PUBLIC SUMMARY DOCUMENT
Product: Dalteparin sodium (low molecular weight heparin sodium-porcine mucous), injection, 7,500 units (anti-Xa) in 0.75 mL, 10,000 units (anti-Xa) in 1 mL, 12,500 units (anti-Xa) in 0.5 mL, 15,000 units (anti-Xa) in 0.6 mL and 18,000 units (anti-Xa) in 0.72 mL, single dose pre-filled syringe, Fragmin®
Sponsor: Pfizer Pty Ltd
Date of PBAC Consideration: November 2010

1. Purpose of Application
The submission sought a Restricted Benefit listing for the treatment of symptomatic venous thromboembolism (VTE) in cancer patients with active solid tumour; and secondary prevention of VTE in cancer patients with solid tumours and previous VTE.

2. Background
Dalteparin had not previously been considered by the PBAC for this indication. Dalteparin was first listed in the Schedule of Pharmaceutical Benefits on 1 December 1994.

The 2,500 units, 5,000 units, 7,500 units and 10,000 units strengths are currently listed as an unrestricted benefit and as a Restricted Benefit (with higher maximum quantities and repeats) for haemodialysis. Dalteparin's strengths of 12,500 units, 15,000 units and 18,000 units are not currently PBS listed.

3. Registration Status
Dalteparin's TGA registration was expanded on 1 April 2010 to include the extended treatment of symptomatic VTE (proximal deep vein thrombosis and/or pulmonary embolism) to reduce the recurrence of VTE in patients with solid tumour cancers.

Dalteparin is also TGA registered for the following indications:
- Prophylaxis against thrombotic complications during haemodialysis and treatment of acute deep vein thrombosis (DVT).
- 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 thrombo-embolic complications in the peri- or postoperative period of surgery.

4. Listing Requested and PBAC's View
Restricted Benefit
1. Treatment of symptomatic VTE in patients with active solid cancer tumours.
2. Secondary prevention of VTE in patients with active solid tumours and previous VTE.

For PBAC's view, see Recommendations and Reasons.

5. Clinical Place for the Proposed Therapy
There are many causes of thrombosis in patients with cancer. Cancer can often lead to thrombosis and aggressive anti-tumour therapy can also increase the thrombosis risk. Central venous catheters, commonly inserted for chemotherapy and hyperalimentation, are also associated with a risk of thrombosis and embolism.

The submission claimed that dalteparin sodium would be an alternative option for the treatment of VTEs in cancer patients with solid tumours.

6. Comparator

The submission nominated enoxaparin as the comparator.

The submission stated that the choice of comparator was based on a survey of oncologists which indicated that enoxaparin was the most commonly used anticoagulant in patients for treatment and secondary prevention of VTE in cancer patients. Further, the American College of Chest Physicians (ACCP) guidelines recommend extended treatment of VTE with enoxaparin and other low molecular weight heparins (LMWHs) in cancer patients.

For PBAC's view, see Recommendations and Reasons.

7. Clinical Trials

The submission presented three randomised controlled trials (RCTs): CLOT 2003, Deitcher 2006 and Meyer 2002.

CLOT compared dalteparin 200 IU/kg subcutaneously (sc) once daily for 1 month plus 150 IU/kg sc once daily for the following 5 months, with oral anticoagulant (OAC) for 6 months plus dalteparin 200 IU/kg sc once daily for a minimum of 5 days in patients with acute VTE and with active cancers. Deitcher 2006 compared treatment outcomes with enoxaparin 1.0 mg/kg sc twice a day (bid) for 5 days followed by enoxaparin 1.5 mg/kg sc once daily for 175 days with enoxaparin 1.0 mg/kg sc bid for 5 days followed by enoxaparin 1.0 mg/kg sc once daily for 175 days, and with enoxaparin 1.0 mg/kg sc every 12 hours for at least 5 days until a stable international normalised ratio of 2 to 3 was achieved on oral warfarin begun on day 2 and continued for 6 months, in patients with acute VTE and with active cancers. Meyer 2002 compared enoxaparin 1.5 mg/kg sc once daily for 3 months, with warfarin for 3 months plus enoxaparin for a minimum of 4 days in patients with VTE and with solid cancers.

Patients with haematological malignancies were included in both the Deitcher trial (all cancers except leukaemia) and in the CLOT study (all cancers). A post hoc subgroup analysis of patients with solid tumours in the CLOT trial provided data on the treatment effects of dalteparin in the proposed PBS population.

The studies published at the time of the submission are as follows:

Trial ID / First author	Protocol title / Publication title	Publication citation
Dalteparin versus warfarin		
CLOT (2003)		
Kovacs et al	Anti-Xa effect of a low molecular weight heparin (dalteparin) does not accumulate in extended therapy for venous thromboembolism in cancer patients	Thromb Haemost 2005; 93:1185-8
Lee et al	Impact of dalteparin low-molecular-weight heparin (LMWH) on survival: Results of a randomized trial in cancer patients with venous thromboembolism (VTE)	Proc Am Soc Clin Onc 2003; 22:211, Abstract 846

Lee et al	Long-term treatment with dalteparin low-molecular weight heparin (LMWH) may improve survival in patients with nonmetastatic malignancy and venous thromboembolism (VTE)	Thromb Haem 2003; 1 (suppl. 1), Abstract OC004, XIX International Society on Thrombosis and Haemostasis (ISTH) Congress
Lee et al	Long-term treatment with dalteparin low-molecular-weight heparin (LMWH) is more effective than oral anticoagulant (OA) therapy in cancer patients with venous thromboembolism (VTE)	Thromb Haem 2003: 1 (supp. 1), Abstract OC398, XIX ISTH Congress
Lee et al	Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer	N Engl J Med 2003; 349:146-53
Lee et al	Randomised comparison of low molecular weight heparin and coumarin derivatives on the survival of patients with cancer and venous thromboembolism	J Clin Oncol 2005; 23:2123-9
Levine et al	A randomized trial of long term dalteparin low molecular weight heparin (LMWH) versus oral anticoagulant (OA) therapy in cancer patients with venous thromboembolism (VTE)	Blood 2002; 100:82a, Abstract 298, 44th Annual Meeting of the American Society of Hematology
Enoxaparin versus warfarin		
Deitcher et al	Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period	Clin Appl Thromb Hemost, 2006; 12:389-396
Meyer et al	Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study	Arch Intern Med 2002; 162:1729-35

No direct RCTs comparing dalteparin with enoxaparin were identified.

8. Results of Trials

The results of the primary indirect comparison of dalteparin versus enoxaparin for recurrent VTE and mortality are presented in the following table.

Results of the primary indirect comparison of dalteparin vs enoxaparin for recurrent VTE and mortality

	CLOT			Deitcher 2006			Indirect estimate of effect[c] (95% CI)
	Treatment effect[a] (95% CI)	Dalteparin % (n/N)	OAC % (n/N)	Warfarin % (n/N)	Enoxaparin 1.5mg/kg % (n/N)	Treatment effect[b] (95% CI)	
CLOT (all cancers) vs Deitcher 2006 (all cancers except leukaemia)							
Recurrent VTE[d] during 6 months							
RR	0.51 (0.33, 0.79)	8.0% (27/338)	15.7% (53/338)	10.0% (3/30)	6.3% (2/32)	0.63 (0.11, 3.48)	0.81 (0.13, 4.89)
RD	-0.08 (-0.13, -0.03)					-0.04 (-0.17, 0.10)	-0.04 (-0.18, 0.10)

All-cause mortality during 6 months[e]							
RR	0.96 (0.79, 1.15)	38.8% (131/338)	40.5% (137/338)	32.4% (11/34)	41.7% (15/36)	1.29 (0.69, 2.40)	0.74 (0.39, 1.43)
RD	-0.02 (-0.09, 0.06)					0.09 (-0.13, 0.32)	-0.11 (-0.34, 0.12)
CLOT (solid cancers) vs Deitcher 2006 (all cancers except leukaemia)							
Recurrent VTE[d] during 6 months							
RR	0.45 (0.28, 0.71)	7.7% (23/298)	17.2% (53/308)	10.0% (3/30)	6.3% (2/32)	0.63 (0.11, 3.48)	0.71 (0.12, 4.36)
RD	-0.09 (-0.15, -0.04)					-0.04 (-0.17, 0.10)	-0.05 (-0.19, 0.09)
All-cause mortality during 6 months[e]							
RR	0.99 (0.82, 1.19)	41.6% (124/298)	42.2% (130/308)	32.4% (11/34)	41.7% (15/36)	1.29 (0.69, 2.40)	0.77 (0.40, 1.48)
RD	-0.01 (-0.08, 0.07)					0.09 (-0.13, 0.32)	-0.10 (-0.33, 0.13)

OAC = oral anticoagulant; CI = confidence interval; RR = relative risk; VTE = venous thromboembolism; RD = risk difference

[a] Dalteparin over OAC

[b] Enoxaparin over warfarin

[c] Dalteparin over enoxaparin via the 'common reference'

[d] Recurrent VTE defined differently between the CLOT trial and the Deitcher 2006 study

[e] The mortality rates reported in the Deitcher 2006 trial were during the 7-month observation period

The results of the primary indirect comparison of dalteparin and enoxaparin via the common reference groups between CLOT (all cancers) and Deitcher 2006 (all cancers except leukaemia) were similar to that between CLOT (solid cancers subgroup) and Deitcher 2006 with respect to relative risk and risk difference for recurrent VTE/all-cause mortality during 6 months.

Numerically the point estimate of treatment effect favoured dalteparin over enoxaparin in terms of recurrent VTE and all-cause mortality. However, there were limitations in interpreting the results, as differences in the definitions of recurrence of VTE were noted between the two trials. In addition, the mortality rates reported in the CLOT trial and those in the Deitcher 2006 study were for different follow-up periods (6 months in the CLOT trial and 7 months in the Deitcher 2006 trial). Furthermore, the CLOT study only considered proximal VTEs while Deitcher 2006 included both proximal and distal VTEs.

The wide confidence intervals (CIs) for the indirect estimate of relative risks (RRs) and risk differences (RDs) indicated that the trials in the indirect comparison, especially the Deitcher 2006 study, were not sufficiently powered to reliably assess relative effectiveness of dalteparin versus enoxaparin in terms of recurrent VTE and mortality. The difference in the rates of VTE recurrence between the warfarin arm of the Deitcher 2006 study and the OAC arm of the CLOT study also suggested relevant disparity between the study outcome definitions or populations.

The Pre-Sub-Committee response acknowledged the limitation of the analysis but attributed this solely to the inadequacies of the Deitcher 2006 study. The view of the PBAC was that the relevant head-to-head trial had not been performed, although it was noted that, pragmatically, one would expect the efficacy of dalteparin and enoxaparin to be the same.

The primary safety outcome in the indirect comparison was major bleeding. An indirect comparison of dalteparin versus enoxaparin for major bleeding and serious adverse events

(AE) was performed during the evaluation to provide additional information on the relative safety of the two drugs.

Evidence from the CLOT trial and the Deitcher 2006 study indicated a trend for higher rates of major bleeding in patients treated with low molecular weight heparins (LMWHs) over a 6-month period than in OAC/warfarin patients. However, both of the trials were statistically underpowered to show any true difference in major bleeding between the two drugs.

The submission provided additional data, including safety data from published studies investigating the use of dalteparin in patients with cancer, the dalteparin risk management plan (RMP), dalteparin periodic safety update report (PSUR) and Core Data Sheet (CDS), and medicine summary reports from the TGA, for extended assessment of the safety of dalteparin beyond the included trials. This evidence did not provide any additional significant information to alter the interpretation of the established safety profile of dalteparin.

9. Clinical Claim

The submission claimed that dalteparin was non-inferior to enoxaparin in terms of both effectiveness and safety. This was accepted by the PBAC.

10. Economic Analysis

The submission presented a cost minimisation analysis. The equi-effective doses were considered to be dalteparin 200 IU/kg daily for 1 month, then 150 IU/kg (max 18,000 IU) daily for 5 months, equivalent to enoxaparin 1.5 mg/kg daily for entire treatment course of 6 months. This was consistent with the therapeutic relativity sheets for enoxaparin and dalteparin, which describe a dosage relativity between enoxaparin and dalteparin of between 1 mg: 100 units and 1 mg: 125 units.

11. Estimated PBS Usage and Financial Implications

The likely number of patients per year was estimated in the submission to be less than 10,000 in Year 5. The financial cost per year to the PBS (revised during the evaluation) was estimated to be less than $10 million in Year 5. The submission's estimate originally incorporated calculation errors with respect to dalteparin pack usage and unreasonable assumptions with respect to enoxaparin usage.

12. Recommendation and Reasons

The PBAC recommended the listing of dalteparin on the PBS as a Restricted Benefit for the management of symptomatic venous thromboembolism in a patient with a solid tumour(s) on a cost-minimisation basis compared with enoxaparin. The equi-effective doses were considered to be dalteparin 200 IU/kg daily for 1 month, then 150 IU/kg (max 18,000 IU) daily for 5 months (i.e. the dose used in the CLOT study), equivalent to enoxaparin 1.5 mg/kg daily for entire treatment course of 6 months (based on the daily dose used in the Meyer study).

The PBAC considered that the requested restriction might be ambiguous and not entirely aligned with the TGA registered indication. The requested PBS listing could be interpreted as being for the acute treatment of a VTE followed by continuing treatment of that patient to prevent recurrence; or it could be interpreted as to be used as prophylaxis in cancer patients with a past history of VTE. However, the PBAC considered that changing the wording of the

restriction to "management of VTE" might address this ambiguity by indicating that dalteparin may be used for both treatment and prophylaxis of the same episode of VTE.

The PBAC agreed that the appropriate comparator was enoxaparin. The PBAC noted that both the survey of oncologists and the American College of Chest Physicians Guidelines recommend extended treatment of VTE with enoxaparin and other low molecular weight heparins in cancer patients. The PBAC noted that enoxaparin was not specifically TGA registered for this indication. However, prescribers may prescribe enoxaparin for this indication as the current PBS listing is as an unrestricted benefit.

The PBAC noted that the evidentiary basis of the submission was an indirect comparison of the dalteparin arm of the CLOT trial versus the 1.5 mg/kg enoxaparin arm of the Deitcher 2006 study. Two sensitivity analyses were also performed (a meta-analysis of the 1.5 mg/kg enoxaparin arms from the Deitcher 2006 study and from the Meyer 2002 study compared to the dalteparin arm in the CLOT trial; the other compared the CLOT trial with combined results of the two enoxaparin arms (1.5 mg/kg arm and 1.0 mg/kg arm) in the Deitcher 2006 study). The PBAC also noted that the treatment in the 'common reference groups' was not the same: in the CLOT trial, patients in the oral anti-coagulant (OAC) arm were treated with dalteparin for a minimum of 5 days; while, the warfarin patients in the Deitcher 2006 study and in the Meyer 2002 study received a short course of enoxaparin treatment (≥ 4 days). There was also insufficient information available to fully assess if the INR optimisation protocols were similar across the common reference groups. However, although there was some uncertainty regarding the indirect comparison, the PBAC considered that this was a valid comparison.

The PBAC accepted the submission's claim that dalteparin was non-inferior to enoxaparin in terms of both effectiveness and safety and accepted the therapeutic equivalence of dalteparin versus enoxaparin based on the clinical trials presented in the submission.

Recommendation:
DALTEPARIN SODIUM (low molecular weight heparin sodium-porcine mucous), injection, 7,500 units (anti-Xa) in 0.75 mL, 10,000 units (anti-Xa) in 1 mL, 12,500 units (anti-Xa) in 0.5 mL, 15,000 units (anti-Xa) in 0.6 mL and 18,000 units (anti-Xa) in 0.72 mL, single dose pre-filled syringe

Extend the current restriction to include:

Restriction:	<u>Restricted Benefit</u> Management of symptomatic venous thromboembolism in a patient with a solid tumour(s). <u>NOTE:</u> No applications for increase maximum quantities will be authorised.
Maximum quantity:	30
Repeats:	5

13. 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.

14. Sponsor's Comment

The sponsor has no further comment.