Australian Government
Department of Health and Aged Care
Therapeutic Goods Administration

Australian Public Assessment Report for Heparin InterPharma

Active ingredient: Heparin sodium

Sponsor: InterPharma Pty Ltd

July 2024

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and Aged Care and is responsible for regulating therapeutic goods, including medicines, medical devices, and biologicals.
- 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.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to the Australian public outweigh any risks associated with the use of therapeutic goods.
- The TGA relies on the public, healthcare professionals and industry to report problems with therapeutic goods. The TGA investigates reports received to determine any necessary regulatory action.
- To report a problem with a therapeutic good, please see the information on the TGA website.

About AusPARs

- The 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. Further information can be found in Australian Public Assessment Report (AusPAR) guidance.
- AusPARs are prepared and published by the TGA.
- AusPARs are static documents that provide information that relates to a submission at a particular point in time. The publication of an AusPAR is an important part of the transparency of the TGA's decision-making process.
- A new AusPAR may be provided to reflect changes to indications or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of abbreviations

Abbreviation	Meaning
ACM	Advisory Committee on Medicines
A_{max}	Maximum observed activity
ARTG	Australian Register of Therapeutic Goods
AUAC	Area under the activity time curve
aPTT	Activated partial thomboplastin time
AT-III	Antithrombin-III
CMI	Consumer Medicines Information
CPD	Certified Product Details
DOAC	Direct oral anticoagulants
E_{max}	Maximum measured effect attributable to the drug over the specified time span
FIIa	Factor IIa
FXa	Factor Xa
IU	International units
IV	Intravenous(ly)
LMWH	Low molecular weight heparin
PI	Product Information
PPC	Pharmaceutical Partners Canada
RMP	Risk management plan
SC	Subcutaneous(ly)
TGA	Therapeutic Goods Administration
T_{max}	Time after administration of a drug when the maximum plasma concentration is reached
UFH	Unfractionated heparin
USP	United States Pharmacopoeia (Equivalent to international unit)
VKA	Vitamin K antagonist(s)
VTE	Venous Thromboembolism

Product submission

Submission details

Type of submission:	New biological entity
Product name:	Heparin InterPharma
Active ingredient:	Heparin sodium
Decision:	Approved
Date of decision:	15 November 2023
Date of entry onto ARTG:	24 November 2023
ARTG number:	394930
, *Black Triangle Scheme*	No
Sponsor's name and address:	InterPharma Pty Ltd Suite 103, 39 East Esplanade Manly NSW 2095
Dose form:	Solution for injection
Strength:	5,000 international units (IU)/0.5 mL
Container:	Pre-filled syringe
Pack size:	10
Approved therapeutic use for the current submission:	*Prophylaxis and treatment of deep vein thrombosis for use in patients 18 years and older.*
Routes of administration:	Heparin may be given by intermittent intravenous injection, intravenous infusion or deep subcutaneous injection. It should not be given intramuscularly because of the danger of haematoma formation.
Dosage:	A guide to is presented in Table 1 of the Product Information. For information regarding dosage, such as dosage schedules for prophylaxis and treatment and dosage modifications to manage adverse reactions, refer to the Product Information.
Pregnancy category:	C Drugs which, owing to their pharmacological effects, have caused or may be suspected of causing, harmful effects on the human fetus or neonate without causing malformations. These effects may be reversible. The use of any medicine during pregnancy requires careful consideration of both risks and benefits by the treating health professional. The pregnancy database must not be used as the sole basis of decision making in the use of medicines during pregnancy. The TGA does not provide advice on the use of medicines in pregnancy for specific cases. More information is available from obstetric drug information services in your state or territory.

Product background

This AusPAR describes the submission by InterPharma Pty Ltd (the Sponsor) to register Heparin InterPharma (heparin sodium) for the following proposed indication:[1]

> *Prophylaxis of and treatment of thromboembolic disorders such as thrombophlebitis, pulmonary embolism and occlusive vascular disease*
>
> *Prevention of thromboembolic complications arising from cardiac and vascular surgery, dialysis and other perfusion procedures*
>
> *Use as an anticoagulant in blood transfusions.*

The condition

In Australia at least 17,000 people develop venous thromboembolism (VTE, comprising deep vein thrombosis with or without pulmonary embolism) each year, reflecting an annual incidence of 0.83 per 1,000 population. Other estimates suggest that 60,000 to 100,000 Americans die each year of VTE. About 10% to 30% of people will die within one month of diagnosis.

The incidence of VTE in hospitalised patients is high, ranging from 10% up to 90% of admissions. These may be associated with orthopaedic and other speciality surgery, complications following cardiac or vascular surgery, or other perfusion or dialysis processes. Prophylaxis is recommended for a proportion of these patients.[2]

Current treatment options

Several treatment options are currently available for the prevention or treatment of deep vein thrombosis and pulmonary embolism, as well as for use in perfusion or dialysis situations. Treatment decisions will vary depending on whether the indication is for treatment or prophylaxis, the underlying cause of thrombosis, the location of the thrombosis, the general health of the patient, individual bleeding risk, and requirement for short term or long-term therapy.

Current pharmacological anticoagulation options[3] include:

- Unfractionated heparin sodium, intravenous (IV) or subcutaneous (SC): often preferred in situations where there is a high likelihood that anticoagulation will need to be discontinued or reversed, as it has a short half-life and a known reversal agent.
- Low molecular weight heparin (LMWH), typically SC: for example, enoxaparin, dalteparin, tinzaparin have a longer duration of effect compared to unfractionated heparin (UFH) and may have a lower bleeding risk than UFH. The comparative literature is of variable quality.
- Direct oral anticoagulants (DOAC), including oral factor Xa (FXa) inhibitors (rivaroxaban, apixaban) or direct thrombin (factor IIa (FIIa) inhibitors (dabigatran), are useful for intermediate term anticoagulation in outpatient settings, but generally not appropriate in patients with significant renal insufficiency.
- Oral vitamin K antagonists (VKA, for example, Warfarin).

[1] This is the original indication proposed by the sponsor when the TGA commenced the evaluation of this submission. It may differ to the final indication approved by the TGA and registered in the Australian Register of Therapeutic Goods.

[2] Gresele, P. et al. Heparin in the prophylaxis and treatment of venous thromboembolism and other thrombotic diseases, *Handb Exp Pharmacol*. 2012:(207): 179-209. doi: 10.1007/978-3-642-23056-1_9.

[3] Lip, G.Y.H. et al. Venous thromboembolism: initiation of anticoagulation, *UpToDate*, last updated 15 March 2023, accessed 3 August 2023.

Clinical rationale

Unfractionated heparin is a well-established product having been first described as an anticoagulant more than 100 years ago. Heparin is widely used in clinical practice and remains one of the mainstays of the prophylaxis and treatment of thromboembolic disorders.

Unfractionated Heparin is a preferred anticoagulant in clinical practice for several indications due to its safety in certain circumstances due to its short half-life and the availability of a reversal agent.

In recent years, Pfizer Australia has reported several shortages of DBL heparin sodium 5000 IU/0.2 mL injection in Australia.

Heparin is a naturally occurring mucopolysaccharide which inhibits the clotting of blood *in vitro* and *in vivo*. It enhances the rate at which antithrombin III neutralises thrombin and activated factor X (Xa). Antithrombin III also neutralises other activated coagulation factors, for example, factors IX, XI, XII and plasmin.

With low dose heparin therapy, anticoagulation appears to result from neutralisation of Xa which prevents the conversion of prothrombin to thrombin. With full dose heparin therapy, anticoagulation appears to result primarily from neutralisation of thrombin which prevents the conversion of fibrinogen to fibrin. Full dose heparin therapy also prevents the formation of a stable fibrin clot by inhibiting activation of fibrin stabilising factor.

Regulatory status

Australian regulatory status

This product is a new biological entity for Australian regulatory purposes.

International regulatory status

At the time the TGA considered this submission, the Sponsor had applied for approval of heparin sodium to other regulatory agencies. Table 1 summarises these submissions and provides the indications where approved.

Table 1: International regulatory status of Heparin InterPharma

Region	Submission date	Status	Approved indications
Canada	9 December 2015	Approved on 18 August 2016	*For administration by subcutaneous (SC) injection:* • *Prophylaxis of venous thrombosis and its extension* • *Prophylaxis of pulmonary embolism* • *Prophylaxis of thromboembolic complications associated with atrial fibrillation* • *Prophylaxis of peripheral arterial embolism*

Region	Submission date	Status	Approved indications
United States	31 October 2016	Approved on 19 November 2018	*For administration by SC and intravenous (IV) injection:* • *Anticoagulant therapy in prophylaxis and treatment of venous thrombosis and its extension;* • *Low-dose regimen for prevention of postoperative deep venous thrombosis and pulmonary embolism in patients undergoing major abdominothoracic surgery who are at risk of developing thromboembolic disease,* • *Prophylaxis and treatment of pulmonary embolism;* • *Atrial fibrillation with embolization;* • *Treatment of acute and chronic consumptive coagulopathies (disseminated intravascular coagulation);* • *Prevention of clotting in arterial and cardiac surgery;* • *Prophylaxis and treatment of peripheral arterial embolism;* • *Heparin may also be employed as an anticoagulant in blood transfusions, extracorporeal circulation, and dialysis procedures*
European Union	10 December 2019	Withdrawn on 27 October 2020	*Prophylaxis of thromboembolic disorders in adults*

Registration timeline

This submission was evaluated under the standard prescription medicines registration process.

Table 2 captures the key steps and dates for this submission.

Table 2: Registration timeline for Heparin InterPharma (submission no. PM-2022-03499-1-3) – Key Dates.

Description	Date
Submission dossier accepted and first round evaluation commenced	4 October 2022
First round evaluation completed	10 March 2023
Sponsor provides responses on questions raised in first round evaluation	15 June 2023

Description	Date
Second round evaluation completed	15 August 2023
Sponsor's notification to the TGA of errors/omissions in evaluation reports	29 August 2023
Delegate's[4] Overall benefit-risk assessment and request for Advisory Committee advice	5 September 2023
Sponsor's pre-Advisory Committee response	22 September 2023
Advisory Committee meeting	5 and 6 October 2023
Registration decision (Outcome)	15 November 2023
Administrative activities and registration in the ARTG completed	24 November 2023
Number of working days from submission dossier acceptance to registration decision*	214

*Statutory timeframe for standard submissions is 255 working days

Submission overview and risk/benefit assessment

A summary of the TGA's assessment for this submission is provided below.

Relevant guidelines or guidance documents referred to by the Delegate are listed below:

- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Clinical Investigation of Medicinal Products for Prophylaxis of High Intra- and Post-operative Venous Thromboembolic Risk, CPMP/EWP/707/98 Rev. 1, 15 November 2007.
- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins, EMEA/CHMP/BMWP/14327/2006, 13 December 2007.
- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on the Investigation of Bioequivalence, CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **, 20 January 2010.
- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Similar Biological Medicinal Products, CHMP/437/04 Rev 1, 23 October 2014.
- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Active Substance: Non-clinical and Clinical Issues, EMEA/CHMP/BMWP/42832/2005 Rev 1, 18 December 2014
- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Similar Biological Medicinal Products Containing

[4] In this report the 'Delegate' is the Delegate of the Secretary of the Department of Health and Aged Care who decided the submission under section 25 of the Act.

Biotechnology-derived Proteins as Active Substances: Quality Issues (Revision 1), EMA/CHMP/BWP/247713/2012, 22 May 2014.

- European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Similar Biological Medicinal Products Containing Low-molecular-weight-heparins, EMEA/CHMP/BMWP/118264/2007, 24 April 2008.

Quality evaluation summary

The application and the supporting data relating to the composition, development, manufacture, quality control, stability and bioavailability of the product were assessed and checked for compliance, as applicable, with Australian legislation and requirements for new medicines and in accordance with pharmacopoeial standards and the technical guidelines adopted by the TGA.

The product is the sodium salt of a sulfated polysaccharide belonging to the family of glycosaminoglycans. Heparin is an unbranched, linear polysaccharide constituted by alternating 1,4-linked uronic acid and α-D-glucosamine residues.

The finished product is presented in a prefilled syringe for subcutaneous injection or intravenous infusion containing 5,000 IU heparin sodium as active substance. Other ingredients are sodium hydroxide (for pH-adjustment), hydrochloric acid (for pH-adjustment) and water for injection.

The overall quality of the active substance was demonstrated via adequate control of the starting material, control of critical steps and intermediates, process validation, extensive characterisation, control of impurities and contaminants, generation of robust reference materials and batch analyses that covered multiple manufacturing campaigns.

The product is available in a ready-to-use non-graduated sterile 1 mL siliconised glass syringe with a needle, protected by a needle shield. Syringes are distributed in blisters inside a carton box (one syringe per blister and 10 blisters per box).

The sponsor has proposed the shelf-life of 24 months when stored below 25°C. Based upon stability data submitted by the sponsor, the recommended shelf life and storage conditions of the drug product is 24 months below 25°C Do not refrigerate or freeze.

All characterisation and extended characterisation parameters met the limits outlined in the relevant monograph. Testing results were found to be within ±10% of the acceptance criteria of the British Pharmacopeia monograph for heparin sodium injection. This is considered acceptable from a quality perspective.

There are no objections on quality grounds to the registration of Heparin InterPharma (heparin sodium) 5000 IU in 0.5 mL solution for injection.

Nonclinical (toxicology) evaluation summary

The nonclinical dossier consisted of three *in vitro* comparative pharmacodynamic studies conducted by the sponsor, and published literature reports to support other aspects of the nonclinical review. There were no objections to registration of Heparin InterPharma on nonclinical grounds, however this was contingent on supportive evaluations of efficacy and immunogenicity of the product comparable to already registered heparin sodium products.

Two studies compared *in vitro* physicochemical and potency factors of Heparin InterPharma (heparin sodium) injection, 5,000 IU/0.5 mL, DBL Heparin Sodium 5,000 IU/0.2 mL injection BP ampoule (Pfizer), Heparin-Natrium-5000-Ratiopharm 5,000 IU/0.2 mL (RatioPharm GmBH),

and Heparin Sodium Injection (Fresenius Kabi/Pharmaceutical Partners Canada (PPC). Differences in anti-FIIa and anti-FXa activities were slightly greater when compared to the DBL product than with other comparators, but the anti-FIIa to anti-FXa activity ratio was highly similar across all comparator products (Range: 0.97, 1.03). While there was some variability in anti-FXa and anti-FIIa activity among the products, all are considered effective heparin products in comparable jurisdictions.

A further study demonstrated comparable neutralisation by protamine sulfate of heparin activity for both the InterPharma and comparator PPC heparin sodium products. Heparin neutralisation assays using platelet factor 4 or protamine showed neutralisation was qualitatively similar. However, the nonclinical evaluation questioned whether this assay was sensitive enough or adequately validated to identify meaningful differences between the two heparins.

The nonclinical evaluation recommended that, should Heparin InterPharma be registered, several changes were required to the draft Product Information. The sponsor accepted the recommended changes.

Clinical evaluation summary

Summary of clinical studies

The clinical submission was based on published literature identified using a systematic literature search strategy approved by the TGA. Bridging to the Heparin InterPharma product was claimed based on the nonclinical studies described above, and one clinical pharmacology study, Study HPI-P3-740.

Study HPI-P3-740 was a single centre, randomised, single dose, blinded, 2-period, 2-sequence, crossover design in healthy male subjects to compare the pharmacokinetics and pharmacodynamics and thus the equivalence of Sterinova Heparin Sodium Injection 5,000 IU/0.5 mL (Sterinova, Canada, the same product as Heparin InterPharma) and Heparin Sodium Injection 5,000 IU/0.5 mL (PPC, Canada), after a single IV bolus administration.

The clinical evaluation supported registration of InterPharma heparin sodium injection for a limited restricted indication as below, subject to negotiation of an acceptable PI:

Prophylaxis and treatment of deep vein thrombosis in patients 18 years and older.

Pharmacology

Heparin is a complex glycosaminoglycan composed of chains of alternating d-glucosamines and hexuronic acid (glucuronic acid and its epimer iduronic acid) residues. The unique pentasaccharide (GlcNAc/NS(6S)-GlcA-GlcNS(3S,6S)-IdoA(2S)-GlcNS(6S) element and presence and location of O-sulphate groups, in particular a 3-O-sulphate substituent, is essential for the anticoagulant activity of heparin.

The molecular weight of UFH varies between 3 to 30 kDa, with a peak around 15 kDa. Along with its natural structural diversity and variability, a somewhat varying anticoagulant efficacy of different heparin batches may occur.

Pharmacokinetics

Heparin is poorly absorbed from the gastrointestinal tract and IV and SC routes of administration are preferred. Peak plasma concentration of heparin (Time after administration

of a drug when the maximum plasma concentration is reached (T_{max})) was achieved two hours following SC injection of 10 000 IU of radio labelled UFH. About one third of an administered dose of UFH binds to antithrombin-III (AT-III) *in vivo*, responsible for most of the anticoagulant activity. The bioavailability of SC UFH decreases when doses less than 35,000 IU/24 hour are used. At high doses, anti-FXa activity increases with increasing dose.

Clearance of UFH occurs by two major pathways, a rapidly saturable phase that involves binding of UFH to receptors on endothelial cells and macrophages which results in depolymerisation of the heparin, and a slower mechanism via renal clearance. Heparin is also partially metabolised to uroheparin by heparinase in the human liver. Uroheparin has limited AT-III binding activity.

The half-life of UFH therefore varies based on the dose and route of administration. Reports include a half-life of 30 min following an intravenous bolus dose of 25 IU/kg, of 60 min with a bolus of 100 IU/kg, and 150 min with a bolus of 400 IU/kg.

Heparin clearance is also dependent on molecular size. Higher molecular-weight species are cleared from the circulation more rapidly than the lower molecular-weight species. This differential clearance results in an accumulation *in vivo* of the lower molecular-weight species that have a reduced ratio of AT-III to anti-FXa activity. The half-life of heparin might be either increased or decreased in patients with liver disorders. With severe renal impairment, the half-life of heparin may be slightly prolonged. Men clear heparin more rapidly than women.

Pharmacodynamics

The anticoagulant effect of heparin is mainly due to interaction with coagulation factors and inhibitors. The major plasma coagulation inhibitor is AT-III, which targets activated coagulation factors. Heparin increases the rate of this inhibition, but in a manner that is dependent on its dose. The negatively charged heparin binds to positively charged residues on AT inducing a conformational change that converts AT from a slow to a rapid inhibitor of serine proteases. Thrombin and FXa are most responsive to the effects of heparin/AT-III complex inhibition. Heparin also has some effect on platelet function, inhibits formation of a stable fibrin clot, and has antilipaemic effects. By inactivating thrombin or attenuating its generation, heparin not only prevents fibrin formation but also inhibits thrombin-induced activation of platelets and coagulation factors V, VIII and XI.

Study HPI-P3-740

Study HPI-P3-740 was a blinded, randomised, single dose, 2-period, 2-sequence, crossover design in healthy male subjects The objective was to compare the pharmacokinetics and pharmacodynamic profiles and assess the equivalence of two formulations of heparin after a single IV bolus administration. Anti-FXa activity was the primary pharmacodynamic surrogate to assess the therapeutic equivalence of heparin. Activated partial thomboplastin time (aPTT) was assessed as a secondary pharmacodynamic parameter. The study was conducted between 17 October 2014 and 16 December 2014 in Canada.

The study enrolled 30 participants of whom one discontinued. Six participants were excluded from the anti-FXa pharmacokinetic and/or aPTT pharmacodynamics analyses after completing the study, for medication dose error (one participant), analytic reasons (three participants), or sample collection problems (two participants).

A single dose of 5000 USP (United States Pharmacopoeia (Equivalent to IU)) units (0.5 mL) of heparin sodium (test or reference) was administered in each study period. The drug administrations were separated by a wash-out of seven or eleven calendar days. Blood samples for anti-FXa activity and for aPTT were collected from each participant pre-dose and at various intervals up to six hours following the injection.

The pre-determined bioequivalence margin was set at 80% to 125%, based on the geometric least square mean ratio of the natural log-transformed maximum observed anti-FXa activity (A_{max}) of the reference product (PPC) and test product (Sterinova/InterPharma). Comparisons were also performed for the cumulative area under the FXa activity time curve (AUAC) of the reference and test products. Both A_{max} (IU/mL) and AUAC (IU.h/mL) with the test product were statistically significantly higher than with the reference product but upper and lower 90% confidence intervals fell within the pre-determined bioequivalence range. The investigator concluded that the statistically significant differences between the treatments had no impact on the bioequivalence assessment. Median T_{max} for both products was 5 minutes. The sponsor reported this to be comparable to reports of heparin pharmacokinetics in the published literature.

Table 3: Summary of the statistical analysis of anti-Xa activity

PARAMETER	INTRA-SUBJECT C.V. (%)	GEOMETRIC LSMEANS *		RATIO (%)	90% CONFIDENCE LIMITS (%)	
		TEST (n=24)	REFERENCE (n=24)		LOWER	UPPER
Anti-Xa A_{max}	5.7	1.4176	1.2959	109.40	106.32	112.57
$AUAC_{0-T}$	7.4	2.3261	2.0510	113.42	109.32	117.66

Abbreviations: A_{max} = maximum observed activity; $AUAC_{0-T}$ = cumulative area under the activity-time curve calculated from 0 to the last quantifiable effect; C.V. = coefficient of variation; Xa = factor Xa.

* Units are United States Pharmacopoeia (USP) units/mL for anti-Xa A_{max} and USP units·h/mL for $AUAC_{0-T}$.

Although direct comparisons across different studies should be examined with caution, Schmitt (2015)[5] reported maximum observed anti-FXa activity of 1.84 IU/mL for their UFH after IV dosing, and area under the concentration time curve from time zero to time of last quantifiable serum concentration (AUC_{last}) of 2.47 IU.h/mL. It is worth noting that anti-FXa activity of 0.3 to 0.7 IU/mL is considered therapeutic. In an unrelated report,[6] estimates of anti-FXa activity in porcine mucosa sourced from three different manufacturers, including Bioibérica,[7] ranged from 195 to 210 U/mg, supporting that there is a level of acceptability of variability of activity among different heparin products.

Measures of aPTT post dose exceeded the limit of the analytic procedure (180 sec) in both reference and test participant groups. The investigator stated that in this situation it was not possible to reliably estimate the maximum measured effect over the specified time span (E_{max}). Noting this, the pharmacodynamic parameters as calculated (baseline adjusted) are presented below.

[5] Schmitt, C. et al. Absence of pharmacodynamic interaction between inclacumab and heparin in healthy smokers, *J Cardiovasc Pharmacol*. 2015;65(4):386-92. doi: 10.1097/FJC.0000000000000211.

[6] Bertini, S. et al. Characterization of PF4-Heparin Complexes by Photon Correlation Spectroscopy and Zeta Potential, *Clin Appl Thromb Hemost*. 2017;23(7):725-734. doi: 10.1177/1076029616685430.

[7] The single source of porcine-derived mucosa for the manufacturer of Heparin InterPharma

Table 4: Summary of the statistical analysis of activated partial thomboplastin time-baseline corrected (all subjects)

Parameter	Intra-Subject C.V. (%)	Geometric LSmeans[a]		Ratio (%)	90% Confidence Limits (%)	
		Test (n=27)	Reference (n=27)		Lower	Upper
E_{max}	1.3	143.9	143.6	100.18	99.57	100.79
$AUEC_{0-T}$	6.5	270.3	256.6	105.34	102.20	108.57

Abbreviations: $AUEC_{0-T}$ = cumulative area under the effect-time curve calculated from 0 to the last quantifiable effect using the linear trapezoidal method; C.V. = coefficient of variation; E_{max} = Maximum measured effect over the time span specified; LS = least square.

a. Units are sec for E_{max} and sec·h for $AUEC_{0-T}$

Given this limitation of the assessment, the comparative data is presented only for information. The sponsor however emphasises that the results are comparable to other assessments of heparin effect on aPTT in the published literature.

Efficacy

No clinical efficacy studies were performed with the proposed product. A comprehensive clinical literature review identified 799 published reports of which 88 were appropriately selected for detailed review. These included nine systematic reviews or meta-analyses and 23 reports of controlled clinical trials which in early trials compared the efficacy of UFH and no treatment, or in later trials compared the efficacy of UFH with a range of alternative treatments (predominantly LMWH). Additional supportive literature included several general reviews, clinical guidance documents and book chapters. The reports confirm that heparin has been used in the treatment and prophylaxis of VTE following a range of surgical procedures. Both IV and SC administration of UFH were confirmed as effective.

The clinical evaluation noted '*There are several brands of unfractionated heparin used in the studies. The brand and even the source (porcine/bovine) is not always given and in reviews/meta-analyses it is almost always not distinguished…*'. Notwithstanding this concern, the published literature was acknowledged to have provided sufficient evidence of efficacy to support the use of UFH for prophylaxis and treatment of deep vein thrombosis, but the evidence for prevention of conditions including thrombophlebitis, pulmonary embolism and vascular occlusive disease was less conclusive.

Safety

A comprehensive literature review confirmed that bleeding is the most frequently associated adverse event with heparin. Bleeding risk varies considerably with the nature of any surgical procedure, the underlying disease and health of the patient, and other patient factors including age, obesity, and renal function. The most serious adverse event is heparin-induced thrombocytopaenia type II that normally manifests within 10 to 14 days of dosing. Anaphylactic or allergic reactions are relatively rare and may be associated with contaminants or excipients, rather than heparin itself. Osteoporosis or osteopaenia have been reported, usually with prolonged use. Heparin is generally safe in pregnancy and sometimes indicated in pregnant women with certain hypercoagulable conditions. Other reported adverse events include heparin-induced thrombocytopaenia type I, local irritation, skin necrosis, hypoaldosteronism and hypereosinophilia, usually short-term and clinically manageable. Immunogenicity of UFH

from different porcine sources has not been studied in detail and there have been no major safety concerns reported with any specific porcine-derived heparin.

Most of the presented safety data compared the relative risk of adverse events with UFH compared to LMWH. Canadian post-marketing reports of adverse events with the proposed product have not identified any new or increasing safety concerns.

The clinical evaluation concluded that '*while the sponsor's particular Unfractionated heparin is unlikely to feature in most if not all of the clinical literature, the general nature of the literature suggests that many of the authors and all the reviewers consider that the literature would apply to any unfractionated heparin*'.

Other

Real world data included in the submission consisted of post-marketing safety reports.

Risk management plan evaluation summary

The sponsor is required to comply with product vigilance and risk minimisation requirements.

The TGA decided a risk management plan (RMP) was not required for this submission in accordance with TGA guidelines for biosimilar submission. The RMP that the sponsor has submitted will not be evaluated unless issues are identified during the evaluation process for which an RMP evaluation may be warranted, or if the Delegate requests it.

See TGA's guidance on 'when an RMP is required'.

The TGA may request an updated RMP at any stage of a product's life-cycle, during both the pre-approval and post-approval phases. Further information regarding the TGA's risk management approach can be found in risk management plans for medicines and biologicals and the TGA's risk management approach. Information on the Australia-specific annex (ASA) can be found on the TGA website.

Risk-benefit analysis

Delegate's considerations

The Delegate notes that while this product has been authorised in the Canada and in the United States of America, the European Union decentralised evaluation resulted in withdrawal of a submission for this product.

The proposed UFH product, Heparin InterPharma, is manufactured by the same manufacturer applying the same materials and processes as a Sterinova product marketed in Canada for seven years. Strictly speaking this history of use does not satisfy TGA requirements for a literature-based submission or mixed approach to registration, where a history of ten years is generally required. However, various UFH solutions have been in use in Australia and in multiple comparable jurisdictions for several decades. To date there does not appear to be significant literature expressing concern with changes from one brand or source of UFH to another, other than a collective move away from UFH of bovine origin owing to concerns regarding transmission of bovine spongiform encephalopathy. The Delegate drew on guidance regarding requirements for a new chemical entity, and the following key principles from biosimilars guidance adopted by the TGA, while considering this submission:

- *'The Marketing Authorisation (MA) application dossier of a biosimilar medicinal product shall provide a full quality dossier together with data demonstrating comparability with the reference medicinal product by using appropriate physico-chemical and in vitro biological tests, non-clinical studies and clinical studies.'*[8]
- *'Demonstration of comparable efficacy and safety in surgical patients at high risk for VTE as recommended may allow extrapolation to other indications of the reference medicinal product if appropriately justified by the applicant.'*[9]
- *'If biosimilarity has been demonstrated in one indication, extrapolation to other indications of the reference product could be acceptable with appropriate scientific justification.'*[10]

As previously noted, this submission is not a biosimilar application. UFH solutions 'grandfathered' on to the Register in Australia 30 years ago may not have been subjected to the current standards for evidence applied to new chemical entities and therefore new efficacy or safety information may be available for the proposed product, which should be included in the product information. The TGA agreed to accept reports of studies of similarity to other heparin products, in addition to a full manufacturing and quality package and reports for other UFH in published literature as appropriate evaluable data, that with justification may support clinical equivalence between the proposed UFH product and earlier-registered products.

Absolute biosimilarity is difficult to prove when a product such as UFH is intrinsically variable. UFH consists of a mixture of different length chains of polysaccharides, which vary in molecular weight and in relative content and location of active O-sulphate groups necessary for activity. Different batches of UFH from the same manufacturer from similar starting material can vary in relative effectiveness. The relative immunogenicity of an UFH product could also vary between brands or even between batches of the same brand of product, which is an important consideration. UFH, specifically as an IV medication, is typically commenced and used in a hospital setting and there is limited information publicly available regarding brand 'substitutions' at the hospital pharmacy level. Further, while shortages of UFH requiring substitution with other unregistered brands have been relatively regularly reported, there have been minimal if any reports of adverse events of greater severity or seriousness occurring more frequently with one brand of UFH than another.

The CHMP clinical guideline[8] considers that in exceptional cases, a confirmatory clinical trial (for bioequivalence between a biosimilar and a reference product) may be waived if alternative robust evidence for comparability is available. The sponsor has chosen to provide results of *in vitro* and/or *in vivo* comparisons with internationally and or Australian registered products as justification of the relevance of published literature to the proposed product. Critical to the argument for comparability is a published report by Hogwood and colleagues,[11] which compared the anticoagulant properties of a range of different heparin-containing tissues (starting materials prior to manufacture of commercial heparin) including porcine mucosa supplied by Bioibérica. While the study focussed on the ability of protamine sulfate to neutralise heparin from different tissues, it does provide support for an argument that the activities of

[8] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Similar Biological Medicinal Products Containing Biotechnology-derived Proteins as Active Substance: Non-clinical and Clinical Issues, EMEA/CHMP/BMWP/42832/2005 Rev 1, 18 December 2014

[9] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Similar Biological Medicinal Products Containing Low-molecular-weight-heparins, EMEA/CHMP/BMWP/118264/2007, 24 April 2008.

[10] European Medicines Agency (EMA), Committee for Medicinal Products for Human Use (CHMP), Guideline on Similar Biological Medicinal Products, CHMP/437/04 Rev 1, 23 October 2014.

[11] Hogwood, J. et al. Precipitation and Neutralization of Heparin from Different Sources by Protamine Sulfate, *Pharmaceuticals (Basel)*. 2017;10(3):59. doi: 10.3390/ph10030059.

different porcine tissue derived heparins are broadly comparable. Finished product standards are applied to further manufacturing steps.

The same guidance recommends that a significant difference within a justified acceptance range for a pharmacokinetic or pharmacodynamic parameter should be explained and justified. An equivalence margin of 80% to 125% is generally accepted for generic drug comparisons. It would seem appropriate that the same margin is applied to comparisons of biological medicines manufactured by two different manufacturers. However, the sponsor does not appear to have addressed why in Study HPI-P3-740 the Anti-FXa A_{max} and cumulative area under the activity time curve calculated from 0 to the last quantifiable concentration ($AUAC_{0-T}$) are statistically significantly higher in the proposed product compared to the reference.

An additional question that this submission raises is related to the intersection of registration of a new chemical entity, which in the normal case would present a 'new' product information form, with registration of a biosimilar, which would be expected to adopt the product information of the reference product.

The proposed product information appears to be a blend of currently approved product information for a registered UFH product (either in Australia or elsewhere) and additional data based on submitted literature. The newer literature does not always align with the information in 'older' product information documents, as has been noted by the clinical evaluation. While some clinical studies performed since the 'grandfathering' of heparin sodium products (usually as the active comparator for a newer anti-coagulant approach) have confirmed its efficacy and safety in some indications, the use of UFH in other indications has less confirmatory information, if any. The problematic issue then, for a new chemical entity, is which if any of the proposed indications should be included in the product information. If the TGA considers that the dossier presents sufficient evidence of quality, safety and efficacy of Heparin InterPharma in one use, sensible application of the appropriate and relevant guidelines on biosimilars could support extrapolation to other indications. This would not be straightforward as UFH products authorised in Australia and elsewhere do not share all the indications.

It appears to this Delegate that even though there is a long history of clinical efficacy and safety of a range of porcine-derived UFH products, which may provide sufficient evidence to support this application, the justification of the relevance of this mixed data to the proposed product could have been more robust. On the other hand, module evaluations have noted the deficiencies but have not recommended rejection of the submission, and the clinical evaluation has pointed out: *'…while the sponsor's particular unfractionated heparin is unlikely to feature in most if not all of the clinical literature, the general nature of the literature suggests that many of the authors and all the reviewers consider that the literature would apply to any unfractionated heparin*'.

Proposed action

The sponsor has provided a dossier for this atypical submission for registration that addresses the key issues of clinical safety and efficacy by presenting a literature review and limited comparability (physical and pharmacodynamic) studies rather than a standalone head-to-head clinical study in a relevant patient population with a placebo or active control (alternative heparin).

It is likely that the long history of use of various heparin sodium solutions from a range of manufacturers in multiple comparable jurisdictions provides sufficient evidence of safety and efficacy of UFH of porcine origin in multiple indications. Evidence for absolute biosimilarity between the different products and the proposed Heparin InterPharma product is not required and has not been established. *In vitro* and *in vivo* studies with the proposed product, in the

context of published reports appear to support 'comparability' with UFH products authorised here and internationally.

Standard dosing approaches for UFH are implemented within and across different hospitals but ultimately dosing is individualised. Particularly in the case of IV use, ongoing dosing is linked to validated laboratory measurements of clotting. Individual patient factors, as well as the variability intrinsic to heparin itself may affect these measurements between products and between batches of the same product.

Pending consideration by the Advisory Committee for Medicines, the Delegate is inclined to approve the registration of Heparin InterPharma (heparin sodium) 5000 IU/0.5 mL solution for injection as a new chemical entity. If approved, the authorised indications will be subject to negotiation.

Advisory committee on medicines considerations

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

Specific advice to the Delegate

1. ***What is the opinion of the Committee regarding the adequacy of the comparability data provided to bridge efficacy and safety data from the published literature to the proposed product?***

The ACM agreed that the literature provided within the dossier relates to heparin in general rather than to the proposed product. The ACM noted deficiencies of the data, including limitations identifying the brand and source of UFH within some of the literature.

The ACM acknowledged the natural variability in heparin both between products and between batches and the challenges this can create for bridging.

The ACM also considered the current long history of use of grandfathered products in Australia and the safe use of this product in Canada and the United States over the past 4 to 6 years.

On balance, and when considering real world evidence and the long history of use of UFH, the ACM was of the view that there is adequate evidence of safety and efficacy available to support the proposed product.

2. ***If the supporting clinical studies using intravenous administration of heparin are considered acceptable, can suitability for intravenous use be extrapolated to suitability for subcutaneous use in relevant indications?***

The ACM was of the view that it is appropriate for the suitability of IV use to be extrapolated to suitability for SC use.

The ACM noted that the efficacy of UFH is predominately related to how quickly the activated partial thromboplastin clotting time (aPPT) is elevated to within the therapeutic range rather than the route of administration. Clinicians are familiar with monitoring and adjusting heparin to therapeutic effect when using either SC or IV routes of administration.

The ACM discussed the use of IV and SC administration of UFH and noted that in general the SC route is mainly used for prophylaxis, while the IV route is generally used for treatment. Further noting that given other treatment options IV administration of UFH would likely be limited to a small group of patients.

3. If Heparin InterPharma was approved for registration, what is the opinion of the Committee on extrapolation of the supported indication to all indications currently approved for the Australian registered product?

On balance the ACM was supportive of including the majority of the established indications currently approved for the Australian registered product. The ACM noted that thrombophlebitis should not be included within the indication as it is not treated with an anticoagulant.

In this instance the ACM was of the view that a pragmatic approach was warranted and considered the historical evidence supporting the use of heparin for these established indications.

The indications proposed by the ACM are:

> *Prophylaxis and treatment of thrombotic and thromboembolic disorders such as ~~thrombophlebitis~~, pulmonary embolism and occlusive vascular disease including deep vein thrombosis for use in patients 18 years and older.*
>
> *Prevention of thromboembolic complications arising from cardiac and vascular surgery, dialysis and other perfusion procedures.*
>
> *Use as an anticoagulant in blood transfusions.*

The ACM suggested that limiting Heparin InterPharma to the single indication 'Prophylaxis and treatment of deep vein thrombosis in patients 18 years and older' would be an impractical approach for clinical practice noting the current well-established uses of heparin.

The ACM acknowledged the regulatory challenges associated with this approach noting the deficiencies in the submitted literature based clinical data set and the requirement to satisfactory establish efficacy.

The ACM supported the inclusion of a statement within the PI to highlight the limited and largely historical evidence base. For example:

> *There is no data comparing heparin to placebo, and data comparing heparin to alternate anticoagulation has resulted in much anticoagulation therapy delivered by LMWH and OAC* [oral anticoagulant] *alternatives (both DOAC and VKA). Nonetheless, clinical situations where UFH may be the clinician anticoagulant of choice are recognized to exist.*

4. Other advice

The ACM noted that Heparin InterPharma is proposed for use in patients over 18 years of age as it is to be supplied within the pre-filled syringe and dosing would be challenging for paediatrics. The ACM commented that UFH is used within the paediatric population and identified the importance of availability of products in this population.

The ACM noted numerous suggested updates to both the PI and CMI to improve accuracy and readability.

ACM conclusion

The ACM considered this product to have an overall positive benefit-risk profile for the indication:

> *Prophylaxis and treatment of thrombotic and thromboembolic disorders such as pulmonary embolism and occlusive vascular disease including deep vein thrombosis for use in patients 18 years and older.*
>
> *Prevention of thromboembolic complications arising from cardiac and vascular surgery, dialysis and other perfusion procedures.*

Use as an anticoagulant in blood transfusions.

Outcome

Based on a review of quality, safety, and efficacy, the TGA decided to register Heparin Interpharma (heparin sodium) 5,000 IU/0.5 mL, solution for injection, pre-filled syringe, indicated for:

Prophylaxis and treatment of deep vein thrombosis for use in patients 18 years and older.

Specific conditions of registration applying to these goods

- Laboratory testing and compliance with Certified Product Details (CPD)
  - All batches of Heparin InterPharma (heparin sodium) supplied in Australia must comply with the product details and specifications approved during evaluation and detailed in the CPD.
  - When requested by the TGA, the sponsor should be prepared to provide product samples, specified reference materials and documentary evidence to enable the TGA to conduct laboratory testing on the product. Outcomes of laboratory testing are published biannually in the TGA Database of Laboratory Testing Results
- Certified Product Details

  The CPD, as described in Guidance 7: Certified Product Details of the Australian Regulatory Guidelines for Prescription Medicines (ARGPM) 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.

Product Information

The Product Information (PI) approved with this submission for Heparin InterPharma which is referred to in this AusPAR (and can be accessed on this AusPAR's webpage) may have been superseded. For the most recent PI and Consumer Medicines Information (CMI), please refer to the TGA PI/CMI search facility.

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Reference/Publication #