



Australian Government

Department of Health

Therapeutic Goods Administration

Australian Public Assessment Report for Enoxaparin sodium

Proprietary Product Name: Enoxapo

Sponsor: Apotex Pty Ltd

July 2020

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.

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Common abbreviations

Abbreviation	Meaning
AAT	Administrative Appeals Tribunal
ACM	Advisory Committee on Medicines
ACPM	Advisory Committee on Prescription Medicines
AE	Adverse event
Anti-Xa	Anti-factor Xa
Anti-IIa	Anti-factor IIa
ANOVA	Analysis of variance
APTT	Activated partial thromboplastin time
ARTG	Australian Register of Therapeutic Goods
AUAC _{0-t}	Area under the activity time curve from time zero to the last determined activity-time point.
AUC _{inf}	Area under the curve from the time zero point to infinity
AUAC _{0-∞}	Area under the activity time curve from the time zero point to infinity
CER	Clinical evaluation report
CI	Confidence Interval
A _{max}	Maximum observed plasma activity
CRF	Case Report Form
CV	Coefficient of variation
ECG	Electrocardiogram
EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EU	European Union
FDA	Food and Drug Administration (United States)
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice

Abbreviation	Meaning
GMR	Geometric mean ratio
hepTest	Clot-based assay measuring heparin in human plasma
HIT	Heparin induced thrombocytopenia
HITT	Heparin induced thrombocytopenia and thrombosis
HP4	Heparin platelet factor 4
hr(s)	Hour(s)
Kel	Apparent first order terminal elimination rate constant
kg	Kilogram(s)
IV/	Intravenous
LLOQ	Lower limit of quantitation
LMWH	Low molecular weight heparin
Ln	Natural logarithm
LSM	Least square mean
m	Metre(s)
min	Minute(s)
mL	Millilitre(s)
µL	Microlitre(s)
N/A	Not applicable
PCI	Percutaneous coronary intervention
PD	Pharmacodynamic(s)
PE	Pulmonary embolus
PF4	Platelet factor 4
Ph. Eur.	European Pharmacopoeia
PK	Pharmacokinetic(s)
SAS	Statistical Analysis System
SC	Subcutaneous

Abbreviation	Meaning
SD	Standard deviation
STEMI	ST-segment elevation myocardial infarction
T _{1/2}	Apparent first-order terminal elimination half-life
TGA	Therapeutic Goods Administration
TPD	Therapeutic Products Directory
TFPI	Tissue factor pathway inhibitor
T _{max}	Time of maximum observed plasma activity
US(A)	United States (of America)
USP	United States Pharmacopeia
VTE	Venous thrombo-embolism

I. Introduction to product submission

Submission details

<i>Type of submission:</i>	Biosimilar
<i>Initial TGA decision:</i>	Rejected
<i>Final TGA decision:</i>	Rejected
<i>Date of initial TGA decision:</i>	13 February 2015
<i>Date of TGA section 60 review decision:</i>	9 July 2015
<i>TGA decision following AAT outcome:</i>	Approved
<i>Date of decision letter:</i>	4 February 2020
<i>Date of entry onto ARTG:</i>	10 February 2020
<i>ARTG numbers:</i>	210340, 210337, 210333, 210324, 210320, 210318 and 210312
<i>▼ Black Triangle Scheme</i>	No
<i>Active ingredient:</i>	Enoxaparin sodium
<i>Product name:</i>	Enoxapo
<i>Sponsor's name and address:</i>	Apotex Pty Ltd PO Box 280, North Ryde BC NSW, 1670
<i>Dose form:</i>	Solution for injection
<i>Strengths:</i>	100 mg/mL (20 mg in 0.2 mL, 40 mg in 0.4 mL, 60 mg in 0.6 mL, 80 mg in 0.8 mL and 100 mg in 1.0 mL presentations) and solution for injection 150 mg/mL (120 mg in 0.8 mL, and 150 mg in 1.0 mL presentations); all presentations being pre-filled syringes.
<i>Container:</i>	Pre-filled syringe
<i>Pack size:</i>	10
<i>Approved therapeutic use:</i>	<i>Prevention of thromboembolic disorders of venous origin in patients undergoing orthopaedic and general surgery.</i> <ul style="list-style-type: none"> <i>Prophylaxis of venous thromboembolism in medical patients bedridden due to acute illness.</i>

- *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).'*

Routes of administration: Subcutaneous; extracorporeal circulation, haemodialysis

Dosage:

Prophylaxis of venous thrombosis

Prophylaxis against thromboembolism should be tailored according to the patient's risk. Risk factors include age over 40 years, history of deep vein thrombosis or pulmonary embolism, surgery and other trauma, prolonged immobilisation, cardiac disease, obesity, malignancy, varicose veins, hypercoagulable states, pregnancy and the puerperium, oral contraceptives, severe infection, inflammatory bowel disease.

a) High risk patients

In patients with high risk of thromboembolism, an Enoxaparin dosage of 40 mg (0.4 mL; anti-Xa: 4,000 IU) should be administered subcutaneously once daily. In high risk patients undergoing surgery, the initial dose should be given approximately 12 hours preoperatively. The timing of the first dose may need to be modified if spinal/epidural anaesthesia is to be performed (see Section 4.4 – Special Warnings and Precautions for Use: Spinal/Epidural Anaesthesia).

b) Moderate risk patients

In patients with a moderate risk of thromboembolism, the recommended enoxaparin dosage is 20 mg (0.2 mL; anti-Xa: 2,000 IU) subcutaneously once daily. In moderate risk patients undergoing surgery, the initial dose should be given approximately 2 hours preoperatively. The timing of the first dose may need to be modified if spinal/epidural anaesthesia is to be performed (see Section 4.4 – Special Warnings and Precautions for Use: Spinal/Epidural Anaesthesia).

Duration of therapy

High to moderate risk: Prophylaxis should be continued for 7 to 10 days or until the risk of thromboembolism has diminished.

Prolonged thromboprophylaxis

Therapy with 40 mg once daily for 30 post-operative days has been proven to be beneficial in total hip replacement surgery.

Under normal conditions of use, enoxaparin does not modify global clotting tests and therefore there is no need to perform these tests in order to monitor therapy.

Prophylaxis of venous thromboembolism in medical patients

The recommended dose should be 40 mg once daily by subcutaneous injection for a minimum of 6 days, continuing for a maximum of 14 days or less if the patient returns to full ambulation earlier than 14 days.

Treatment of deep venous thrombosis

The initial clinical trials which established the efficacy of Enoxaparin in the treatment of deep venous thrombosis were conducted on patients who were initially treated with heparin and then changed to Enoxaparin when a definitive diagnosis was established. However, the use of heparin prior to Enoxaparin is not currently recommended. The average duration of therapy in the clinical trials was 10 days. No data are available on the safety of long term treatment. Data on use in patients over 65 years of age in these trials were limited.

The recommended dosage for treatment of established deep vein thrombosis with enoxaparin is 1.5 mg/kg body weight once daily (150 IU anti-Xa activity/kg bodyweight) or 1 mg/kg body weight (100 IU anti-Xa activity/kg bodyweight) twice daily subcutaneously. In high risk patients, for example in obesity or patients with baseline iliac vein thrombosis or cancer, a dose of 1 mg/kg body weight administered twice daily may be more beneficial.

Warfarin sodium therapy should be initiated when appropriate (usually within 72 hours of commencing enoxaparin initiation). Enoxaparin should be continued for a minimum of 5 days and until a therapeutic oral anticoagulant effect has been achieved (International Normalization Ratio 2.0 to 3.0).

Treatment of unstable angina and non-Q-wave-myocardial infarction

The recommended dose of Enoxaparin is 1 mg/kg (100 IU anti-Xa activity/kg) every 12 hours by subcutaneous injection, administered concurrently with oral aspirin.

Treatment with Enoxaparin in these patients should be prescribed for a minimum of 2 days and a maximum of 8 days.

Treatment of acute ST-segment elevation myocardial infarction

In patients with acute ST-segment elevation myocardial infarction, administered in conjunction with a fibrinolytic (fibrin-specific or non-fibrin specific), the recommended dose of Enoxaparin is a single IV bolus of 30 mg plus a 1 mg/kg SC dose, followed by 1 mg/kg administered SC every 12 hours (maximum 100 mg for each of the first two SC doses only, followed by 1 mg/kg dosing for the remaining doses). For dosage in patients \geq

75 years of age, see Section 4.2 – Dose and Method of Administration: Use in Renal Impairment and Use in the Elderly.

When administered in conjunction with thrombolytic (fibrin-specific or non-fibrin specific), Enoxaparin should be given between 15 minutes before and 30 minutes after the start of fibrinolytic therapy. All patients should receive aspirin as soon as they are identified as having STEMI (unless contraindicated). The recommended duration of Enoxaparin treatment is 8 days or until hospital discharge, whichever comes first.

For patients further managed with Percutaneous Coronary Intervention (PCI): If the last Enoxaparin SC administration was given less than 8 hours before balloon inflation, no additional dosing is needed. If the last Enoxaparin SC administration was given more than 8 hours before balloon inflation, an IV bolus of 0.3 mg/kg of Enoxaparin should be administered (see Section 4.4 – Special Warnings and Precautions for Use: Percutaneous Coronary Revascularisation Procedures).

Haemodialysis

In patients undergoing repeated sessions of haemodialysis, the prevention of thrombosis in the extracorporeal blood circuit is obtained by injection of a dose of 1 mg/kg (100 IU anti-Xa activity/kg) into the arterial line of the dialysis circuit at the start of the session. This dose is usually sufficient for a 4-hour haemodialysis session. If fibrin rings are formed, a fresh injection of 0.5 to 1 mg/kg (50 to 100 IU anti-Xa activity/kg) should be made depending on the time before the end of the dialysis.

In haemodialysed patients with a high risk of haemorrhage, (in particular, in pre or postoperative dialysed patients) or with a progressive haemorrhagic disorder, the dialysis sessions may be carried out by using a dose of 0.5 mg/kg (50 IU anti-Xa activity/kg) (double vascular access) or 0.75 mg/kg (75 IU anti-Xa activity/kg) (single vascular access).

For further information refer to the Product Information.

Product background

This AusPAR describes the application by Apotex Pty Ltd (the sponsor) to register the biosimilar, enoxaparin sodium (a low molecular weight heparin (LMWH)) solution for injection, as Enoxapo for the indications currently approved for Clexane and Clexane Forte sponsored by Sanofi-Aventis Australia Pty Ltd.

Clexane covers the presentations 20 mg in 0.2 mL, 40 mg in 0.4 mL, 60 mg in 0.6 mL, 80 mg in 0.8 mL and 100 mg in 1.0 mL, that is, the presentations with a concentration of 100 mg/mL while Clexane Forte covers the presentations 120 mg in 0.8 mL and 150 mg in 1.0 mL, that is, the presentations with a concentration of 150 mg/mL.

The sponsor of this submission is applying for all the same indications approved for the innovator products and these are:

- *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).*

The proposed instructions for dosage and administration for each of the indications are identical to those for Clexane and they are complex. There are three possible routes of administration, namely subcutaneous (SC), intravenous (IV) and into the arterial line of a haemodialysis circuit. See the Product Information (PI) as Attachment 1 for more details.

Australian application background

The following bullet list provides the Australian regulatory timeline for this product:

- In July 2013, Apotex submitted a Category 1 application to the TGA to register enoxaparin sodium (PM-2012-03777-1-3).
- The entity enoxaparin sodium was first registered in Australia under the trade name Clexane on 12 February 1993 by (the sponsor) Sanofi-Aventis Australia Pty Ltd. Currently on the Australian Register of Therapeutic Goods (ARTG), Sanofi-Aventis Australia Pty Ltd has enoxaparin products, Clexane, Clexane Forte and Enoxaparin Winthrop registered. Clexane (Australian trade name and Lovenox the corresponding Canadian/US trade name) is the reference medicine in this Category 1 submission.
- The application from Apotex, the sponsor of this submission to register enoxaparin is a biosimilar submission, with Clexane as the reference product.
- A clinical evaluation of that application was completed on 8 July 2014. The evaluator recommended rejection of the application on efficacy and safety grounds.
- A non-clinical evaluation of that application was completed with amendments on 29 October 2014. That evaluator concluded that the proposed product has not demonstrated similarity with the reference product.
- The Advisory Committee on Prescription Medicines (ACPM; now called Advisory Committee on Medicines) provided advice to reject that application. The initial Delegate rejected the application in a letter dated 13 February 2015. The grounds for rejection were that the quality, safety and efficacy of the goods have not been satisfactorily established for the purposes for which they are to be used.
- On 13 February 2015, the TGA wrote to Apotex regarding the decision by a Delegate of the Secretary of the Department of Health to reject the application (the initial decision). The Delegate decided that the data supplied by the sponsor indicated that there is a difference in the biophysical characteristics of the proposed product and that of the reference product, specifically:
 - The molecular weight of Apotex's enoxaparin was different to that of Clexane.
 - The average 1, 6-anhydro content of Apotex's enoxaparin was different to Clexane.
 - There was a difference in the chromatograms for hexasaccharide analysis.
- On 12 May 2015, Apotex sought reconsideration of the initial decision under section 60 (s60) of the Therapeutic Goods Act 1989 (the Act).

- On 9 July 2015, a Delegate of the Minister confirmed the initial decision that the quality, safety and efficacy of the Apotex's enoxaparin products have not been satisfactorily established. In relation to physicochemical characteristics, the variability of the method used, and the quality of the submitted data do not support Apotex's claim of physicochemical 'sameness' to its reference medicine.
- On 9 July 2015, Apotex applied for review of the section 60 decision with the Administrative Appeals Tribunal (AAT), claiming that the quality, safety and efficacy of enoxaparin has been satisfactorily established.
- A review of the quality issues raised by the section 60 Delegate was conducted in light of data subsequently made available to the TGA. In brief, the following issues were found to be outstanding: cytokine secretion, Zeta potential and photon correlation studies, and murine immunogenicity studies.
- In August 2018 a series of study reports investigating factors related to immunogenic and immunomodulatory potential of the Apotex product were submitted to the AAT. The evaluation of these new reports are detailed towards the end of this AusPAR under the heading *Outcome, Quality findings from the additional study reports submitted*.
- In February 2019, the AAT remitted the matter to the Minister. On 4 February 2020, following newly supplied information and data, a Delegate of the Minister reconsidered the decision under review and made a substituted decision to register the product.

Regulatory status

This was the first Australian submission seeking to register a biosimilar of a LMWH, which is a version of a particular LMWH, in this case, enoxaparin sodium, already on the ARTG.

Enoxaparin was first registered in Australia under the trade name Clexane on 12 February 1993. The innovator products Clexane and Clexane Forte are sponsored by Sanofi-Aventis Australia Pty Ltd.

At the time the TGA considered this application, similar applications had been approved in several countries across the world (see Table 1 below). It had not been approved in Canada, the European Union (EU), Switzerland or New Zealand and at this time, and was being evaluated in the United States of America (USA).

Table 1: International regulatory status

S.No	Country Name	Strength	Registration No.	Registration Date
1.	Srilanka	20 mg/0.2 mL	PR-052551	16/08/13
		40 mg/0.4 mL	PR-052550	15/08/13
		60 mg/0.6 mL	PR-052521	16/08/13
2.	Belarus	20 mg/0.2 mL	10068/12/14	28/12/12
		40 mg/0.4 mL	10068/12/14	28/12/12
		60 mg/0.6 mL	10068/12/14	28/12/12
		80 mg/0.8 mL	10068/12/14	28/12/12
3.	Brazil	20 mg/0.2 mL	25351.031684/01-13	24/07/2002
		40 mg/0.4 mL		
		60 mg/0.6 mL		
		80 mg/0.8 mL		
4.	Thailand	40 mg/0.4 mL	1C90002/48(NG)	26/10/06
		60 mg/0.6 mL	1C90003/48(NG)	26/10/06

Table 1 (continued): International regulatory status

5.	Colombia	20 mg/0.2 mL	2010M-0011277	30/09/10
		40 mg/0.4 mL	2010M-0011244	20/08/10
		60 mg/0.6 mL	2010M-0011453	12/10/10
		40 mg/0.4 mL	2010M-0011662	03/12/10
		60 mg/0.6 mL	2010M-0011523	02/11/10
6.	Georgia	80 mg/0.8 mL	2011M-0012132	04/05/11
		20 mg/0.2 mL	004337	04/01/11
		40 mg/0.4 mL	004342	04/01/11
		60 mg/0.6 mL	004343	04/01/11
		80 mg/0.8 mL	004344	04/01/11
7.	Peru	20 mg/0.2 mL	EG-4008	09/07/03
		40 mg/0.4 mL	BE-00860	27/04/12
		60 mg/0.6 mL	BE-00857	26/04/12
		80 mg/0.8 mL	EG-3997	03/07/08
8.	Uganda	40 mg/0.4 mL	7456/10/11	10/06/11
		80 mg/0.8 mL	7455/10/11	10/06/11
9.	Cambodia	40 mg/0.4 mL	CAMR14141P-07	04/04/12
		60 mg/0.6 mL	CAMR14142IP-07	04/04/12
10.	Zambia	40 mg/0.4 mL	246/017	27/06/08
		60 mg/0.6 mL	246/018	27/06/08
		80 mg/0.8 mL	246/016	27/06/08
11.	Nicaragua	40 mg/0.4 mL	01112741010	01/10/10
12.	Venezuela	20 mg/0.2 mL	P.B.1.198/09	08/07/09
		40 mg/0.4 mL		
		60 mg/0.6 mL		
		80 mg/0.8 mL		
13.	Bolivia	20 mg/0.2 mL	11-35203/2013	31/01/2013
		40 mg/0.4 mL	11-35228/2013	
		60 mg/0.6 mL	11-35202/2013	
		80 mg/0.8 mL	11-35266/2013	
14.	Chile	20 mg/0.2 mL	B-1.819/04	01/09/04
		40 mg/0.4 mL	B-1.820/04	01/09/04
		60 mg/0.6 mL	B-1.821/04	01/09/04
		80 mg/0.8 mL	B-1.822/04	01/09/04
15.	Philippines	20 mg/0.2 mL	DR-XY33115	March 2007
		40 mg/0.4 mL	DRP-1748	04/06/13
		60 mg/0.6 mL	DR-XY34632	June 2008
		80 mg/0.8 mL	DR-XY34634	04/06/08
16.	Vietnam	20 mg/0.2 mL	VN-3724-07	May 2007
		40 mg/0.4 mL	VN-17147-13	01/10/13
		60 mg/0.6 mL	VN-3725-07	May 2007
17.	India	20 mg/0.2 mL	103/AP/RR/97/F/R	12/10/2000
		40 mg/0.4 mL		
		60 mg/0.6 mL		
		80 mg/0.8 mL		

Update: Apotex's enoxaparin has now also been approved in the USA (28 September 2018).

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 time line

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

Table 2: Timeline for Submission PM-2012-03777-1-3

Description	Date
Submission dossier accepted and first round evaluation commenced	22 July 2013
First round evaluation completed	19 March 2014
Sponsor provides responses on questions raised in first round evaluation	30 May 2014
Second round evaluation completed	23 July 2014
Delegate's overall benefit-risk assessment and request for Advisory Committee advice	4 November 2014
Sponsor's pre-Advisory Committee response	18 November 2014
Advisory Committee meeting	1 December 2014
Registration decision (Initial rejection)	13 February 2015
Number of working days from submission dossier acceptance to initial registration decision*	253
Registration decision (Internal review of initial decision; section 60 review)	9 July 2015
Administrative Appeals Tribunal (AAT) outcome	25 February 2019

Description	Date
Registration decision (Outcome: approval)	4 February 2020
Completion of administrative activities and registration on ARTG	10 February 2020

*Statutory timeframe for standard applications is 255 working days

III. Overall conclusion and risk/benefit assessment

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

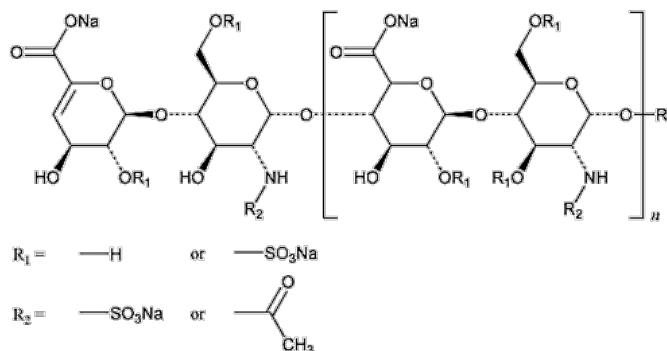
Quality

Drug substance

Structure

The drug substance has the following structure derived from the United States Pharmacopeia (USP).¹

Figure 1: Chemical structure of enoxaparin sodium



$R =$	$X = 15 - 25\%$		$n = 0 \text{ to } 20$
	100-X	H	$n = 1 \text{ to } 21$

Enoxaparin sodium is the sodium salt of a depolymerised heparin. It is obtained by alkaline depolymerisation of heparin benzyl ester. Enoxaparin sodium consists of a complex set of oligosaccharides that have not yet been completely characterised. The majority of the components have a 4-enopyranose urinate structure at the nonreducing end of their chain. About 20% of the materials contain a 1,6-anhydro derivative on the reducing end of the chain, the range being between 15% and 25%.

¹ USP. Enoxaparin Sodium United States Pharmacopeia. Volume 39. USP; Rockville, MD, USA: 2016. pp. 3695–3697

Physical and chemical properties

Enoxaparin sodium (as defined by the European Pharmacopoeia (Ph.Eur.);² is the sodium salt of a low-molecular mass heparin that is obtained by alkaline depolymerisation of the benzyl ester derivative of heparin from porcine intestinal mucosa. Enoxaparin sodium consists of a complex set of oligosaccharides that have not yet been completely characterised.

Specifications

The proposed specifications, which control identity, content, potency, purity and other biological and physical properties of the drug substance are relevant to the dose form and its intended clinical use.

Appropriate validation data have been submitted in support of the test procedures used for release testing.

Drug product**Formulation**

- Dosage forms: injectable (subcutaneous/intravenous)
- Strengths: 100 mg/mL and 150 mg/mL
- Presentations:
 - 100 mg/mL:
 - 30 mg/0.3 mL in 0.5 mL pre-filled syringe
 - 40 mg/0.4 mL in 0.5 mL pre-filled syringe
 - 60 mg/0.6 mL in 1.0 mL graduated pre-filled syringe
 - 80 mg/0.8 mL in 1.0 mL graduated pre-filled syringe
 - 100 mg/1.0 mL in 1.0 mL graduated pre-filled syringe
 - 150 mg/mL:
 - 120 mg/0.8 mL in 1.0 mL graduated pre-filled syringe
 - 150 mg/1.0 mL in 1.0 mL graduated pre-filled syringe

The drug product consists only of the active ingredient dissolved in water for injection as a solvent. The water for injection used is of USP grade and is also compliant with the Ph.Eur./British Pharmacopoeia (BP).

Specifications

The proposed specifications, which control identity, potency, purity, dose delivery and other physical, chemical and microbiological properties are relevant to the clinical use of the product.

Stability

All batches tested through both filling lines met specification after the proposed shelf life period of 24 months at room temperature. Likewise, under accelerated conditions of 40°C all batches tested met specification after 6 months. The data provided support the proposed shelf life.

² European Pharmacopoeia 8.0 volume II, Enoxaparin sodium monograph 1097, (2014), Council of Europe.

Sterility, endotoxin, viral safety, and container safety

All issues were resolved during the evaluation of sterility, endotoxin and container safety evaluations. The viral safety evaluator raised issues with the testing method used for species identification. This issue was not concluded during evaluation but was not considered to be controlled through other aspects of the manufacturing details and through Good Manufacturing Compliance (GMP) compliance.

The quality of the finished product has been determined to be compliant with the relevant standard. The manufacturing process has been validated and assessed as appropriately consistent and controlled through relevant process controls and release specifications.

Labelling, packaging and documentation

The proposed trade names are Enoxaparin Apotex and APO-Enoxaparin.

Both trade names have the active ingredient name and APO-Enoxaparin has part of the company name.

Both the trade name and the active name do not comply with the TGA's Guidance on the evaluation of biosimilars.³

Biosimilar medicines are required to have a trade name clearly distinguishable from all other products, especially the reference medicine and other biosimilar medicines.

The sponsor was required to revise the trade names and update the labels.

Conclusion and recommendation

The manufacture of the proposed enoxaparin has been assessed as being of appropriate quality and compliant with an appropriate pharmacopeial monograph.

The TGA has determined that the data supplied by the sponsor indicates that there is a difference in the biophysical characteristics of the proposed product and that of the reference product, specifically in:

- content of the 1,6-anhydro structure; and
- percentage of hexasaccharide, peak shapes and mass spectra in oligosaccharide sequence analysis.

The differences demonstrated are sufficient to conclude that the proposed product:

- Does not have the same quantitative composition of therapeutically active substances, being substances of similar quality to those used in the registered medicine or previously registered medicine as defined as a generic product in schedule 9 of the *Therapeutic Goods Regulations 1990*.
- Does not have equivalence of physiochemical properties and hexasaccharide species with the reference product according to the FDA 'Criteria Used for Sameness Determination of Enoxaparin Sodium'.
- Cannot be considered as similar with the reference product on the quality data alone. Residual uncertainty due to the demonstrated differences remains and the link from the proposed product to the supporting clinical knowledge of the reference product has not been made. The clinical relevance of the clinical differences would need to be supported by relevant clinical comparability studies as suggested in the TGA adopted biosimilars guidelines.

³ Therapeutic Goods Administration; Guidance on the Evaluation of biosimilars. TGA Canberra, ACT. Version 1.0, July 2013.

In addition, the product is not considered an acceptable presentation as the tradename, labelling and PI are not compliant with the TGA biosimilars guidance.

Therefore, the recommendation from the quality evaluators is that the data provided is not sufficient to support approval of the application.

Nonclinical

No actual nonclinical study reports were submitted. Literature references consisted of a copy of the USA regulatory review of the reference product, a copy of the Lovenox product monograph issued by Health Canada, and 63 supportive published papers which dealt with various pharmacotoxicological aspects of enoxaparin and low molecular weight heparins but none specifically involved Apotex's enoxaparin (this was not a formal literature-based submission with a search strategy approved by the TGA). There was no nonclinical data to support the equivalence in *in vivo* pharmacodynamic profile. It is assumed that the sponsor is relying on clinical data to support this criterion.

No original nonclinical studies investigating the pharmacology, pharmacokinetics or toxicology of Apotex's enoxaparin were included. Therefore, a specific nonclinical risk assessment on the Apotex's enoxaparin formulation cannot be conducted and the only issue to consider is whether the absence of comparative *in vivo* nonclinical data is acceptable. This is particularly dependent on the outcome of the quality evaluation, and to some extent, the clinical evaluation as well (where *in vivo* pharmacodynamic data are available).

The conclusion of the nonclinical/toxicological evaluator was that:

'The acceptability of the absence of comparative nonclinical data in vivo clearly depends on the assessment of the degree of similarity demonstrated by the Quality comparative data (including the in vitro pharmacodynamic studies) and the robustness of any submitted comparative clinical safety and efficacy data.'

Clinical

As noted by the clinical evaluator, this submission consisted of an abbreviated clinical dossier.

The two clinical studies, which formed the contents of clinical, were single dose, biopharmaceutic studies, the first of which compared enoxaparin Apotex with the Australian innovator product, Clexane and the second of which compared enoxaparin Apotex with the USA innovator (Lovenox). There were no clinical efficacy and safety studies comparing enoxaparin Apotex with either Clexane or Lovenox.

The relevant TGA adopted EU guideline;⁴ (EMA/CHMP/BMWP/118264/2007) states that

'due to the heterogeneity of low molecular weight heparins (LMWHs) conventional pharmacokinetic studies cannot be performed. Instead the absorption and elimination characteristics of LMWHs should be compared by determining pharmacodynamic activities, including anti-factor Xa and anti-factor IIa, as surrogate markers for their circulating concentrations'.

⁴ EMA/CHMP/BMWP/118264/2007: Guideline on Non-clinical and Clinical Development of Similar Biological Medicinal Products containing Low-Molecular-Weight Heparins. European Medicines Agency, 2007.

Pharmacology

Study ZPS-452

The first study was a Phase I, single-centre, single dose (1 mg/kg), randomised, double-blind, two-way cross-over biopharmaceutical study comparing enoxaparin (Apotex, Australia) with Clexane (Sanofi-Aventis, Australia) under fasting conditions in healthy volunteers. The study was undertaken in New Zealand.

The pharmacodynamics parameters were all analysed using validated bioanalytical methods for human plasma. The pivotal endpoint was that of anti-Xa activity and the second endpoints studied comprised anti-IIa activity, tissue factor pathway inhibitor (TFPI) activity (total and free) and finally activated partial thromboplastin time (aPTT) and HepTest (indicative of anti-Xa activity).

The various parameters were calculated as follows:

- Maximum observed plasma activity (A_{max}).
- Area under the activity-time curve from time zero to infinity ($AUAC_{0-\infty}$).
- Area under the activity-time curve from time zero to the last determined activity-time point ($AUAC_{0-t}$).
- Time of the maximum observed plasma activity (T_{max}).
- Apparent first-order plasma terminal elimination half-life calculated as $0.693/Kel$ ($t_{1/2}$).
- Apparent first-order terminal elimination rate constant calculated from a semi-log plot of the plasma activity versus time curve (Kel).

There were 24 healthy adult participants, 14 male and 10 female.

Pivotal endpoint (anti-Xa)

The 90% confidence intervals for the geometric mean ratios (GMR; test/reference) of $AUAC_{0-t}$, $AUAC_{0-\infty}$ and A_{max} for anti-Xa were all within the pre-specified limits of 0.80 to 1.25. There was no statistically significant sequence or period effects for any of the three parameters. The results are displayed in Table 3 below:

Table 3: Study ZPS-452 anti-Xa results; geometric means and geometric mean ratios

	AUA _{0-∞} (IU.hr/ml)	AUA _{0-t} (IU.hr/ml)	Amax (IU/ml)	Tmax (hr)
<i>Enoxaparin 1 mg/kg injection (Batch No.: CS901) (Test)</i>				
Geometric Mean	9.138	8.192	0.797	3.78
S.D. ^c	1.583	1.287	0.091	1.04
Range	6.259-11.714	5.841-10.713	0.654-0.970	2.00-6.00
<i>Clexane® 1 mg/kg injection (Batch No.: 21161) (Reference)</i>				
Geometric Mean	10.417	9.344	0.900	3.85
S.D. ^c	1.902	1.415	0.132	0.84
Range	7.683-16.489	7.303-13.615	0.734-1.270	2.50-6.00
P-Values	0.0001	0.0001	0.0008	-
Sequence	0.0760	0.0904	0.2424	-
Period	0.1735	0.1443	0.8505	-
<i>Enoxaparin injection (Batch No.: CS901) (Test) vs Clexane® injection (Batch No.: 21161) (Reference)</i>				
Mean Ratio % ^a	87.72	87.67	88.57	98.28
90% CI ^b	(0.851,0.904)*	(0.853,0.901)*	(0.839,0.935)*	-

*90% CI criteria used to establish that the GMR (test/reference) should lie between 0.80 and 1.25. ^amean ratio % = geometric mean (test)/geometric mean (reference) x 100%. ^b90% CI = 90% confidence interval ^cS.D. = Jackknife standard deviation

Supportive or secondary endpoints (Anti-IIa)

The 90% confidence intervals (CI) for the GMRs (test/reference) of $AUAC_{0-t}$ and A_{max} for anti-IIa were both within the pre-specified limits of 0.80 to 1.25. The GMR was not calculated for $AUAC_{0-\infty}$, as the terminal phase had not been established for most subjects due to the high inter-subject variability of the data near the terminal phase. There was no statistically significant sequence or period effects for the three parameters.

Supportive or secondary endpoints (Total tissue factor pathway inhibition)

The 90% CIs for the GMRs (test/reference) of $AUAC_{0-t}$, $AUAC_{0-\infty}$ and A_{max} for baseline adjusted TFPI were all within the pre-specified limits of 0.80 to 1.25. There was no statistically significant sequence or period effects for any of the three parameters.

Supportive or secondary endpoints (Free tissue factor pathway inhibition)

The 90% CIs for the GMRs (test/reference) of $AUAC_{0-t}$ and A_{max} for baseline adjusted free TFPI were both within the pre-specified limits of 0.80 to 1.25. The GMR was not calculated for $AUAC_{0-\infty}$, as the terminal phase had not been established for most subjects due to the high inter-subject variability of the data near the terminal phase. There was no statistically significant sequence or period effects for the three parameters.

Supportive or secondary endpoints (Activated partial thromboplastin time)

The 90% CIs for the GMRs (test/reference) of $AUAC_{0-t}$ and A_{max} for baseline APTT were both within the pre-specified limits of 0.80 to 1.25. The GMR was not calculated for $AUAC_{0-\infty}$, as the terminal phase had not been established for most subjects due to the high inter-subject variability of the data near the terminal phase. There were no statistically significant sequence effects for the three parameters. There were statistically significant period effects for $AUAC_{0-\infty}$ and $AUAC_{0-t}$. The latter are unlikely to be of any clinical significance.

Supportive or secondary endpoints (HepTest (anti-Xa))

The 90% CIs for the GMRs (test/reference) of $AUAC_{0-t}$, $AUAC_{0-\infty}$ and A_{max} for the HepTest (anti-Xa) were all within the pre-specified limits of 0.80 to 1.25. There were no statistically significant effects for any of the three parameters. There were statistically significant period effects for $AUAC_{0-\infty}$ and $AUAC_{0-t}$. The latter are unlikely to be of any clinical significance.

Supportive or secondary endpoints (Anti-Xa/Anti-IIa ratio)

The 90% CIs for the GMRs (test/reference) of $AUAC_{0-t}$ and A_{max} for the anti-Xa/anti-IIa ratio were both within the pre-specified limits of 0.80 to 1.25. The GMR was not calculated for the $AUC_{0-\infty}$, as the terminal phase had not been established for most subjects due to the high inter-subject variability of the data near the terminal phase. There were no statistically significant sequence or period effects for the three parameters, apart from a significant period effect for $AUAC_{0-t}$.

Study AA29102

This, the second study, was a Phase I, single-centre, open label, randomised, two-way cross-over, two sequence, single dose, biopharmaceutical study comparing enoxaparin (Apotex Inc) with Lovenox (Aventis) in healthy male volunteers, undertaken in Canada. The study population consisted of 24 healthy adult male volunteers.

The 90% CIs for the GMRs (test/reference) of $AUAC_{0-t}$, $AUAC_{0-\infty}$ and A_{max} for anti-Xa activity and for anti-IIa activity were all within the pre-specified limits of 0.80 to 1.25. The 90% CIs for the GMRs (test/reference) of A_{max} and maximum measured blood activity compared to Baseline (change in time of A_{max}) for APPT were both within the pre-specified limits of 80% & 125%.

Efficacy

No Phase III clinical efficacy studies were submitted.

Safety

No Phase III clinical safety studies were submitted. However, there were two single dose (1 mg/kg) bioequivalence studies conducted in healthy volunteers and these provided some limited safety data.

In the first study, Study ZPS-452, 24 healthy male and female volunteers were given single 1 mg/kg doses of Apotex's enoxaparin and Clexane, separated by a 14 day washout period. During this study, there were 14 non-serious adverse events experienced by 7 of the 24 participants, and these events were reasonably evenly distributed between the test and reference products. There were no deaths or other serious adverse events. There were no serious or significant laboratory test results.

In the second study, Study AA2910, 6 subjects had 11 adverse events following Apotex's enoxaparin and 1 subject had 7 adverse events following Lovenox. Overall, 2 subjects experienced at least 1 mild or moderate adverse event which was considered by the investigator to be possibly or probably related to Apotex's enoxaparin (1 abdominal bruise and 1 bruise at venepuncture site on arm). No subjects experienced any adverse events (AEs) that were possibly or probably related to Lovenox. As with the first study, there were no deaths or other serious adverse events nor any clinically significant laboratory results.

The clinical evaluator also asked for some clarification from the sponsor concerning the draft risk management plan (RMP), in particular the effectiveness with which that document dealt with rare serious adverse events such as heparin induced thrombocytopenia (HIT) type II;⁵ as well as anaphylactoid and anaphylactic reactions.

Clinical evaluator's recommendation

The clinical evaluator recommended that the application to register Apotex's enoxaparin for the proposed indications be rejected.

Risk management plan

The sponsor submitted a RMP (Enoxaparin Sodium Australian-RMP (AUS-RMP) version 1.0, dated 25 October 2012, Enoxaparin Sodium AUS-RMP version 2.0, dated 22 May 2014) which was reviewed by the TGA.

⁵ Heparin-induced thrombocytopenia (HIT) is a rare form of thrombocytopenia (low platelet count) arising from the administration of various forms of the anticoagulant heparin. HIT is caused by the formation of abnormal antibodies that activate platelets (also known as thrombocytes) and may result in a predisposition to thrombosis formation (the abnormal formation of blood clots inside a blood vessel) when platelets release microparticles that activate thrombin (also known as factor Xa), thereby leading to thrombosis. Heparin-induced thrombocytopenia and thrombosis (HITT) is said to have occurred when thrombosis has developed or worsened following HIT.

HIT may be subdivided into type I and type II HIT; Type I HIT presents early, typically within the first 2 days after heparin exposure, whereby a modest decrease in the platelet count (mild thrombocytopenia) normalises with continued heparin therapy and is typically self-limiting. Type I HIT is a nonimmune disorder that results from the direct effect of heparin on platelet activation. Type II HIT is an immune-mediated disorder typically occurring following 4 to 10 days of exposure to heparin; it is more severe on presentation and has life- and limb-threatening thrombotic complications. Without use of a qualifier, the term HIT typically refers to type II HIT.

Safety specification

The sponsor provided a summary of ongoing safety concerns, which are shown in Table 4.⁶

Table 4: Summary of ongoing safety concerns

Summary of ongoing safety concerns	
Important identified risks	Haemorrhages
	Thrombocytopaenia and thrombocytosis
	Neuraxial haematoma
	Prosthetic heart valve thrombosis
	Injection site reactions
	Anaphylactic shock
Important potential risks	Congenital anomalies
	Fetal death
Important missing information	Lack of effect

Pharmacovigilance plan

Routine pharmacovigilance has been proposed for all the identified safety concerns.

Risk minimisation activities

Routine risk minimisation is proposed for all the identified safety risks.

In the opinion of the RMP evaluator the sponsor's response to the TGA questions has adequately addressed all of the issues identified in the RMP evaluation report.

The Delegate endorses Recommendations 7 and 8 of the evaluation report, the former concerning a proposed revision to the PI and the latter concerning a proposed revision to the Consumer Medicines Information (CMI). The details of these are beyond the scope of this AusPAR.

⁶ Routine risk minimisation activities may be limited to ensuring that suitable warnings are included in the product information or by careful use of labelling and packaging.

Routine pharmacovigilance practices involve the following activities:

- All suspected adverse reactions that are reported to the personnel of the company are collected and collated in an accessible manner;
- Reporting to regulatory authorities;
- Continuous monitoring of the safety profiles of approved products including signal detection and updating of labelling;
- Submission of PSURs;
- Meeting other local regulatory agency requirements.

Risk-benefit analysis

Delegate's considerations

This submission seeks to register Apotex's enoxaparin, a biosimilar to the registered form of enoxaparin, Clexane. The innovator product Clexane is sponsored by Sanofi Aventis Australia Pty Ltd. Enoxaparin is one of the so-called LMWH.

Summary of Issues

- The quality evaluator has pointed to the lack of comparability between the test and reference products for at least two parameters, 1,6-anhydro content and hexasaccharide analysis. This does not permit automatic assumption of the reference product's clinical profile by the test product.
- The lack of any nonclinical/toxicological data.
- The only clinical data are studies in healthy volunteers of surrogate pharmacodynamics characteristics.
- The heterogeneity of LMWH products and the heterogeneity of molecular composition of the test product.
- The absence of any rigorously collected or analysed safety data in human patients requiring the product for an approved indication.

Proposed action

The Delegate is not in a position to say, at this time, that the application for Apotex's enoxaparin should be approved for registration.

Request for ACPM advice

The Advisory Committee on Prescription Medicines (ACPM) is requested to give advice on the following specific issues:

1. Does the lack of comparability demonstrated by the quality evaluator raise doubts as to the ability of the sponsor to assume the reference product's clinical profile for its own product?
2. Should no-clinical data be required to support registration of this enoxaparin biosimilar product?
3. Should clinical efficacy and safety data in patients be required to support the registration of this enoxaparin biosimilar product?
4. Are there significant clinical implications of the heterogeneity of LMWH products and of the heterogeneity of molecular composition of the test product?
5. What are the implications of the absence of any rigorously collected or analysed safety data including immunogenicity data in human patients requiring the product for an approved indication?
6. Does the ACPM agree that there is a need for the TGA to be able to view and to evaluate the information relayed to the sponsor in its response to the Complete Response Letter of the US Food and Drug Administration (FDA), that is, the information concerning the three unresolved immunogenicity domains?

7. What are the ACPM's views on how the fact that this product is a biosimilar product should be communicated and reported in the PI and on the labels of the product? How should interchangeability with the reference product be reported?
8. What post-registration education activities for potential prescribers does the ACPM view as important in relation to the biosimilarity to and interchangeability with the reference product?

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.

Advisory Committee considerations⁷

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The ACPM, taking into account the submitted evidence of pharmaceutical quality, safety and efficacy agreed with the Delegate that Apotex's Enoxaparin solution for injection containing 100 mg/mL, 150 mg/mL of enoxaparin sodium has an overall negative benefit-risk profile for the proposed indication.

In making this recommendation the ACPM considered that the proposed product is a biosimilar under the definitions adopted by the TGA and that as such the application should be assessed by the TGA in accordance with the TGA's biosimilar Guidelines, which requires clinical data to demonstrate comparability.

Specific advice

The ACPM advised the following in response to the Delegate's specific questions on this submission:

1. Does the lack of comparability demonstrated by the Quality evaluator raise doubts as to the ability of the sponsor to assume the reference product's clinical profile for its own product?

The ACPM considered that the lack of comparability demonstrated by the Quality evaluation raised sufficient doubt as to similarity of the clinical profile between the proposed product and the innovator.

2. Should nonclinical data be required to support registration of this enoxaparin biosimilar product?

The ACPM noted that the innovator product is considered to be a biological product and therefore for consistency 'similar' products should be considered under the category of a biosimilar. In addition, if a product is a biosimilar, the TGA Guideline requires nonclinical data be provided to support use in humans. Therefore, the ACPM advised that nonclinical data should be provided to support registration.

⁷ The Advisory Committee on Prescription Medicines (ACPM) which was formed in January 2010, was set up to provide independent medical and scientific advice to the Minister for Health and the Therapeutic Goods Administration (TGA) on issues relating to the safety, quality and efficacy of medicines supplied in Australia. As of January 2017, it has been replaced by the Advisory Committee on Medicines (ACM) including issues relating to pre-market and post-market functions for medicines. ACM encompass 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. Both the ACPM and the ACM were established under Regulation 35 of the *Therapeutic Goods Regulations 1990*. Members are appointed by the Minister.

3. Should clinical efficacy and safety data in patients be required to support the registration of this enoxaparin biosimilar product?

As noted above, the innovator product is considered to be a biological product and therefore for consistency 'similar' products should be considered under the category of a biosimilar. In addition, if a product is a biosimilar, the TGA Guideline requires that clinical efficacy and safety data in patients be provided to support the registration. Therefore, the ACPM advised that clinical efficacy and safety data should be provided to support registration.

4. Are there significant clinical implications of the heterogeneity of LMWH products and of the heterogeneity of molecular composition of the test product?

The ACPM noted the article by Fareed, J et al (*Thrombosis Journal, 2007*);⁸ which highlighted the fact that different LMWHs have individual therapeutic effects and have been approved for specific indications. The article also noted that it is important to differentiate these drugs and caution should be exercised for therapeutic interchange. The ACPM agreed that there are significant clinical implications of the heterogeneity of LMWH, which are unknown at present due to lack of data.

5. What are the implications of the absence of any rigorously collected or analysed safety data, including immunogenicity data, in human patients requiring the product for an approved indication?

The ACPM considered that in the absence of any rigorously collected or analysed safety data in human patients or clear proof of similarity the implications for safety in particular are unknown and therefore un-assessable.

6. Does the ACPM agree that there is a need for the TGA to be able to view and to evaluate the information relayed to the sponsor in its response to the Complete Response Letter of the US FDA, that is, the information concerning the three unresolved immunogenicity domains?

The ACPM noted the immunogenicity assessment provided to the committee. The data comprised of *in vitro* comparative testing of multiple lots of the Apotex product and the reference product, Lovenox. The evaluator noted that currently, there is no *in vitro* system that has been proven to be able to accurately and reliably predict immunogenic potential of a particular substance. The ACPM was of the view that the frequency of immunogenic events is such that they would only be captured by post marketing surveillance, i.e. a trial would not be big enough to establish incidence prior to clinical use experience.

7. What are the ACPM's views on how the fact that this product is a biosimilar product should be communicated and reported in the PI and on the labels of the product? How should interchangeability with the reference product be reported?

The ACPM considered that any views on the PI and labelling of the product at this stage are premature.

8. What post-registration education activities for potential prescribers does the ACPM view as important in relation to the biosimilarity to, and interchangeability with, the reference product?

The ACPM considered that any views on the PI and labelling of the product at this stage are premature.

⁸ Fareed, J., Walenga, J.M. Why differentiate low molecular weight heparins for venous thromboembolism?. *Thrombosis J* 5, 8 (2007).

Initial outcome

Based on a review of quality, safety and efficacy, the TGA decided not to register Apotex's enoxaparin solution for injection in 20 mg/0.2 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/1 mL, 120 mg/0.8 mL and 150 mg/1 mL pre-filled syringes, on the grounds that the quality, safety and efficacy of the goods have not been satisfactorily established for the purposes for which they are to be used.

Reasons for decision

Evaluation of quality, safety and efficacy of Apotex's enoxaparin

Having set out why the TGA evaluated Apotex's enoxaparin as a biosimilar medicine, the Delegate now turns to the criteria in s25 of the Therapeutic Goods Act, which requires *inter alia* that the Delegate have regard to whether the quality, safety and efficacy of the medicine for the purposes for which it is to be used have been satisfactorily established: s25(1)(d).

1. The quality of Apotex's enoxaparin for the proposed indications has not been satisfactorily established for the following reasons:
 - a. There are differences in the biophysical profile of Apotex's enoxaparin compared with the reference product. The sponsor was requested to explain the significance of these differences.

The Delegate considers the differences between the sponsor's enoxaparin and Clexane to be sufficient to conclude that the quality of the goods has not been satisfactorily established and that the known efficacy and safety of the reference product cannot be extrapolated to the sponsor's proposed enoxaparin.
2. The safety and efficacy of Apotex's enoxaparin for the proposed indications has not been satisfactorily established for the following reasons:
 - a. It is unknown how the differences observed in the hexasaccharide peak shapes may affect the efficacy and safety of the proposed product, as the sponsor has not submitted any efficacy or safety studies to determine the clinical relevance of this difference. Thus, the Delegate considers the immunogenicity assessment to be insufficient at present.
 - b. The sponsor has not submitted any comparative nonclinical pharmacodynamic (*in vivo*) and/or toxicological studies comparing Apotex's enoxaparin with Clexane (or Lovenox).
 - c. Although the submitted pharmacokinetic/pharmacodynamic studies have satisfactorily demonstrated the bioequivalence between Apotex's enoxaparin and Clexane/Lovenox via the subcutaneous route in healthy subjects, there is an incomplete understanding of the mode of action of LMWHs and uncertainty around the predictability of the biomarkers such as anti-FXa activity and anti-FIIa activity in predicting clinical outcomes and therefore these studies alone are insufficient to conclude the safety and efficacy of the sponsor's product.
 - d. The sponsor has not submitted any clinical studies in any of the requested indications to demonstrate the comparability of Apotex's enoxaparin with Clexane in terms of comparing the efficacy and safety profiles.
 - e. The sponsor has indicated that their enoxaparin product has been marketed in a number of countries around the world, mostly in Asia and South America, however the potential effects of the differences listed between the proposed product for registration and the product sold internationally, which also has not been assessed by TGA, are unknown and does not provide adequate reassurance as to the safety of the proposed product for registration. There are no postmarket

data specific to the sponsor's product available to address potential safety concerns, including immunogenicity concerns.

For the reasons set out above, the Delegate has decided not to register the products because the quality, safety and efficacy of the goods have not been satisfactorily established for the purposes for which they are to be used.

Other issues which the sponsor should consider in future submissions for this product

1. A postmarket study or patient registry in a large population to detect rare but serious adverse effects including immunogenicity risks that are known to occur with LMWHs. The recommendations from the RMP evaluator should also be addressed.
2. The PI, CMI and labelling of the product along with educational activities to inform health professionals and consumers in relation to the biosimilar aspects of the medicine.
3. The naming convention for the product consistent with the TGA's Guideline on biosimilars that is current at the time of the submission.
4. The immunogenicity data provided to the US FDA in May 2014 by Apotex but not submitted to the TGA, and referred to in the email correspondence from 20 January 2015 and previous correspondence should be included. The Delegate notes the sponsor suggested a mutual stop clock in its Pre-ACPM Response to enable the evaluation of this additional data but given that the evaluation period has been completed and that there are other matters to be addressed with the dossier as discussed above, then such information should be provided in the context of a new submission.
5. The outcome of the submission to the US FDA.

Other Issues in relation to this application

1. The sponsor requested a mutual stop clock for this submission until the US FDA had made their decision on the Apotex's enoxaparin currently undergoing evaluation for the US market. The Delegate considered this request but have not accepted it for the following reasons:
 - a. It is not usual practice for the TGA to delay a decision on an application until the outcome from another jurisdiction has become available.
 - b. It is unknown when a decision is likely given that the application in the US was submitted in 2007 and there is no indication of when the submission is likely to be completed.
 - c. Any outcome from the US FDA is likely to result in further data being submitted which would require full evaluation and may involve seeking further expert advice. This would be best handled in the context of a new submission when the totality of the data can be fully considered.

Outcome of section 60 review

For the reasons referred to below, the section 60 review Delegate decided to confirm the initial decision, that is, to reject the application to register Apotex Enoxaparin.

The Delegate's reasons

The Delegate reasons for confirming the original decision were set out under the following headings:

Lack of evidence supporting claims

In several instances, the sponsor has made claims in the appeal documentation that have not been adequately supported by the documentation provided. In such cases the Delegate not been satisfied or been able to adequately test the claims that have been made.

Failure to satisfactorily establish quality, safety and efficacy

The Delegate provided separate reasons with respect to each of the following matters:

- physicochemical characteristics
- immunogenicity studies
- immunogenicity studies assessing the interaction with platelet factor 4 (PF4)
- immunogenicity studies assessing other immunogenic effects
- clinical efficacy and bioequivalence
- clinical safety.

For these reasons, the Delegate has decided to confirm the initial decision.

Appeal to the Administrative Appeals Tribunal

Following the Minister's reconsideration of the initial decision, which resulted in the initial decision being confirmed, Apotex applied for review of the section 60 decision with the Administrative Appeals Tribunal (AAT) in July 2015.

In August 2018 a series of study reports investigating factors related to immunogenic and immunomodulatory potential of the Apotex product were submitted to the AAT.

In February 2019, the AAT remitted the matter to the Minister. On 4 February 2020, following newly supplied information and data, a Delegate of the Minister reconsidered the decision under review and made a substituted decision to register the product.

Quality findings from the additional study reports submitted by the sponsor

Summary

This physiochemical assessment has been undertaken in order to determine the difference(s) in the biophysical characteristics of Apotex's Enoxaparin and its reference medicine Clexane as a follow up to (or reconsideration of) the TGA's previous evaluation and the section 60 appeal process.

The quality evaluator reviewed relevant information contained in the dossier and additional materials provided by Apotex during the section 60 appeal and AAT process, particularly the new comparison analysis performed after changes made to the drug substance manufacturing process and to the specifications for the raw material, intermediate and active ingredient.

The evaluation focused on issues around oligosaccharide analysis, 1,6-anhydro structure content and molecular weight profile of Apotex's Enoxaparin. Other aspects in relation to manufacturing, product quality and presentation have also been reviewed.

The evaluator concluded that the residual issues regarding physiochemical comparability of Apotex's enoxaparin have been resolved. Concerns about comparability of

oligosaccharide profile, 1,6-anhydro structure content and molecular weight distribution have been satisfactorily addressed.

Overall, in terms of comparative analyses of physicochemical and biological attributes, Apotex's enoxaparin produced from the revised manufacturing process is considered similar to its reference medicine Clexane (which is also called Lovenox). Additionally, the sponsor updated the dossier to include up to date information about PI, labels, manufacturers and stability study, following TGA's request for further information.

There are no outstanding issues about the GMP clearances.

Physical and chemical properties

The enoxaparin is compliant to the specification of the USP.

All analytical procedures are validated.

Overall conclusion on physicochemical comparison

- Residual issues regarding physicochemical comparability from the initial Category 1 assessment, S60 process and AAT have been resolved. Apotex's enoxaparin produced from the revised manufacturing process is considered similar to its reference medicine in physicochemical characteristics.
- Compared to the drug substance from the initial Category 1 submission, the drug substance from the revised manufacturing process is closer to the reference medicine in terms of the molecular weight profile and 1,6,-anhydro content.
- The revised specifications for drug substance comply with Ph.Eur. Monograph 01/2017:0828 Heparins, low-molecular weight and Ph.Eur. Monograph 04/2014:1097 Enoxaparin sodium. The specifications for the drug substance was also tightened and are comparable to those for the reference medicine or stricter.

Stability

Stability data have been generated under stressed and real time conditions to characterise the stability profile of the product.

The assessment on updated stability data supported a shelf life of 24 months at 25°C/60% room humidity ± 5% room humidity for the drug product.

The product is photostable.

Immunogenic potential and immunomodulatory comparison

Additional immunogenicity and immunomodulatory studies conducted by the sponsor went a considerable way to addressing the concerns identified by the Section 60 Delegate and those raised by the external expert evaluator in the earlier reviews of this product. For the most part, the investigations appear to have been well conducted.

In terms of the Section 60 Delegate's outstanding issues, further data was supplied for physicochemical and immunomodulatory studies, however no data was presented in regard to murine immunogenicity studies.

The additional data clarified physicochemical similarities between Apotex's enoxaparin and Lovenox or Clexane when these were complexed with a relevant ligand, in this case platelet factor 4 (PF4), in terms of size (Z-average measurements) and surface charge when measured as zeta potential.

Evidence is presented for similarities in cytokine secretion profiles from peripheral blood mononuclear cells as well as B cell activation status after challenge with enoxaparin with co-stimulation. These generally support claims of similarity of Apotex's enoxaparin to Lovenox/Clexane, however some differences are noted which may reflect either variability in the assay system or be genuine differences. The key issue with the latter data is the

biological relevance of the artificial system used. Here co-stimulatory ligands were used to increase the sensitivity of cytokine responses to the heparin stimuli and so differences observed may be an *in vitro* phenomena of little consequence. Equally, however, these may be relevant *in vivo*.

Following a round of questions from the TGA, the sponsor presented justification as to why these differences should not be considered significant or meaningful. These have been assessed and considered acceptable based on the weight of evidence provided.

The range of *in vitro* studies presented implies a broad similarity between the test (Apotex Enoxaparin) and the reference medicine, especially in terms of enoxaparin-heparin platelet 4 (HP4) complex binding, which leads to the acceptance on balance that Apotex's enoxaparin and the reference medicine are sufficiently similar.

Conclusion

There are no objections to the registration of this product from sterility, endotoxin, container safety and viral safety related aspects.

Overall, sufficient evidence has been provided to demonstrate that the risks related to the manufacturing quality of Enoxapo have been controlled to an acceptable level.

With respect to quality matters, the PI, consumer medicine information and labels as detailed are acceptable.

There are no objections on quality grounds to the approval this product.

The product is a biosimilar to Clexane. In terms of comparative analyses of physicochemical and biological attributes, the drug product produced from the revised manufacturing process is considered sufficiently similar to the reference medicine, Clexane. All outstanding issues regarding physicochemical and biological comparability have now been resolved.

Proposed conditions of registration

The following conditions of registration are recommended:

Batch release testing

- a. It is a condition of registration that all batches of Enoxapo imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
- b. It is a condition of registration that up to five (5) initial batches of Enoxapo imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results <http://www.tga.gov.au/ws-labs-index>.
- c. The sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories branch. The Sponsor must contact Biochemistry.Testing@health.gov.au for specific material requirements related to the batch release testing/assessment of the product. More information on TGA testing of biological medicines is available at <https://www.tga.gov.au/publication/testing-biological-medicines>.
- d. This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.

Certified Product Details

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [<http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm>], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Final outcome

The following sets out the Delegate's decision following the AAT's remittal of the decision under review to the Minister for Health (the Minister) for reconsideration.

The decision under review was the decision by the Minister dated 13 February 2015 not to register Apotex's enoxaparin solution for injection in 20 mg/0.2 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/1 mL, 120 mg/0.8 mL and 150 mg/1 mL pre-filled syringes (the initial decision). The initially proposed tradenames have been withdrawn. The current proposed tradename is Enoxapo.

Result of reconsideration of the decision under review

1. The Delegate decided to set aside the decision under review and, in substitution for that decision, make a decision to register Enoxapo (enoxaparin sodium) solution for injection in 20 mg/0.2 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL, 100 mg/1 mL, 120 mg/0.8 mL and 150 mg/1 mL pre-filled syringes on the basis that the safety, quality and efficacy of the products have now been satisfactorily established.
2. For Apotex's enoxaparin sodium to be registered and entered on the ARTG the quality, safety and efficacy of Apotex's enoxaparin sodium must be satisfactorily established with respect to:
 - a. Physicochemical characteristics;
 - b. Immunogenicity studies, that is, immunogenicity studies assessing the interaction with PF4, and immunogenicity studies assessing other immunogenic effects;
 - c. Clinical efficacy and bioequivalence;
 - d. Clinical safety.
3. Enoxaparin meets the definition of a biological medicine, as described in the Therapeutic Goods Regulations 1990 because it is of biological origin. It has been evaluated as a biological medicine and guidelines applying to those products should apply to Apotex's enoxaparin sodium, not those of a generic medicine.
4. Subsequent to the adoption by the TGA of the EMA guideline document, EMEA/CHMP/BMWP/118264/2007 *Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins* there have been advances in the field of physicochemical characterisation such that convincing analytical data can substitute for clinical data, at least for clinical efficacy in some cases.
5. In keeping with those advances, the EMA guidance document was revised. As part of that revision clinical data requirements were amended such that clinical trial data is no longer considered essential, providing similarity of physicochemical characteristics of the biosimilar and the reference LMWH has been convincingly shown and similar efficacy and safety can be ensured by other means.

6. Additional data demonstrating the similarity of physicochemical characteristics of the product with the innovator product has now been evaluated.
7. While this application was under consideration by the AAT, the TGA continued to apply the earlier version of EMEA/CHMP/BMWP/118264/2007.⁴ The reasons provided for rejection of the application in both the initial decision letter and the internal review decision letter referred to the requirements of EMEA/CHMP/BMWP/118264/2007, and it was clear that those requirements had not been met by the data in the application.
8. Consistent with the TGA's approach to revisions to EMA guidelines that the TGA has previously adopted, the Delegate considers that the revised guideline should also be adopted by the TGA, and that its recommendations should apply to this application to register Apotex's enoxaparin sodium. The Delegate notes that the TGA has taken no view to date on the revised EMA guideline, and that no objections to the guideline revisions have been expressed by the TGA.
9. The Delegate considered the quality evaluator's report and noted that there are no objections on quality grounds to the approval of Enoxapo. The product is a biosimilar to Clexane. In terms of comparative analyses of physicochemical and biological attributes, the drug product produced from the revised manufacturing process is considered sufficiently similar to the reference medicine, Clexane. All outstanding issues regarding physicochemical and biological comparability have now been resolved.
10. To claim biosimilarity between two products the extent of similarity and the requirements to demonstrate that similarity are subjective and based on a benefit /risk approach. In the absence of compelling reasons not to, the TGA has adopted guidance documents developed by the EMA and has from time to time provided comment on the development of individual guidelines. While the FDA guidelines assess LMWHs using different criteria, the absence of a firm recommendation for clinical trials to assess efficacy and safety is common to both approaches.
11. There are substantial differences between the previous and current versions of the EMA guideline. Compared with the previous version of the guideline the revised version includes the following:
 - Generally, separate repeated dose toxicity studies are not required.
 - Pharmacodynamic properties should be investigated in a randomised, single-dose, two-way crossover and preferably double-blind study in healthy volunteers using SC administration. Since subcutaneous administration covers both absorption and elimination of LMWH, additional pharmacology studies for IV or intra-arterial use, if applicable, are not required.
 - Pivotal evidence for similar efficacy will be derived from the similarity demonstrated in physicochemical, functional and pharmacodynamic comparisons. A dedicated comparative efficacy trial is therefore not considered necessary.
 - Demonstration of biosimilarity, based on physicochemical and functional characterisation, pharmacodynamic profiles, and, where needed, safety/immunogenicity trial, will allow extrapolation to other routes of administration and indications licensed for the reference medicinal product, if applicable and appropriately justified.
 - Biosimilar and reference LMWH should exhibit convincingly similar physicochemical and functional characteristics and pharmacodynamic profiles. Under this premise, adverse effects that are related to exaggerated pharmacological effects (for example, bleeding) can be expected at similar frequencies. If, in addition, the impurity profile and the nature of excipients of the

biosimilar do not create uncertainties with regard to their impact on safety/immunogenicity, a safety/immunogenicity study may not be needed. In this case, further exploration of the immunogenic potential as suggested in Non-clinical studies should be performed.

12. The revisions to manufacturing processes, test procedures and product specifications have not been such that the revised product constitutes a new formulation. The formulation refers to the materials that make up the product together with the way those materials are put together or presented as a dosage form (including the quantities of the materials used). This does not include the method used to manufacture the therapeutic good.
13. While there is no formal definition of 'formulation' in the Regulations the TGA's application form 'Application form to register or vary the registration of prescription medicines' section on formulation refers only to active ingredients and excipients. This also includes specifications for active ingredients and excipients. The changes to manufacturing processes, test procedures and specifications have not altered the composition of the product, other than to narrow the specifications.
14. The results of the bioequivalence study conducted with the Apotex product and the innovator product prior to the manufacturing, test procedure and specification changes are accepted as applicable to the current Apotex product because those changes do not constitute a new formulation.
15. In Study ZPS-452 bioequivalence of Apotex's enoxaparin with Clexane (Australia), the innovator comparator was demonstrated, in that study the 90% CIs for the GMRs (test/reference) of AUC_{0-t} , $AUC_{0-\infty}$ and A_{max} for anti-Xa were within the predefined bioequivalence interval of 0.80 to 1.25. There were no statistically significant sequence or period effects for the three parameters.
16. For supportive purposes for the assessment of bioequivalence, the geometric data for the anti-IIa pharmacodynamic parameters showed that the 90% CIs for the GMRs (test/reference) of AUC_{0-t} and A_{max} for anti-IIa were within the pre-defined bioequivalence interval of 0.80 to 1.25. However, the GMR was not calculated for the $AUC_{0-\infty}$, as the terminal phase had not been established for most subjects due to the high inter-subject variability of the data near the terminal phase. There were no statistically significant sequence or period effects for the three parameters.
17. Having regard to the recommendations in the revised EMA guideline, the Delegate does not consider that a clinical trial to demonstrate efficacy and safety of the revised formulation is required to conclude biosimilarity of Apotex's enoxaparin sodium with Clexane.
18. Having regard to the quality evaluator's findings the Delegate considers that similar efficacy and safety can clearly be deduced from the similarity of physicochemical characteristics, biological activity/potency, and PK and/or PD profiles of the biosimilar and the reference product. In addition, the impurity profile and the nature of excipients of the biosimilar itself do not give rise to concern.
19. With regard to immunogenicity potential, the Delegate notes that a published paper included in papers presented to the AAT;⁹ did not demonstrate statistically or clinically significant differences in the incidence of heparin-induced thrombocytopenia (HIT) in patients in the USA given the innovator product, Lovenox or a generic enoxaparin product, of which four were available when the retrospective

⁹ Grampp G et al (2015). Active and passive surveillance of enoxaparin generics: A case study relevant to biosimilars. *Expert Opinion on Drug Safety* 14(3):1-12.

analysis was conducted, though none of these generic products were Apotex's enoxaparin. This strongly suggests that differences in the incidence of HIT in patients given different enoxaparin products, whether assessed using criteria for a generic medicine or for a biosimilar medicine, will be so small as to be clinically insignificant.

20. The Delegate notes that given the low incidence of HIT in patients given LMWHs it would be inappropriate to determine equivalence of incidence of this event in a clinical trial. The incidence of a rare adverse event is best examined in a post-market setting given that very large numbers of patients are required for a comparison of incidences of the event with different products.
21. The requirements of the revised EMEA/CHMP/BMWP/118264/2007 Rev 1 *Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins* are consistent with those of the TGA adopted guideline CHMP/437/04 Rev 1 *Guideline on similar biological medicinal products* in that in neither document is there an absolute requirement for a comparative clinical safety and efficacy assessment for a biosimilar product. This is dependent whether similar efficacy and safety can clearly be deduced from the similarity of physicochemical characteristics, biological activity/potency, and pharmacokinetic and/or pharmacodynamic profiles of the biosimilar and the reference product. In addition, it requires that the impurity profile and the nature of excipients of the biosimilar itself do not give rise to concern.
22. The consideration of similarity for biosimilar products does not require that there be no differences between products to conclude similarity, just as there is no requirement that there be no differences between batches of the same product. A benefit/ risk approach is taken. The Delegate is satisfied that for the current Apotex's enoxaparin product the quality, safety and efficacy of the goods have now been satisfactorily established.

For the reasons referred to above, the Delegate decided to set aside the decision under review and register Enoxapo (enoxaparin sodium) in the following presentations:

Ready-to-use, pre-filled syringes (with automatic safety lock system):

20 mg injection: enoxaparin sodium 20 mg/0.2 mL (anti-Xa: 2,000 IU)

40 mg injection: enoxaparin sodium 40 mg/0.4 mL (anti-Xa: 4,000 IU)

Ready-to-use, pre-filled syringes with graduated markings (with automatic safety lock system):

60 mg injection: enoxaparin sodium 60 mg/0.6 mL (anti-Xa: 6,000 IU)

80 mg injection: enoxaparin sodium 80 mg/0.8 mL (anti-Xa: 8,000 IU)

100 mg injection: enoxaparin sodium 100 mg/1 mL (anti-Xa: 10,000 IU)

Ready-to-use, pre-filled syringes with double graduated markings (with automatic safety lock system):

120 mg injection: enoxaparin sodium 120 mg/0.8mL (anti-Xa: 12,000 IU)

150 mg injection: enoxaparin sodium 150 mg/1 mL (anti-Xa: 15,000 IU).

indicated for:

Prevention of thromboembolic 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).

Specific conditions of registration

1. Implement the Enoxapo Australian Risk Management Plan (AUS-RMP) version 2.0, dated 22 May 2014, included with submission PM-2012-03777-1-3, and any future updates as agreed with the TGA as a condition of registration.
2. *Batch release testing & compliance with Certified Product Details (CPD)*

Batch release testing

(i) It is a condition of registration that all batches of Enoxapo imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).

(ii) It is a condition of registration that up to five (5) initial batches of Enoxapo imported into/manufactured in Australia is not released for sale until samples and/or the manufacturer's release data have been assessed and endorsed for release by the TGA Laboratories Branch. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results <http://www.tga.gov.au/ws-labs-index>.

(iii) The Sponsor should be prepared to provide product samples, reference materials and documentary evidence as defined by the TGA Laboratories branch. The Sponsor must contact Biochemistry.Testing@health.gov.au for specific material requirements related to the batch release testing/assessment of the product.

More information on TGA testing of biological medicines is available at <https://www.tga.gov.au/publication/testing-biological-medicines>.

This batch release condition will be reviewed and may be modified on the basis of actual batch quality and consistency. This condition remains in place until you are notified in writing of any variation.

Certified Product Details

The Certified Product Details (CPD), as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) [<http://www.tga.gov.au/industry/pm-argpm-guidance-7.htm>], in PDF format, for the above products should be provided upon registration of these therapeutic goods. In addition, an updated CPD should be provided when changes to finished product specifications and test methods are approved in a Category 3 application or notified through a self-assessable change.

Attachment 1. Product Information

The PI for Enoxapo 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>. The PI for other tradenames is identical except for the product name.

Therapeutic Goods Administration

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