter the treatment algorithm for antithrombotic agents, but will provide an additional clinical choice in the obese population.
- 4.3 The submission claimed that it is possible for nadroparin to be used 'without the need to make arbitrary, and as yet unsubstantiated, dose adjustments' due to its weight-based dosing. Nadroparin has a fixed dose for prophylaxis associated with general surgery. The tabulated nadroparin weight-based dosing regimens in the Product Information document may result in effective 'caps' for nadroparin in clinical practice. The submission provided limited data on the use of nadroparin among patients with high body weight.

For more detail on PBAC's view, see section 7 "PBAC outcome"

5 Comparator

- 5.1 Enoxaparin. The PBAC agreed that this was the appropriate comparator.

6 Consideration of the evidence

Sponsor hearing

- 6.1 The sponsor requested a hearing for this item.
- 6.2 The sponsor presented the history of the PBS listing of nadroparin and the clinical benefits of nadroparin that make it an important additional LMWH choice for patient and prescribers. The sponsor views that nadroparin finds its use :
- obese patients (BMI>30) who constitute 35% of 55-74 year olds of the Australian population and the possibility for nadroparin to be used without the need to make arbitrary, and as yet unsubstantiated, dose adjustments due to its weight-based dosing).
 - as a fixed dose for DVT prophylaxis associated with general surgery and claim of bio-equivalence between once a day and twice a day presentation.
 - contains calcium salt, unlike the other LMWHs (sodium salt) and The submission argued that this translates to a safety/tolerability advantage with less painful injection.
- 6.3 The PBAC considered that the hearing was moderately informative

Consumer comments

6.4 There were no consumer comments received for this item.

Clinical trials

6.5 The submission was based on one head-to-head randomised trial comparing nadroparin to enoxaparin in colorectal surgery for cancer, which provided evidence in general surgery (Simonneau, 2006); and a series of indirect comparisons using 41 trials across different indications via various common references, summarised in the table below.

Table 1: Summary of the indirect comparisons presented in the submission

Indication	Prophylaxis against DVT – major orthopaedic surgery				Treatment of DVT	Haemodialysis	
	THR		TKR	Hip # ^a			
No. nadro. trials	1 trial	2 trials	1 trial	1 trial	3 trials	6 trials	2 trials
Common comparator	PBO or no LMWH	UFH	Extended PBO or no LMWH	Mechanical prophylaxis	PBO or no LMWH	UFH	UFH
No. enoxa. trials	5 trials	5 trials	3 trials	3 trials	1 trial	7 trials	1 trial

Abbreviations: # = fracture; DVT = deep vein thrombosis; enoxa = enoxaparin; LMWH = low molecular weight heparin; nadro = nadroparin; PBO = placebo; THR = total hip replacement; TKR = total knee replacement; UFH = unfractionated heparin
Source: Adapted from Tables B.2-2, pB-15, B.2-3, ppB-16 to B-22; B.2-4, ppB-22 to B-23; and B.2-5, ppB-22 to B-23 of the submission

^a These trials were only included in Section B.2. No data on hip fracture were presented in subsequent sections.

6.6 Details of the trials presented in the submission are provided in the table below.

Table 2: Trials and associated reports presented in the submission

Trial ID	Protocol title/ Publication title	Publication citation
Nadroparin vs. enoxaparin (general surgery)		
Simonneau 2006	Simonneau G, Laporte S, Mismetti P, Derlon A, Samii K, Samama CM, Bergman JF. A randomized study comparing the efficacy and safety of nadroparin 2850 IU (0.3 mL) vs. enoxaparin 4000 IU (40 mg) in the prevention of venous thromboembolism after colorectal surgery for cancer.	Journal of Thrombosis and Haemostasis 2006; 4(8): 1693-1700
Nadroparin vs. placebo (total hip replacement)		
Yoo 1997	Yoo, MC, Kang CS, Kim YH, Kim SK. A prospective randomized study on the use of nadroparin calcium in the prophylaxis of thromboembolism in Korean patients undergoing elective total hip replacement.	International Orthopaedics 1997; 21(6): 399-402
Enoxaparin vs. placebo (total hip replacement)		
Fuji 2008	Fuji T, Ochi T, Niwa S, Fujita S. Prevention of postoperative venous thromboembolism in Japanese patients undergoing total hip or knee arthroplasty: two randomized, double-blind, placebo-controlled studies with three dosage regimens of enoxaparin.	Journal of Orthopaedic Science 2008; 13(5): 442-451
Kalodiki 1996	Kalodiki EP, Hoppensteadt DA, Nicolaides AN, Fareed J, Gill K, Regan F, al-Kutoubi A, Cunningham DA, Birch R, Harris N, Hunt D, Johnson J, Marx C. Deep venous thrombosis prophylaxis with low molecular weight heparin and elastic compression in patients having total hip replacement. A randomised controlled trial.	International Angiology 1996; 15(2): 162-168
Samama 1997	Samama C, Clergue F, Barre J, Montefiore A, III P, <i>et al.</i> Low molecular weight heparin associated with spinal anaesthesia and gradual compression	Br J Anaesth 1997; 78(6): 660-665

Trial ID	Protocol title/ Publication title	Publication citation
	stockings in total hip replacement surgery. Arar study group.	
Turpie 1986	Turpie AG, Levine MN, Hirsh J, Carter CJ, Jay RM, Powers PJ, Andrew M, Hull RD, Gent M. A randomized controlled trial of a low-molecular-weight heparin (enoxaparin) to prevent deep-vein thrombosis in patients undergoing elective hip surgery.	New England Journal of Medicine 1986; 315(15): 925-929
Warwick 1995	Warwick D, Bannister G, <i>et al.</i> Perioperative low-molecular-weight heparin: Is it effective and safe?	Journal of Bone and Joint Surgery - British volume 1995; 77-B(5): 715-719
Nadroparin vs. unfractionated heparin (total hip replacement)		
GHAT 1992	The German Hip Arthroplasty Trial (GHAT) Group. Prevention of deep vein thrombosis with low molecular-weight heparin in patients undergoing total hip replacement.	Arch Orthop Trauma Surg 1992; 111: 110-120.
Leyvraz 1991	Leyvraz PF, Bachmann F, Hoek J, Buller HR, Postel M, Samama M, Vandebroek MD. Prevention of deep vein thrombosis after hip replacement: randomised comparison between unfractionated heparin and low molecular weight heparin. <u>Study Report</u> Sterling Winthrop 515.6.029 Prophylaxis of deep venous thrombosis (DVT) in orthopaedic surgery for total hip replacement: Fraxiparine versus subcutaneous standard heparin. TGA Submission.	BMJ 1991; 303(6802): 543-548. Erratum in BMJ 1991; 303 (6812): 1243
Enoxaparin vs. unfractionated heparin (total hip replacement)		
Avikainen 1995	Avikainen V, von Bonsdorff H, Partio E, Kaira P, Hakkinen S, Usenius JP, Kaaja R. Low molecular weight heparin (enoxaparin) compared with unfractionated heparin in prophylaxis of deep venous thrombosis and pulmonary embolism in patients undergoing hip replacement.	Annales Chirurgiae et Gynaecologiae 1995; 84(1): 85-90
Colwell 1994	Colwell CW Jr, Spiro TE, Trowbridge AA, Morris BA, Kwaan HC, Blaha JD, Comerota AJ, Skoutakis VA. Use of enoxaparin, a low-molecular-weight heparin, and unfractionated heparin for the prevention of deep venous thrombosis after elective hip replacement. A clinical trial comparing efficacy and safety. Enoxaparin Clinical Trial Group.	Journal of Bone & Joint Surgery - American Volume 1994; 76(1): 3-14 Erratum in J Bone Joint Surg Am 1994; 76(3): 4741
Perhoneimi 1996	Perhoneimi V, Vuorinen J, Myllynen P, Kivioja A, Lindevall K. The effect of enoxaparin in prevention of deep venous thrombosis in hip and knee surgery--a comparison with the dihydroergotamine-heparin combination.	Annales Chirurgiae et Gynaecologiae 1996; 85(4): 359-363
Planes 1988	Planes A, Vochelle N, Mazas F, Mansat C, Zucman J, <i>et al.</i> Prevention of postoperative venous thrombosis: A randomized trial comparing unfractionated heparin with low molecular weight heparin in patients undergoing total hip replacement.	Thrombosis & Haemostasis 1988; 60(3): 407-410
Senaran 2006	Senaran H, Acaroglu E, Ozdemir HM, Atilla B. Enoxaparin and heparin comparison of deep vein thrombosis prophylaxis in total hip replacement patients.	Archives of Orthopaedic & Trauma Surgery 2006; 126(1): 1-5
Nadroparin vs. no extended prophylaxis (total hip replacement)		
Haentjens 2001	Haentjens P, Delince P, The Belgian nadroparin post-hospital discharge in orthopaedics (NPHDO) study group. Prevention of venous thromboembolism after hospital discharge. Continued pharmacological prophylaxis versus no prophylaxis in patients undergoing total hip replacement.	Hip International 2001; 11(1): 25-36
Enoxaparin vs. extended duration placebo (total hip replacement)		
Bergqvist 1996	Bergqvist D, Benoni G, Bjorgell O, Fredin H, Hedlundh U, Nicolas S, Nilsson P, Nylander G. Low-molecular-weight heparin (enoxaparin) as prophylaxis against venous thromboembolism after total hip replacement.	New England Journal of Medicine 1996; 335(10): 696-700

Trial ID	Protocol title/ Publication title	Publication citation
Comp 2001	Comp PC, Spiro TE, Friedman RJ, Whitsett TL, Johnson GJ, Gardiner GA Jr, Landon GC, M. Jove, Enoxaparin Clinical Trial Group. Prolonged enoxaparin therapy to prevent venous thromboembolism after primary hip or knee replacement. Enoxaparin Clinical Trial Group.	Journal of Bone & Joint Surgery - American Volume 2001; 83-A(3): 336-345
Planes 1996	Planes A, Vochelle N, Darmon JY, Fagola M, Bellaud M, <i>et al.</i> Risk of deep-venous thrombosis after hospital discharge in patients having undergone total hip replacement: Double-blind randomised comparison of enoxaparin versus placebo. Planes A, Vochelle N, Darmon JY, Fagola M, Bellaud M, Compan D, Saliba E, Weisslinger N, Huet Y. Efficacy and safety of postdischarge administration of enoxaparin in the prevention of deep venous thrombosis after total hip replacement. A prospective randomised double-blind placebo-controlled trial.	Lancet 1996; 348(9022): 224-228 Drugs 1996; 52 Suppl 7: 47-54
Nadroparin vs. mechanical prophylaxis – intermittent pneumatic compression (IPC) or foot pump (total knee replacement)		
Blanchard 1999	Blanchard J, Meuwly JY, Leyvraz PF, Miron MJ, Bounameaux H, Hoffmeyer P, Didier D, Schneider PA. Prevention of deep-vein thrombosis after total knee replacement. Randomised comparison between a low-molecular-weight heparin (nadroparin) and mechanical prophylaxis with a foot-pump system.	Journal of Bone & Joint Surgery - British Volume 1999; 81(4): 654-659
Enoxaparin vs. mechanical prophylaxis – intermittent pneumatic compression (IPC) or foot pump (total knee replacement)		
Chin 2009	Chin P L, Amin MS, Yang KY, Yeo SJ, Lo MN. Thromboembolic prophylaxis for total knee arthroplasty in Asian patients: a randomised controlled trial.	Journal of Orthopaedic Surgery (Hong Kong) 2009; 17(1): 1-5
Norgren 1998	Norgren L, Toksvig-Larsen S, Magyar G, Lindstrand A, Albrechtsson U. Prevention of deep vein thrombosis in knee arthroplasty. Preliminary results from a randomized controlled study of low molecular weight heparin.	Int Angiol 1998; 17(2): 93-96
Warwick 2002	Warwick D, Harrison J, Whitehouse S, Mitchelmore A, Thornton M. A randomised comparison of a foot pump and low-molecular-weight heparin in the prevention of deep-vein thrombosis after total knee replacement.	Journal of Bone & Joint Surgery - British Volume 2002; 84(3): 344-350.
Nadroparin vs. placebo (hip fracture surgery)		
Kew 1999	Kew J, Lee YL, Davey IC, Ho SY, Fung KC, <i>et al.</i> Deep vein thrombosis in elderly Hong Kong Chinese with hip fractures detected with compression ultrasound and Doppler imaging: incidence and effect of low molecular weight heparin.	Arch Orthop Trauma Surg 1999; 119: 156-158
Sourmelis 1995a	Sourmelis S, Patoulis G, <i>et al.</i> Prevention of deep vein thrombosis with low molecular weight heparin in fractures of the hip.	Journal of Bone and Joint Surgery - British volume 1995; 77(Suppl 2): 173.
Sourmelis 1995b		
Enoxaparin vs. placebo (hip fracture surgery)		
Jorgensen 1998	Jorgensen P, Strandberg C, Wille-Jorgensen P, Neergaard K, Paaske BP, <i>et al.</i> Early preoperative thromboprophylaxis with Klexane® in hip fracture surgery: A placebo-controlled study.	Clin Appl Thrombosis/Hemostasis 1998; 4(2): 140-142
Nadroparin vs. unfractionated heparin (treatment of DVT)		
Belcaro 1999	Belcaro G, Nicolaidis AN, Cesarone MR, Laurora G, De Sanctis MT, <i>et al.</i> Comparison of low-molecular-weight heparin, administered primarily at home, with unfractionated heparin, administered in hospital, and subcutaneous heparin, administered at home for deep-vein thrombosis.	Angiology 1999; 50(10): 781-787
Galilei 2004	Writing committee for Galilei Investigators, Prandoni, P, <i>et al.</i> Subcutaneous	Archives of Internal

Trial ID	Protocol title/ Publication title	Publication citation
	adjusted-dose unfractionated heparin vs fixed-dose low-molecular-weight heparin in the initial treatment of venous thromboembolism.	Medicine 2004; 164(10): 1077-1083
Koopman 1996	Koopman MM, Prandoni P, Piovella F, Ockelford PA, Brandjes DP, <i>et al.</i> Treatment of venous thrombosis with intravenous unfractionated heparin administered in the hospital as compared with subcutaneous low-molecular-weight heparin administered at home.	New England Journal of Medicine 1996; 334: 682-687 [Erratum in <i>N Engl J Med</i> 1997; 337(17): 1251]
Lopaciuk 1992	Lopaciuk S, Meissner AJ, Filipecki S, Zawilska K, Sowier J, <i>et al.</i> Subcutaneous low molecular weight heparin versus subcutaneous unfractionated heparin in the treatment of deep vein thrombosis: A Polish multicenter trial. <u>Study Report</u> Sterling Winthrop 515.6.067 A multicentre randomised clinical trial: the use of the low molecular weight heparin (LMWH) CY216D (Fraxiparine) in the treatment of deep venous thrombosis (DVT) of the lower limbs. TGA Submission. (Study IVB14)	Thrombosis & Haemostasis 1992; 68(1): 14-18
Ninet 1991	A Collaborative European Multicentre Study, Ninet J, Bachet P, <i>et al.</i> A randomized trial of subcutaneous low molecular weight heparin (CY216) compared with intravenous unfractionated heparin in the treatment of deep vein thrombosis. <u>Study Report</u> Sterling Winthrop 515.6.024 Curative treatment of deep venous thrombosis of lower limbs. Comparison of Fraxiparine (CY216D) and unfractionated heparin. TGA Submission. (Study IVB11)	Thrombosis & Haemostasis 1991; 65(3): 251-256
Prandoni 1992	Prandoni P, Lensing A, Büller HR, Carta M, Cogo A, <i>et al.</i> Comparison of subcutaneous low-molecular-weight-heparin with intravenous standard heparin in proximal deep vein thrombosis. <u>Study Report</u> Sterling Winthrop 515.6.070 Treatment of deep vein thrombosis of the lower extremities: comparative study of nadroparin calcium (Fraxiparine) s.c. versus i.v. standard unfractionated heparin. TGA Submission. (Study IVB12)	Lancet 1992; 339(8791): 441-445
Enoxaparin vs. unfractionated heparin (treatment of DVT)		
Chong 2005	Chong BH, Brighton TA, Baker RI, Thurlow P, Lee CH; ASTH DVT Study Group. Once-daily enoxaparin in the outpatient setting versus unfractionated heparin in hospital for the treatment of symptomatic deep-vein thrombosis.	Journal of Thrombosis & Thrombolysis 2005; 19(3): 173-181
Decousus 1998	Decousus H, Leizorovicz A, Parent F, Page Y, Tardy B, <i>et al.</i> A clinical trial of vena caval filters in the prevention of pulmonary embolism in patients with proximal deep-vein thrombosis. Prévention du Risque d'Embolie Pulmonaire par Interruption Cave Study Group.	New England Journal of Medicine 1998; 338(7): 409-415
Findik 2002	Findik S, Erkan ML, Selçuk MB, Albayrak S, Atici AG, <i>et al.</i> Low-molecular-weight heparin versus unfractionated heparin in the treatment of patients with acute pulmonary thromboembolism.	Respiration 2002; 69(5): 440-444
Levine 1996	Levine M, Gent M, Hirsh J, Leclerc J, Anderson D, <i>et al.</i> A comparison of low-molecular-weight heparin administered primarily at home with unfractionated heparin administered in the hospital for proximal deep-vein thrombosis.	N Engl J Med 1996; 334(11): 677-681
Merli 2001	Merli G, Spiro TE, Olsson CG, Abildgaard U, Davidson BL, <i>et al.</i> Subcutaneous enoxaparin once or twice daily compared with intravenous unfractionated heparin for treatment of venous thromboembolic disease.	Annals of Internal Medicine 2001; 134(3): 191-202
Ramacciotti 2004	Ramacciotti E, Araujo GR, Lastoria S, Maffei FH, Karaoglan de Moura L, <i>et al.</i> An open-label, comparative study of the efficacy and safety of once-daily	Thrombosis Research 2004; 114(3): 149-

Trial ID	Protocol title/ Publication title	Publication citation
	dose of enoxaparin versus unfractionated heparin in the treatment of proximal lower limb deep-vein thrombosis.	153
Simonneau 1993	Simonneau G, Charbonnier B, Decousus H, Planchon B, Ninet J, <i>et al.</i> Subcutaneous low-molecular-weight heparin compared with continuous intravenous unfractionated heparin in the treatment of proximal deep vein thrombosis.	Archives of Internal Medicine 1993; 153(13): 1541-1546
Nadroparin vs. unfractionated heparin (prevention of clotting during haemodialysis)		
Nurmohamed 1991	Nurmohamed M, ten Cate J, Stevens P, Hoek JA, Lins RL, <i>et al.</i> Long-term efficacy and safety of a low molecular weight heparin in chronic haemodialysis patients. <u>Study Report</u> Sterling Winthrop 515.6.051 A randomised, open study comparing the efficacy and safety of CY216D (Fraxiparine) and unfractionated heparin in chronic intermittent haemodialysis. TGA Submission. (Study IVB16)	ASAIO Transactions 1991; 37: M459-M461.
Stefoni 2002	Stefoni S, Cianciolo G, Donati G, Coli L, La Manna G, <i>et al.</i> Standard heparin versus low-molecular-weight-heparin. A medium-term comparison in hemodialysis.	Nephron 2002; 92: 589-600
Enoxaparin vs. unfractionated heparin (prevention of clotting during haemodialysis)		
Saltissi 1999	Saltissi D, Morgan C, Westhuyzen J, Healy H. Comparison of low-molecular-weight heparin (enoxaparin sodium) and standard unfractionated heparin for haemodialysis anticoagulation.	Nephrol Dial Transplant 1999; 14: 2698-2703.

Abbreviations: DVT = deep vein thrombosis

Source: Tables B.2-3, ppB-16 to B-22; B.2-4, ppB-22 to B-23; and B.2-5, ppB-22 to B-23 of the submission

6.7 The submission did not present any data for hip fracture surgery despite the stated inclusion of three nadroparin trials (Kew 1999, Sourmelis 1995a, Sourmelis 1995b) and one enoxaparin trial (Jorgensen 1998). The reasons for this omission were unclear.

6.8 The key features of the randomised trials are summarised in the following table.

Table 3: Key features of the included evidence

Trial	N	Design/ duration	Risk of bias	Patient population	Comparison	Main outcome(s)
Nadroparin vs. enoxaparin (general surgery)						
Simonneau 2006	1,288	DB, R, MC 12 days	Unclear	Elective colorectal cancer surgery	Nadroparin 2,850 IU daily vs enoxaparin 40 mg daily	VTE: DVT (venography) or symptomatic DVT or PE up to day 12
Nadroparin vs. placebo or no LMWH (total hip replacement)						
Yoo 1997 (Korea)	100	OL, R, MC 10 days	High	Elective THR	Nadroparin 41 IU/kg 12 hrs before/after then once daily, 62 IU/kg from 4 th day vs no treatment	DVT (venography) on Day 10
Enoxaparin vs. placebo or no LMWH (total hip replacement)						
Fuji 2008 (Japan)	421	DB, R, MC 14 days	Unclear	Elective THR trial included in submission	Enoxaparin 20 mg daily vs enoxaparin 40 mg daily vs enoxaparin 20 mg BD vs placebo	VTE: DVT (venography) or PE by Day 17
Kalodiki 1996	93 (27 incl.)	Two-part (1 st : DB PBO, 2 nd : OL GCS), R 8-12 days	High	Elective unilateral THR or without cement under	Enoxaparin 40 mg daily (incl. 1 st part) vs enoxaparin 40 mg daily + GCS (not incl.) vs placebo	DVT (venography) on Day 8-12

Trial	N	Design/ duration	Risk of bias	Patient population	Comparison	Main outcome(s)
				GA	± GCS (incl.)	
Samama 1997	170	DB, R, MC 8-12 days	Unclear	THR under regional (spinal) anaesthesia	Enoxaparin 40 mg daily + GCS vs placebo + GCS	VTE: DVT (venography) or PE on Day 10 ± 2
Turpie 1986	100 (76 incl.)	DB, R, MC 14 days (or until discharge)	Unclear	Elective THR	Enoxaparin 30 mg BD vs placebo	DVT (2 screening tests) for 24 pts DVT (venography) at 14 days for 76 pts
Warwick 1995	156	OL, R 3 days treatment	High	THR	Enoxaparin 40 mg daily + GCS vs no treatment + GCS	DVT (venography) on Day 8-10
Nadroparin vs. unfractionated heparin (total hip replacement)						
GHAAT 1992	341	DB, R, MC 15-17 days	Low	Elective THR	Nadroparin ~4,100 IU daily vs. heparin 5,000 IU TDS	DVT (venography) on Day 14 ± 1
Leyvraz 1991	409	OL, R, MC 9-11 days	Unclear	Elective THR under GA	Nadroparin 41 IU/kg 12 hrs before/after then once daily, 62 IU/kg from 4 th day vs. titrated heparin TDS (mean dose: 3,679 IU)	Total DVT and proximal DVT (venography) on Day 9-11
Enoxaparin vs. unfractionated heparin (total hip replacement)						
Avikainen 1995	167	OL, R 10 days	High	Elective THR	Enoxaparin 40 mg daily vs heparin 5,000 IU BD	DVT (ultrasonography) on Day 10 and 14
Colwell 1994	610	OL, R, MC Max 7 days	Unclear	Elective THR	Enoxaparin 30 mg BD vs enoxaparin 40 mg daily vs heparin 5,000 IU TDS	DVT (venography) on Day 7
Perhoneimi 1996	165	PB, R 7 days	Unclear	Hip or knee (prosthesis or fracture) surgery	Enoxaparin 40 mg daily vs dihydroergotamine- heparin 0.5mg + 5,000 IU BD	DVT (ultrasonography) on Day 10 to 12
Planes 1988	237	DB, R, MC Max 14 days	Low	Elective THR	Enoxaparin 40 mg daily vs heparin 5,000 IU TDS	VTE (venography) on Day 12-15
Senaran 2006	100	? OL, R 7-10 days	High	THR	Enoxaparin 40 mg daily vs heparin 5,000 IU TDS	Symptomatic VTE, symptomatic or fatal PE
Nadroparin vs. no extended prophylaxis (total hip replacement)						
Haentjens 2001	346	OL, R, MC 21 days	Unclear	THR	Nadroparin 2,850 IU, 3,800 IU or 5,700 IU daily (weight-based) vs no treatment post-discharge	All DVT (ultrasonography) and PE on Day 21 post- discharge
Enoxaparin vs. extended duration placebo (total hip replacement)						
Bergqvist 1996	262	DB, R 21 days	Unclear	Elective THR	Enoxaparin 40 mg daily vs placebo post-discharge	DVT (venography) on Day 21 post-discharge
Comp 2001	435	DB, R, MC 18-21 days	Unclear	THR included in submission	Enoxaparin 40 mg daily vs placebo post-discharge	VTE: DVT (venography) or symptomatic PE at end of DB treatment
Planes 1996	179	DB, R 21 days	Unclear	THR	Enoxaparin 40 mg daily vs placebo post-discharge	DVT (venography) or PE on Day 21 ± 2 post- discharge
Nadroparin vs. mechanical prophylaxis – IPC or foot pump (total knee replacement)						
Blanchard 1999	130	OL, R, 2 centres 10-12 days	High	TKR	Nadroparin 2,850 IU, 3,800 IU or 5,700 IU 12 hrs before/after then daily	DVT (venography) on Day 8-12

Trial	N	Design/ duration	Risk of bias	Patient population	Comparison	Main outcome(s)
					(weight-based) vs IPC foot pump system	
Enoxaparin vs. mechanical prophylaxis – IPC or foot pump (total knee replacement)						
Chin 2009 (Singapore)	440 (220 incl.)	OL, R 5-7 days	Unclear	TKR	No prophylaxis vs GCS vs IPC vs enoxaparin 40 mg daily	DVT (ultrasonography)
Norgren 1998	40	OL, R	High	Elective knee replacement	Enoxaparin 40 mg daily vs foot pump + GCS	DVT (venography) on Day 7-10
Warwick 2002	229	OL, R	High	Elective unilateral TKR	Enoxaparin 40 mg daily vs foot pump	DVT (venography) on Day 6-8
Nadroparin vs. placebo or no LMWH (hip fracture surgery)						
Kew 1999 (Hong Kong)	100	R	High	Hip fracture	Nadroparin vs control	DVT (ultrasonography) on Day 1, 7 and 14
Sourmelis 1995a	88	DB, R	Unclear	Petrochanteric fracture	Nadroparin 0.3 mL from admission, 0.6 mL from 1 st post-op day vs placebo	DVT (venography) on Day 10-12
Sourmelis 1995b	62			Subcapital fracture		
Enoxaparin vs. placebo or no LMWH (hip fracture surgery)						
Jorgensen 1998	239	DB, R 6-13 days post-op	Unclear	Hip fracture	Enoxaparin 40 mg daily vs placebo	DVT (venography) on Day 6-13
Nadroparin vs. unfractionated heparin (treatment of DVT)						
Belcaro 1999	325	OL, R 3 months (~5 days ^a)	Unclear	Acute proximal DVT	Nadroparin 100 IU/kg BD vs heparin IV vs heparin SC 12,500 IU BD (warfarin ≥ 3 mths for nadroparin & heparin IV)	Symptomatic or asymptomatic (colour duplex scanning) recurrent DVT or DVT extension in 3 months
Galilei 2004	720	OL, R, MC 12 weeks (6.5 days ^a)	Unclear	Acute DVT of lower extremities ± PE	Nadroparin 85 IU/kg BD vs heparin IV bolus + SC (warfarin 12 weeks)	Symptomatic recurrent VTE in 3 months
Koopman 1996	400	OL, R, MC 6 months (6.1-6.5 days ^a)	Unclear	Acute symptomatic proximal DVT	Nadroparin 4,100 IU, 6,150 IU or 8,200 IU BD vs heparin IV bolus + infusion (po anticoagulant ≥3 mths)	Symptomatic recurrent VTE in 6 months
Lopaciuk 1992	149	OL, R, MC 3 months (10 days ^a)	High	Acute proximal or calf DVT	Nadroparin 92 IU/kg BD vs heparin IV bolus followed by SC BD (acenocoumarol ≥ 3 mths)	Change in thrombus size (venography)
Ninet 1991	166	OL, R, MC 3 months (10 days ^a)	High	Acute proximal DVT	Nadroparin 5,125 IU, 6,150 IU or 7,175 IU BD vs heparin IV infusion (as per individual centre's protocol after 10 days)	Change in thrombus size (venography)
Prandoni 1992	170	OL, R 6 months (~10 days ^a)	Unclear	Acute proximal DVT	Nadroparin 5,125 IU, 6,150 IU or 7,175 IU BD vs heparin IV bolus + infusion (warfarin ≥ 3 mths)	Symptomatic recurrent DVT or symptomatic PE in 6 months
Enoxaparin vs. unfractionated heparin (treatment of DVT)						
Chong 2005	298	OL, R, MC 6 months (≥5 days ^a)	Unclear	Symptomatic lower-extremity DVT (proximal)	Enoxaparin 1.5 mg/kg daily vs heparin IV bolus + infusion	Symptomatic recurrent DVT during in 6 months

Trial	N	Design/ duration	Risk of bias	Patient population	Comparison	Main outcome(s)
				or distal)	(warfarin 3 mths)	
Decousus 1998	400	OL, R, MC, 2×2 factorial 2 years (8-12 days ^a)	Unclear	Acute proximal DVT ± PE	Enoxaparin 1 mg/kg BD vs heparin IV bolus + infusion (warfarin/ acenocoumarol ≥ 3 mths) Vena cava filter vs no vena cava filter	PE within 12 days of randomisation
Findik 2002 (Turkey)	59	OL, R 3 months (~7 days ^a)	High	Acute PE	Enoxaparin 1 mg/kg BD vs heparin IV bolus + infusion (po anticoagulant 6 mths)	Symptomatic recurrent VTE in 8 and 90 days
Levine 1996	500	OL, R, MC 90 days (~ 6 days ^a)	Unclear	Acute proximal DVT	Enoxaparin 1 mg/kg BD vs heparin IV bolus + infusion (warfarin ≥ 3 mths)	Symptomatic recurrent VTE in 90 days
Merli 2001	900	PB, R, MC 3 months (~7 days ^a)	Unclear	Symptomatic lower-extremity DVT and/or PE	Enoxaparin 1 mg/kg BD vs enoxaparin 1.5 mg/kg daily vs heparin IV bolus + infusion (warfarin ≥ 3 mths)	Symptomatic recurrent VTE in 3 months
Ramacciotti 2004 (Brazil)	201	OL, R, MC 6 months (7-8 days ^a)	High	Acute proximal DVT (lower limb, unilateral)	Enoxaparin 1.5 mg/kg daily vs heparin IV bolus + infusion (warfarin ≥ 3 mths)	Recurrent DVT in 3 months
Simonneau 1993	134	OL, R, MC 3 months (~10 days ^a)	Unclear	Proximal DVT ± PE	Enoxaparin 1 mg/kg BD vs heparin IV infusion (po anticoagulant ≥3 mths)	Change in thrombus size (venography)
Nadroparin vs. unfractionated heparin (prevention of clotting during haemodialysis)						
Nurmohamed 1991	101	OL, R, 2 centres 6 mths	High	Haemodialysis 2-3 times/wk (4-6 hrs)	Nadroparin ~80 IU/kg or ~60 IU/kg bolus (titrated) vs heparin ~2500 IU bolus + 600-2200 IU/hr	Treatment success (completion of study without significant clotting or bleeding)
Stefoni 2002	54	OL, R, CO 18 mths each period	High	Haemodialysis 3 times/wk (4 hrs)	Nadroparin 64.6 IU/kg bolus vs heparin 1500 IU bolus + 1500 ± 500 IU	Laboratory parameters (anti-Xa levels)
Enoxaparin vs. unfractionated heparin (prevention of clotting during haemodialysis)						
Saltissi 1999	36	OL, R, CO 12 wks each period	High	Haemodialysis 3 times/wk (3-5 hrs)	Enoxaparin 1 mg/kg bolus (titrated) vs heparin 50 IU/kg bolus + 1000 IU/hr	% sessions without clots or with minor clots

Abbreviations: BD = twice daily; CO = cross-over; DB = double blind; DVT = deep vein thrombosis; GA = general anaesthesia; GCS = graduated compression stockings; IPC = intermittent pneumatic compression; IV = intravenously; LMWH = low molecular weight heparin; MC = multi-centre; NR = non-randomised; OL = open label; PB = partially blinded; PBO = placebo; PE = pulmonary embolism; po = orally; R = randomised; SC = subcutaneously; TDS = three times daily; THR = total hip replacement; TKR = total knee replacement; VTE = venous thromboembolism

Source: compiled during the evaluation

Note: The submission double-counted patients from Turpie (1986). The commentary included results from the duration of mandatory venography.

^a Duration of initial therapy with LMWH or unfractionated heparin.

Comparative effectiveness

- 6.9 The submission presented clinical evidence based on the TGA-approved indications of nadroparin: prophylaxis in general surgery, prophylaxis in orthopaedic surgery, treatment of DVT and preventing clotting during haemodialysis.

Table 4: Key efficacy data from Simonneau (2006): nadroparin vs enoxaparin in colorectal surgery for cancer

	Nadroparin n/N (%)	Enoxaparin n/N (%)	Relative risk (95% CI)	Risk difference (95% CI)	NNT
Treatment period (up to day 12)					
Total VTE (primary outcome)	74/464 (15.9)	61/486 (12.6)	1.27 (0.93, 1.74)	3.4% (-1.1%, 7.8%)	-
Asymptomatic DVT	73	56	1.37 (0.99, 1.89)	4.2% (-0.2%, 8.6%)	-
Distal DVT only	58	42	1.45 (0.99, 2.11)	3.9% (-0.1%, 7.8%)	-
Any proximal DVT	15	14	1.12 (0.55, 2.30)	0.4% (-1.8%, 2.5%)	-
Symptomatic VTE	1/643 (0.2)	9/628 (1.4) ^a	0.11 (0.01, 0.85) ^b	-1.3% (-0.1%, -2.4%) ^b	77 ^b
DVT	1	5	0.20 (0.02, 1.67)	-0.6% (-1.4%, 0.1%)	-
PE	0	5	0.09 (0.00, 1.60)	-0.8% (-1.6%, -0.0%)	127
Asymptomatic proximal DVT or symptomatic non-fatal VTE or VTE-related death (EMA 2000)	16/504 (3.2)	20/518 (3.9)	0.82 (0.43, 1.56)	-0.7% (-3%, 1.8%) ^b	-

Abbreviations: CI = confidence interval; EMA = European Medicine Agency; DVT = deep vein thrombosis; NNT = number needed to treat; PE = pulmonary embolism; VTE = venous thromboembolism

Source: Tables B.6-1, p B-101; B.6-2, p B-102; B.6-4, p B-103; and B.6-5, p B-105 of the submission; Table 3, p13 of Attachment 5. Additional data extracted from Simonneau (2006). Additional calculations were conducted during the evaluation to populate the table assuming that the n were patients not events using RevMan and with no adjustment for multiplicity.

^a One patient exhibited both symptomatic DVT and PE

^b Additional values calculated in the submission. There were differences in the 95% CI calculated during the evaluation using RevMan for the risk differences, but were unlikely to change the interpretation of the results.

- 6.10 VTE occurred up to Day 12 in 15.9% of patients receiving nadroparin and 12.6% of patients receiving enoxaparin who were undergoing elective colorectal surgery for cancer (Simonneau 2006). The upper limit of the 95% confidence interval for the relative risk (1.74) exceeded the pre-defined non-inferiority margin of 1.43.
- 6.11 The ESC noted that the head-to-head trial in colorectal cancer surgery failed to demonstrate non-inferiority between nadroparin and enoxaparin in the primary outcome (total VTE).
- 6.12 The submission noted that the primary outcome of total VTE was inconsistent with recommended composite outcome from the EMA guidance document (2013). Therefore, the submission identified the secondary composite outcome (asymptomatic proximal DVT, symptomatic non-fatal VTE, or VTE-related death) as the key efficacy outcome. The submission nominated a non-inferiority margin of 2% to 2.5% (absolute risk difference), described as 50% of the absolute risk reduction of 4% to 5% proposed as being clinically relevant by the PBAC. The derivation of the alternative non-inferiority margin was inadequately justified, as the quoted value of 4% to 5% appeared to be the non-inferiority margin for a different composite outcome in a different surgical procedure.
- 6.13 The submission claimed that non-inferiority of nadroparin and enoxaparin was 'clearly established', as the upper bound of the 95% confidence interval for the absolute risk difference (1.8%) did not exceed the non-inferiority margin of 2% to 2.5%. Disaggregated results for the nominated key composite outcome were not available.

- 6.14 The submission further claimed that nadroparin resulted in a statistically significant reduction in symptomatic VTE compared to enoxaparin during both the treatment period (up to 12 days) and the study period (up to 60 days). Given the failure to meet the primary outcome, secondary outcomes should be interpreted with caution.
- 6.15 No clinical data were presented in patients undergoing general surgery at moderate risk of VTE, for whom prophylaxis is recommended.

Table 5: Indirect comparisons of total DVT and proximal DVT after orthopaedic surgery

	Relative risk (95% CI)	Indirect estimate (95% CI) nadroparin vs enoxaparin
Total DVT at the end of treatment		
Total hip replacement (up to 14 days of treatment)		
Nadroparin vs no LMWH (1 trial; N=100)	0.13 (0.02, 0.96)	0.30 (0.04, 2.15)
Meta-analysis enoxaparin vs PBO/no LMWH (5 trials; N=736)	0.44 (0.28, 0.68)	
Meta-analysis nadroparin vs UFH (2 trials; N=622)	0.91 (0.69, 1.20)	1.44 (0.69, 3.00)
Meta-analysis enoxaparin vs UFH (5 trials; N=1,060)	0.63 (0.32, 1.24)	
Total hip replacement (21 days post-discharge)		
Nadroparin vs no LMWH (1 trial; N=296)	0.20 (0.04, 0.92)	0.50 (0.11, 2.34)
Meta-analysis enoxaparin vs PBO/no LMWH (3 trials; N=696)	0.41 (0.29, 0.56)	
Total knee replacement (up to 12 days of treatment)		
Nadroparin vs IPC/FP (1 trial; N=130)	0.44 (0.27, 0.72)	0.53 (0.27, 1.06)
Meta-analysis enoxaparin vs IPC/FP (3 trials; N=436)	0.83 (0.51, 1.35)	
Hip fracture surgery (up to 14 days measurement)		
Nadroparin vs control (1 trial; N=78)	0.91 (0.49, 1.75)	1.57 (0.58, 4.25)
Enoxaparin vs placebo (1 trial; N=146)	0.58 (0.27, 1.25)	
Proximal DVT at the end of treatment		
Total hip replacement (up to 14 days of treatment)		
Nadroparin vs no LMWH (1 trial; N=100)	0.33 (0.04, 3.10)	0.77 (0.08, 8.00)
Meta-analysis enoxaparin vs PBO/no LMWH (4 trials; N=709)	0.43 (0.21, 0.88)	
Meta-analysis nadroparin vs UFH (2 trials; N=622)	0.37 (0.16, 0.85)	0.74 (0.28, 1.97)
Meta-analysis enoxaparin vs UFH (3 trials; N=800)	0.50 (0.30, 0.82)	
Total hip replacement (21 days post-discharge)		
Nadroparin vs no LMWH (1 trial; N=296)	0.36 (0.07, 1.85)	1.08 (0.18, 6.18)
Meta-analysis enoxaparin vs PBO/no LMWH (3 trials; N=696)	0.34 (0.18, 0.63)	
Total knee replacement (up to 12 days of treatment)		
Nadroparin vs IPC/FP (1 trial; N=130)	0.47 (0.09, 2.48)	0.83 (0.02, 29.18)
Meta-analysis enoxaparin vs IPC/FP (3 trials; N=436)	0.57 (0.02, 13.27)	
Hip fracture surgery (up to 14 days measurement)		
Meta-analysis nadroparin vs PBO/no LMWH (3 trials; N=228)	0.16 (0.05, 0.51)	0.16 (0.03, 0.81)
Enoxaparin vs placebo (1 trial; N=146)	0.97 (0.33, 2.88)	

Abbreviations: CI = confidence interval; DVT = deep vein thrombosis; FP = foot pump; IPC= intermittent pneumatic compression; LMWH = low molecular weight heparin; PBO = placebo; UFH = unfractionated heparin

Source: Adapted from Tables B.6-6 to B.6-9, pp B-108 to B-111 of the submission. *Additional data extraction and calculations conducted during the evaluation.*

Note: Indirect estimate of RR <1 favours nadroparin. Bolded values indicate statistically significant differences between arms.

- 6.16 The submission stated that there were no statistically significant differences between nadroparin and enoxaparin based on the indirect comparisons in orthopaedic surgery, nor any clear trend favouring either LMWH. The numerous indirect comparisons were largely uninformative due to the wide 95% confidence intervals, the limited number of trials informing the comparisons and the lack of exchangeability

across the included trials. The event rates across the common reference arm varied across the trials for a given indirect comparison. The data for nadroparin were generally sparser than for enoxaparin; with the enoxaparin trials more likely to be blinded. No formal non-inferiority testing was conducted.

Table 6: Recurrent VTE in patients with VTE (indirect comparisons via unfractionated heparin)

	Relative risk (95% CI)	Indirect estimate (95% CI) nadroparin vs enoxaparin
Recurrent VTE during initial treatment (up to 12 days treatment; up to 30 days for measurement)		
Meta-analysis nadroparin vs UFH (4 trials; N=882)	0.53 (0.20, 1.39)	1.10 (0.33, 3.64)
Meta-analysis enoxaparin vs UFH (4 trials; N=1,093)	0.48 (0.24, 0.99)	
Recurrent VTE at end of follow-up (3 months or 6 months)		
Meta-analysis nadroparin vs UFH (5 trials; N=1,730)	0.77 (0.52, 1.14)	1.10 (0.63, 1.90)
Meta-analysis enoxaparin vs UFH (6 trials; N=2,291)	0.70 (0.48, 1.03)	

Abbreviations: CI = confidence interval; UFH = unfractionated heparin; VTE = venous thromboembolism

Source: Adapted from Table B.6-15, p B-118 of the submission.

Note: Indirect estimate of RR <1 favours nadroparin. Bolded values indicate statistically significant differences between arms. LMWH or unfractionated heparin was administered initially (between 5 and 10 days), and oral anticoagulants were administered for at least 3 months.

- 6.17 The submission claimed that the totality of the results in the treatment of VTE or DVT showed no differences in efficacy between nadroparin and enoxaparin.
- 6.18 No formal non-inferiority testing was conducted. The 95% confidence intervals of the indirect comparisons of the relative risks were wide, particularly for the comparison during the initial period when nadroparin or enoxaparin was administered. There were potential issues relating to the exchangeability of the included trials, as there were differences in the inclusion criteria, interventions and outcomes across trials. Limited data were available on the time with a therapeutic INR during the follow-up period.
- 6.19 The submission acknowledged that the data were sparser for the prevention of haemodialysis, but stated that the pivotal registration trial for nadroparin (Nurmohamed 1991) demonstrated that nadroparin was effective in the prevention of clotting during dialysis. No indirect comparisons of efficacy outcomes were presented, as there were no comparable outcomes available across the identified small, low quality trials in haemodialysis.
- 6.20 The ESC noted that no formal non-inferiority testing was conducted for prophylaxis in orthopaedic surgery and haemodialysis, and the treatment of VTE or DVT. There were no indirect comparisons of efficacy outcomes for haemodialysis. The indirect comparisons, particularly those for orthopaedic surgery, were limited by the likely lack of exchangeability of the included trials and 95% confidence intervals were generally wide.

Comparative harms

- 6.21 The head-to-head trial by Simmoneau (2006) in colorectal cancer surgery found a statistically significantly lower risk of major bleeding among patients treated with nadroparin (7.3%) versus enoxaparin (11.5%) during the treatment period of up to 12 days (RR 0.64; 95% CI 0.45, 0.91). The first dose of enoxaparin was administered

2-4 hours before surgery, inconsistent with the Product Information document which recommends that the first dose be given 12 hours before surgery.

- 6.22 No comparative data of nadroparin versus the lower dose of enoxaparin (20mg daily) among general surgical patients at moderate risk were presented in the submission.
- 6.23 The submission claimed that there was a ‘trend’ of reduced major haemorrhagic events associated with nadroparin compared to enoxaparin (indirect estimate of RR 0.46; 95% CI 0.14, 1.52). There were few major bleeding events across the trials, with the data informing the enoxaparin arm sparser than the nadroparin arm. There were differences in the dosing of unfractionated heparin, in the definition of major bleeding (when reported) and the event rates in the unfractionated heparin arm across the included trials. The upper limit of the 95% confidence interval was 1.52. Therefore, the results did not support the claim of a ‘trend’ of reduced major bleeding associated with nadroparin.
- 6.24 Limited comparative safety data were available for prophylaxis in orthopaedic surgery and haemodialysis, largely due to the low major bleeding event rates.
- 6.25 The ESC noted that while there were statistically significantly fewer patients reporting at least one major bleeding episode associated with nadroparin versus enoxaparin in the head-to-head trial in colorectal cancer surgery (Simonneau 2006), no data were presented among general surgical patients at moderate risk who would receive a lower dose of enoxaparin. There were no statistically significant differences between nadroparin and enoxaparin in major bleeding based on the indirect comparison for the treatment of venous thromboembolism (VTE) or deep vein thrombosis (DVT). The few major bleeding events reported in the trials for orthopaedic surgery and haemodialysis precluded meaningful indirect comparisons.

Clinical claim

- 6.26 The submission described nadroparin as at least non-inferior in terms of comparative effectiveness and superior in terms of comparative safety over enoxaparin. The PBAC considered that this claim was reasonable in terms of comparative effectiveness, but not in terms of comparative safety. The PBAC considered the ESC interpretation and conclusion that despite the issues raised, overall nadroparin was likely to have non-inferior effectiveness compared to enoxaparin.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Economic analysis

- 6.27 The proposed weighted therapeutic relativity was:
98.7 IU of nadroparin is equivalent to 1 mg of enoxaparin
- 6.28 The proposed therapeutic relativities (or equi-effective doses) were broadly based on recommended dosing of nadroparin and enoxaparin from the respective Product Information documents for each TGA-approved indication for nadroparin. There were also other data sources and assumptions underlying the calculations of the

equi-effective doses for each indication. The equi-effective doses by TGA-approved indications were weighted using adjusted Australian Refined Diagnosis Related Groups (AR-DRG) hospital separations (2012-13) to reflect proportional use within each indication.

- 6.29 The proposed weighted therapeutic relativity was 98.7 IU of nadroparin is equivalent to 1 mg of enoxaparin. The ESC noted that overall, the weighted average therapeutic relativity was likely to favour nadroparin. There were many issues with the derivation of the weighted therapeutic relativity. However, the key issue likely to significantly affect the weighted therapeutic relativity was the deviation of the equi-effective doses for the prevention of clotting in haemodialysis.
- 6.30 The PBAC agreed with the ESC that the equi-effective dose calculation should not include doses for haemodialysis since in Australian settings unfractionated heparin may be used instead of enoxaparin.

Table 7: Derivation of weighted therapeutic relativity nadroparin versus enoxaparin

TGA-approved indication	% weighting (by adjusted AR-DRG separations)	Therapeutic ratio (nadroparin: enoxaparin)
Prophylaxis (general surgery)	73%	109.6 IU: 1mg
Prophylaxis (orthopaedic surgery)	26%	118.6 IU: 1mg
Treatment of DVT	1%	106.4 IU: 1mg
Weighted average therapeutic relativity		111.9 IU: 1 mg

Abbreviations: AR-DRG = Australian Refined Diagnosis Related Groups; DVT = deep vein thrombosis

Source: Adapted from Table D.1.1, p D-2 of the submission and 'Nadroparin – Therapeutic Relativities (ver 6).xlsx'

- 6.31 The ESC considered that the sensitivity analyses conducted during the evaluation using alternative data sources suggested nadroparin 89.4 IU to 126.1 IU and enoxaparin 1 mg were equi-effective (versus the base case of nadroparin 67.7 IU and enoxaparin 1 mg being equi-effective).
- 6.32 The submission claimed that enoxaparin has 'an almost flat price' per mg. The submission estimated the weighted average price to pharmacist of \$0.1219 per mg enoxaparin. The claim of 'an almost flat price' could not be verified. The weighted average price to pharmacist of enoxaparin per mg was higher than the price to pharmacist per mg for all presentations except enoxaparin 20 mg. The two prophylaxis doses (20 mg and 40 mg) have a small price difference per syringe (price to pharmacist of \$4.47 versus \$4.66). The submission did not present data comparing nadroparin against the lower prophylactic dose of enoxaparin (20 mg daily) among surgical patients at moderate risk to VTE.
- 6.33 The sponsor proposed a flat-pricing structure for nadroparin. Using the proposed weighted average therapeutic relativity and the weighted price to pharmacist of enoxaparin, the submission calculated a price to pharmacist of nadroparin of \$ [REDACTED] per 1000 IU anti-Xa.
- 6.34 The ESC noted that the flat-pricing structure in the cost-minimisation analysis may favour nadroparin, as the approach appeared to have resulted in the higher strengths of nadroparin costing relatively more than the higher strengths of enoxaparin.

- 6.35 The PBAC advised negotiating with the sponsor an alternative pricing structure that achieves a flat price per unit against enoxaparin. Given the uncertainty of the assumed equi-effective doses and the low clinical need for a possibly inferior alternative, there was little basis for any strength of nadroparin having a higher price than the comparator.

For more detail on PBAC's view, see section 7 "PBAC outcome"

Drug cost/patient/course:

Table 8: Drug cost/patient/course (assuming supply via community pharmacy and DPMQ applied to the quantities rounded to the closest full pack of 10 unless otherwise specified)

Indication	Dosage	Strength supplied	Duration of course ^a	Drug cost/pt/course
Prophylaxis against DVT (general surgery)				
Nadroparin	2,580 IU daily	2,580 IU	10 days	\$ [redacted] ^b
Enoxaparin (moderate risk)	20 mg daily	20 mg	10 days	\$55.92 ^b
Enoxaparin (high risk)	40 mg daily	40 mg	10 days	\$57.99 ^b
Prophylaxis against DVT (orthopaedic surgery): standard duration				
Nadroparin (broken pack ^c)	Variable	Variable, both strengths	10 days	\$ [redacted] to \$ [redacted]
Nadroparin (full pack ^d)	Variable	Variable, both strengths	10 days	\$ [redacted] to \$ [redacted]
Enoxaparin (moderate risk)	20 mg daily	20 mg	10 days	\$55.92 ^b
Enoxaparin (high risk)	40 mg daily	40 mg	10 days	\$57.99 ^b
Prophylaxis against DVT (orthopaedic surgery): extended duration				
Nadroparin (broken pack ^c)	Variable	Variable, both strengths	30 days	\$ [redacted] to \$ [redacted]
Nadroparin (full pack ^d)	Variable	Variable, both strengths	30 days	\$ [redacted] to \$ [redacted]
Enoxaparin (high risk)	40 mg daily	40 mg	30 days	\$167.21 ^b
Treatment of DVT				
Nadroparin (90 kg; average male in NHS 2011-12 was 89.2 kg)	17,100 IU daily	19,000 IU	10 days	\$ [redacted]
	8,550 IU BD	9,500 IU	10 days	\$ [redacted]
Nadroparin (70 kg; average female in NHS 2011-12 was 73.2 kg)	13,300 IU daily	15,200 IU	10 days	\$ [redacted]
	6,550 IU BD	7,600 IU	10 days	\$ [redacted]
Enoxaparin (90 kg; average male in NHS 2011-12 was 89.2 kg)	140 mg daily	60 mg + 80 mg	10 days	\$171.06
	90 mg BD	100 mg	10 days	\$218.84
Enoxaparin (70 kg; average female in NHS 2011-12 was 73.2 kg)	110 mg daily	60 mg	10 days	\$160.04
	70 mg BD	80 mg	10 days	\$182.08
Haemodialysis (rounded to the closest syringe)				
Nadroparin (as per Section D)	5,007 IU per session	5,700 IU	1 session	\$ [redacted]
Enoxaparin (as per Section D)	74 mg per session	80 mg	1 session	\$8.77
Enoxaparin (reducing mg/kg dosing as per Saltissi et al 1999)	54 mg per session	60 mg	1 session	\$7.66

Abbreviations: BD = twice daily; DVT = deep vein thrombosis; NHS = National Health Survey; pt = patient

Source: compiled during the evaluation

^a Based on the duration of treatment assumptions presented in Section D of the submission. Assumed that supply was entirely via the PBS/RPBS (likely overestimate given the likely at least initial use in the hospital setting).

^b DPMQ calculated by reducing pharmacy mark-up proportionally.

^c Wastage included in calculations: 54% for supply of 4 syringes and 70% for supplier of 6 syringes.

^d Rounded to the 10 syringes (full pack)

- 6.36 Nadroparin appears likely to cost more than enoxaparin for most scenarios, with the exception of prophylaxis in general surgery, and prophylaxis in orthopaedic surgery among patients weighing between 40 kg and 60 kg (unless full packs or the maximum quantity are dispensed for standard duration of therapy). This may relate to the proposed flat-pricing structure (resulting in the higher strengths of nadroparin costing relatively more than the higher strengths of enoxaparin), the estimated weighted therapeutic relativity (mainly driven by the haemodialysis equi-effective dose), as well as wastage/additional dispensing fee for prophylaxis in orthopaedic surgery.
- 6.37 The cost per treatment course may be higher, particularly for prophylaxis against DVT associated with general or orthopaedic surgery should the maximum quantities be supplied.

For more detail on PBAC’s view, see section 7 “PBAC outcome”

Estimated PBS usage & financial implications

- 6.38 This submission was not considered by DUSC. The submission used a market share approach. Substitution was assumed at the syringe level.

Table 9: Estimated use and financial implications

	Year 1 2015 ^a	Year 2 2016	Year 3 2017	Year 4 2018	Year 5 2019	Year 6 2020
Uptake rate	%	%	%	%	%	%
Nadroparin scripts						
Estimated net cost to PBS/RPBS						
Cost of nadroparin (less co-pay)	\$	\$	\$	\$	\$	\$
Substituted therapies	-\$	-\$	-\$	-\$	-\$	-\$
Estimated total net cost						
Net cost to PBS/RPBS	\$	\$	\$	\$	\$	\$
Reduced script processing	-\$	-\$	-\$	-\$	-\$	-\$
Net cost to government budgets	\$	\$	\$	\$	\$	\$

Source: Adapted from pp E-17 to E-52 and 'Nadroparin – Section E Base Case (Ver 18).xlsx'

^a Full year estimate

The redacted table above shows that the estimated use and financial implications of nadroparin calcium is 100,000 – 200,000 scripts and net cost to government budget of less than \$10 million in Year 5.

- 6.39 The estimated use of nadroparin was uncertain, mainly due to the inadequately justified ‘switching matrix’. Other areas of uncertainty included the uptake rates, the assumption of supply of maximum quantity for each script, the assumption of no wastage and the market projections into the future.
- 6.40 The claimed cost-offset from reduced prescription processing may not be realised in practice. The additional nadroparin dispensing for the prophylaxis against DVT in

orthopaedic surgery may not have been adequately incorporated in the estimates. The assumption of a cost-saving of \$■ per service may be an overestimate.

- 6.41 The submission estimated incremental cost to the PBS/RPBS of the listing of nadroparin for the differing maximum quantities and the actual strengths of substituted therapies (as these are dependent on the clinical setting and patient characteristics). Given the likely overestimates and underestimates across the different nadroparin strengths, it was unknown whether the estimated incremental costs were, overall, over- or under-estimates. However, given that the cost (DMPQ) per patient per treatment course was higher for nadroparin than enoxaparin in most scenarios (see Table 8), there are concerns that the listing of nadroparin may result in incremental costs to the government.

Quality Use of Medicines

- 6.42 There is potential for wastage, given the presentation and requested maximum quantities of nadroparin.
- 6.43 There is the potential for medication errors given the complexity of nadroparin dosing.

Financial Management – Risk Sharing Arrangements

- 6.44 The sponsor did not state a willingness to undertake a risk sharing arrangement.

7 PBAC Outcome

- 7.1 The PBAC recommended the listing of nadroparin (as Fraxiaprine and Fraxiparine Forte) as an Unrestricted Benefit and as a Restricted Benefit listing (as Fraxiaprine) for haemodialysis on a cost-minimisation basis against enoxaparin.
- 7.2 The equi-effective doses are nadroparin calcium 111.9 IU is equal to enoxaparin sodium 1 mg. The PBAC advised that this equi-effective dose calculation appropriately excludes doses for haemodialysis, noting that in Australian clinical practice unfractionated heparin may be used in this setting instead of enoxaparin.
- 7.3 The PBAC accepted that enoxaparin was the appropriate comparator.
- 7.4 The PBAC noted the following issues with the data supporting the claim of non-inferior efficacy between nadroparin and enoxaparin:
- the head-to-head trial in colorectal cancer surgery failed to demonstrate non-inferiority between nadroparin and enoxaparin in the primary outcome (total VTE).
 - no formal non-inferiority testing was conducted for prophylaxis in orthopaedic surgery and haemodialysis, and the treatment of VTE or DVT.
 - there were no indirect comparisons of efficacy outcomes for haemodialysis.
 - the indirect comparisons, particularly those for orthopaedic surgery, were limited by the likely lack of exchangeability of the included trials.
 - the 95% confidence intervals were generally wide.

- 7.5 The PBAC recalled that nadroparin had previously been listed on the PBS under a different sponsor, having been recommended for prophylaxis against thrombotic events following major hip surgery and for the treatment of deep vein thrombosis (DVT) at the September 1996 meeting. This previous recommendation had been on a cost-minimisation basis with enoxaparin. The PBAC considered that, notwithstanding the issues with the clinical data presented in this submission, there was no reason to believe that the effectiveness of nadroparin compared with enoxaparin had changed since that initial recommendation. The PBAC therefore considered that it was reasonable to conclude that nadroparin was non-inferior to enoxaparin in terms of comparative effectiveness.
- 7.6 The PBAC noted ESC advice that the claim of superior safety was inadequately supported for the following reasons:
- while there were statistically significantly fewer patients reporting at least one major bleeding episode associated with nadroparin versus enoxaparin in the head-to-head trial in colorectal cancer surgery (Simonneau 2006), no data were presented among general surgical patients at moderate risk who would receive a lower dose of enoxaparin.
 - there were no statistically significant differences between nadroparin and enoxaparin in major bleeding based on the indirect comparison for the treatment of venous thromboembolism (VTE) or deep vein thrombosis (DVT).
 - the few major bleeding events reported in the trials for orthopaedic surgery and haemodialysis precluded meaningful indirect comparisons.
- 7.7 The PBAC considered that although the claim of superior comparative safety was not adequately supported, it was reasonable to conclude that nadroparin has non-inferior comparative safety to enoxaparin. The PBAC recalled from its previous recommendation that nadroparin had been demonstrated to be therapeutically equivalent in term of safety to other low molecular weight heparins listed on the PBS, with particular reference to enoxaparin.
- 7.8 The PBAC noted that nadroparin was likely to cost more than enoxaparin for most scenarios, with the exception of prophylaxis in general surgery, and prophylaxis in orthopaedic surgery among patients weighing between 40 kg and 60 kg (unless full packs or the maximum quantity are dispensed for standard duration of therapy).
- 7.9 The PBAC noted that the cost per treatment course may be higher than for enoxaparin, particularly for where maximum quantities are supplied for use in prophylaxis against DVT associated with general or orthopaedic surgery.
- 7.10 The PBAC considered that there is potential for more wastage with nadroparin, given the presentation and requested maximum quantities of nadroparin and that there is a potential for medication errors given nadroparin's complex dosing regimens. In addition the submission's assumption that the maximum quantity would be supplied for each script was not reasonable. The PBAC also noted the effect of this assumption on the estimates, as substitution was applied at the syringe level. The PBAC noted the sponsor's willingness to provide a 2-syringe pack to address this potential wastage.

- 7.11 The PBAC noted that overall, the weighted average therapeutic relativity presented in the submission was likely to favour nadroparin, due to the proposed flat-pricing structure. This structure resulted in the higher strengths of nadroparin costing relatively more than the higher strengths of enoxaparin. The PBAC considered that a pricing structure that achieves flat price per unit would be appropriate.
- 7.12 Advice to the Minister under section 101 3BA of the National Health Act
In accordance with subsection 101(3BA) of the *National Health Act 1953*, the PBAC advised that it is of the opinion that nadroparin calcium should be treated as interchangeable on an individual patient basis with enoxaparin and dalteparin.
- 7.13 Advice to the Minister under section 101 4AA of the National Health Act
In accordance with subsection 101 (4AA) of the *National Health Act 1953*, the PBAC advised the Minister that the three drugs, nadroparin calcium, enoxaparin sodium and dalteparin sodium should together comprise a therapeutic group
- 7.14 The PBAC advised that nadroparin is suitable for prescribing by nurse practitioners similar to the comparator enoxaparin.
- 7.15 The PBAC recommended that the Safety Net 20 Day Rule should not apply.
- 7.16 The submission is not eligible for an Independent Review, because the PBAC has made a positive recommendation.

Outcome:

Recommended

8 Recommended listing

- 8.1 Add new item:

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Name, Restriction, Manner of administration and form	Max. Qty	№.of Rpts	Proprietary Name and Manufacturer
NADROPARIN CALCIUM			
nadroparin calcium 1900 anti-Xa international units/0.2 mL injection, 2 x 0.2 mL pre-filled syringe	2	-	Fraxiparine Aspen
nadroparin calcium 2850 anti-Xa international units/0.3 mL injection, 2 x 0.3 mL pre-filled syringe	2	-	
nadroparin calcium 3800 anti-Xa international units/0.4 mL injection, 2 x 0.4 mL pre-filled syringe	2	-	
nadroparin calcium 5700 anti-Xa international units/0.6 mL injection, 2 x 0.6 mL pre-filled syringe	2	-	
nadroparin calcium 7600 anti-Xa international units/0.8 mL injection, 2 x 0.8 mL pre-filled syringe	1	1	
nadroparin calcium 9500 anti-Xa international units/1 mL injection, 2 x 1 mL pre-filled syringe	1	1	
nadroparin calcium 11400 anti-Xa international units/0.6 mL injection, 2 x 0.6 mL pre-filled syringe	1	1	Fraxiparine Forte
nadroparin calcium 15200 anti-Xa international units/0.8 mL injection, 2 x 0.8 mL pre-filled syringe	1	1	
nadroparin calcium 19000 anti-Xa international units/1 mL injection, 2 x 1 mL pre-filled syringe	1	1	

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	-
Condition:	-
PBS Indication:	-
Treatment phase:	-
Restriction Level / Method:	Unrestricted

Name, Restriction, Manner of administration and form	Max. Qty	No. of Rpts	Proprietary Manufacturer	Name and
NADROPARIN CALCIUM			Fraxiparine	Aspen
nadroparin calcium 1900 anti-Xa international units/0.2 mL injection, 2 x 0.2 mL pre-filled syringe	2	3		
nadroparin calcium 2850 anti-Xa international units/0.3 mL injection, 2 x 0.3 mL pre-filled syringe	2	3		
nadroparin calcium 3800 anti-Xa international units/0.4 mL injection, 2 x 0.4 mL pre-filled syringe	2	3		
nadroparin calcium 5700 anti-Xa international units/0.6 mL injection, 2 x 0.6 mL pre-filled syringe	2	3		
nadroparin calcium 7600 anti-Xa international units/0.8 mL injection, 2 x 0.8 mL pre-filled syringe	2	3		
nadroparin calcium 9500 anti-Xa international units/1 mL injection, 2 x 1 mL pre-filled syringe	2	3		

Category / Program	GENERAL – General Schedule (Code GE)
Prescriber type:	<input type="checkbox"/> Dental <input checked="" type="checkbox"/> Medical Practitioners <input checked="" type="checkbox"/> Nurse practitioners <input type="checkbox"/> Optometrists <input type="checkbox"/> Midwives
Episodicity:	-
Severity:	-
Condition:	Haemodialysis
PBS Indication:	Haemodialysis
Treatment phase:	-
Restriction Level / Method:	<input checked="" type="checkbox"/> Restricted benefit <input type="checkbox"/> Authority Required - In Writing <input type="checkbox"/> Authority Required - Telephone <input type="checkbox"/> Authority Required – Emergency <input type="checkbox"/> Authority Required - Electronic <input type="checkbox"/> Streamlined

9 Context for Decision

The PBAC helps decide whether and, if so, how medicines should be subsidised in Australia. It considers submissions in this context. A PBAC decision not to recommend listing or not to recommend changing a listing does not represent a final PBAC view about the merits of the medicine. A company can resubmit to the PBAC or seek independent review of the PBAC decision.

10 Sponsor's Comment

Section 6.16: Statement in this section not correct, based on our understanding, confidence limit of 95% is globally accepted standard for such studies.

Section 6.42: To best of our knowledge, there is no published data on wastage of the comparator product and statement in this section is identifying this brand as the only candidate for wastage; which may be incorrect.

Section 7.8: To best of our knowledge there is no direct comparative data between use and cost of nadroparin and enoxaparin in Australian hospitals, so the wastage assumption in this section is not based on any comparative wastage data.