



**Australian Government**  
**Department of Health**  
Therapeutic Goods Administration

# Australian Public Assessment Report for Enoxaparin sodium

Proprietary Product Name: Crusia-AFT, Crusia-AFT Forte

Sponsor: AFT Pharmaceuticals Pty Ltd

**November 2017**

**TGA** Health Safety  
Regulation

## About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance) when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <<https://www.tga.gov.au>>.

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- 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
$^1\text{H}$	Proton
Ab	Antibody
ACM	Advisory Committee on Medicines
ACPM	Advisory Committee on Prescription Medicines
ADEC	Australian Drug Evaluation Committee
AE	Adverse event
ANDA	Abbreviated New Drug Application
Anti-FIIa <sub>max</sub>	Maximal anti-factor IIa concentration
Anti-FXa <sub>max</sub>	Maximal anti-factor Xa concentration
APTT	Activated partial thromboplastin time
ARTG	Australian Register of Therapeutic Goods
ASA	Australian Specific Annex
AT	Anti-thrombin
AUC	Area under the curve
AUEC <sub>0-inf</sub>	Area under the effect curve from dosing to infinity
AUEC <sub>0-t</sub>	Area under the effect curve from dosing to time of last sample
BMI	Body mass index
CHMP	Committee for Medicinal Products for Human Use
C <sub>max</sub>	Maximum plasma concentration
CMC	Chemistry, Manufacturing and Controls
Da	Dalton
DLP	Data lock point
DVT	Deep vein thrombosis
EMA	European Medicines Agency

Abbreviation	Meaning
EPAR	European Public Assessment Report
EU	European Union
FcγIIa	Gamma Fc region receptor IIa
FDA	Food and Drug Administration
FII	Factor II
FXa	Factor Xa
HIT	Heparin induced thrombocytopenia
HSQC	Heteronuclear single quantum coherence
ICH	International Conference on Harmonisation
IFN-γ	Interferon gamma
IgG	Immunoglobulin G
IL-1β	Interleukin 1 beta
IU	International Units
IV	Intravenous
LMWH	Low molecular weight heparin
LPS	Lipopolysaccharide
LS	Least squares
NMR	Nuclear magnetic resonance
PBMC	Peripheral blood mononuclear cells
PCI	Percutaneous coronary intervention
PD	Pharmacodynamics
PF4	Platelet factor 4
Ph. Eur.	European Pharmacopoeia
PI	Product Information
PK	Pharmacokinetics
PSC	Pharmaceutical Subcommittee

Abbreviation	Meaning
R <sub>AU</sub> EC	Ratio of area under the effect curves
RMP	Risk Management Plan
SC	Subcutaneous
SmPC	Summary of Product Characteristics
STEMI	ST-segment elevation myocardial infarction
TAFI	Thrombin actifiable fibrinolysis inhibitor
TFPI	Tissue factor pathway inhibitor
T <sub>max</sub>	Time to maximum concentration
TNF $\alpha$	Tumour necrosis factor alpha
UFH	Unfractionated heparin
US	United States
VTE	Venous thromboembolism

**Submission details**

<i>Type of submission:</i>	New biosimilar entity
<i>Decision:</i>	Application withdrawn by the sponsor
<i>Date of withdrawal:</i>	6 April 2017
<i>Date of entry onto ARTG</i>	Not applicable
<i>Active ingredient:</i>	Enoxaparin sodium
<i>Product name:</i>	Crusia-AFT; Crusia-AFT Forte
<i>Sponsor's name and address:</i>	AFT Pharmaceuticals Pty Ltd 113 Wicks Rd, North Ryde NSW 2113
<i>Dose form:</i>	Solution for injection
<i>Strengths:</i>	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
<i>Container:</i>	Pre-filled syringe
<i>Pack sizes:</i>	Not applicable
<i>Approved therapeutic use:</i>	Not applicable
<i>Routes of administration:</i>	Subcutaneous injection; intravenous injection
<i>Dosage:</i>	Not applicable
<i>ARTG numbers:</i>	Not applicable

**Product background**

This AusPAR describes the application by the sponsor to register Crusia-AFT and Crusia-AFT Forte<sup>1</sup> pre-filled syringe, containing enoxaparin sodium in solution for injection, for the indications listed below.

*'Crusia-AFT and Crusia-AFT Forte are indicated for:*

*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.*

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<sup>1</sup> Products often referred to as 'Crusia' only when discussed together in this AusPAR.



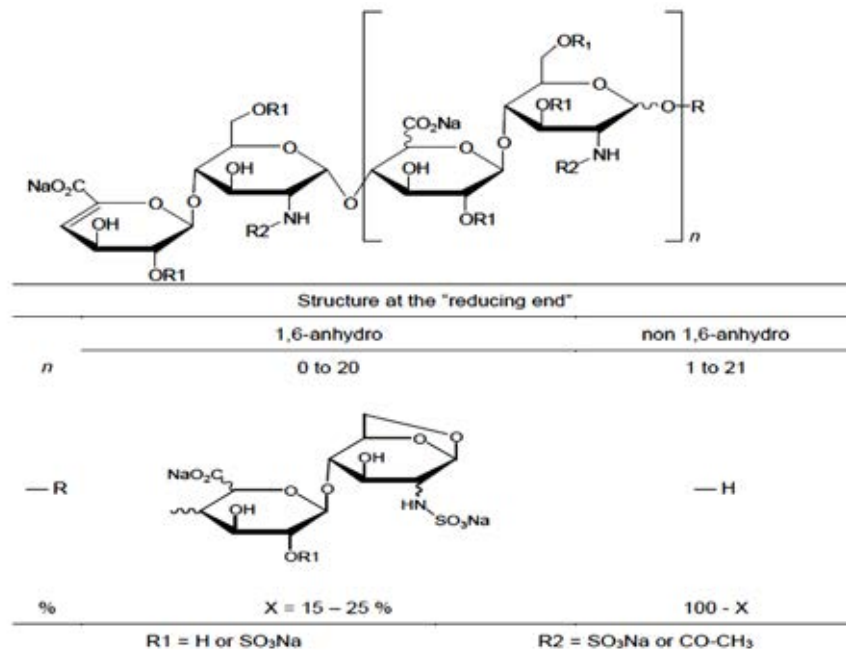
*Treatment of unstable angina and non-Q-wave myocardial infarction, administered concurrently with aspirin.*

*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).*

This application is for a biosimilar version of enoxaparin, that is, a biosimilar version of the reference product, Clexane subcutaneous (SC) injection as sponsored and currently marketed by Sanofi Australia. It was first registered in Australia in 1992. Australia has no biosimilar medicine for enoxaparin entered on the Australian Register of Therapeutic Goods (ARTG). The strengths, indications and dosage instructions proposed are consistent with those for the Australian registered Clexane and Clexane Forte range of products.

Enoxaparin is a low molecular weight heparin (LMWH), derived from porcine mucosa. The molecular weight distribution is < 2000 daltons (Da), 12 to 20%; 2000 to 8000 Da, 68 to 82%; and > 8000 Da, ≤ 18%. The structure is depicted in Figure 1, below. Between the different LMWHs, different methods of depolymerisation result in different products with differences in their pharmacokinetic, anticoagulant profiles and recommended dosage regimens. Enoxaparin sodium is obtained by alkaline depolymerisation of heparin benzyl ester derived from porcine intestinal mucosa. Its structure is characterised by a 4-enopyranose uronate group at the non-reducing end. Between 15% and 25% of the enoxaparin structure contains a 1,6 anhydro derivative on the reducing end of the polysaccharide chain. Enoxaparin sodium also contains water for injection as an excipient.

**Figure 1. Enoxaparin molecular structure**



Enoxaparin is polar, hydrophilic and about 80% renally eliminated.

LMWH produce their major anti-coagulant effect by catalysing anti-thrombin (AT) III mediated inhibition of coagulation factors. Pentasaccharide containing heparin chains composed of at least 18 saccharide units are of sufficient length to bridge AT to thrombin, but 50 to 75% of LMWH chains are too short. These shorter chains are capable of promoting factor Xa (FXa) inactivation via AT because this reaction does not require bridging. Some LMWH have saccharide chains of sufficient length to bind simultaneously to AT and factor II (FII). Reduced binding to macrophages and endothelial cells may explain the longer half-life of LMWH than heparin and binding to platelets and platelet

factor 4 (PF4) may explain the lower incidence of heparin induced thrombocytopenia (HIT).

HIT is a life threatening immune driven adverse effect that occurs in up to 3% of patients receiving unfractionated heparin (UFH) after major surgery but in a much lower proportion of LMWH patients. HIT is caused by antibodies that recognise the chemokine PF4 within ultra large molecular complexes with heparins. PF4 is a member of a family of host defence effector polypeptides. It undergoes conformational changes when complexing with polyanions such as heparin. Exposure of the antigenic site occurs when polyanions induce changes in the structure of PF4, resulting in an increased of the antiparallel  $\beta$ -sheets in the PF4 secondary structure to close to or more than 30%. There is a neutralisation, and a threshold enthalpy of binding (released heat) may be important for the conformational change of PF4 required to expose the antigenic epitope. When these PF4/heparin immunoglobulin G (IgG) complexes bind to platelets, the Fc parts of the antibody (Ab) crosslink gamma Fc region receptor IIa (Fc $\gamma$ IIa) receptors on platelets, inducing platelet activation and aggregation. This results in a prothrombotic state and an increased risk of new thrombosis. Concurrently the platelet count falls.

## Regulatory status

Crusia-AFT has not previously been considered by the Advisory Committee on Prescription Medicines (ACPM) or the Advisory Committee of Medicines (ACM), nor has it been considered by the Pharmaceutical Subcommittee (PSC) of the TGA.<sup>2</sup> Enoxaparin itself has been discussed several times by the Australian Drug Evaluation Committee (ADEC) and the ACPM at meetings.<sup>3</sup>

The sponsor has applied for registration in New Zealand (lodged February 2016), Mexico (lodged December 2015) and via a decentralised procedure in the European Union (EU) (lodged August 2014). The sponsor has indicated that the Reference member state (Germany) reviewing the European submission (that is, the submission to the European Medicines Agency (EMA)) has concluded that 'based on the analytical, functional and preclinical data provided, it concluded that an efficacy/safety trial can be waived'. A decision is expected around 24 January 2017.

## Product Information

There is no Product Information available as this application was withdrawn prior to a decision was reached by the TGA.

## II. Quality findings

### Drug substance (active ingredient)

Enoxaparin consists of a complex set of oligosaccharides that have not yet been completely characterised. Based on current knowledge, the majority of the components

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<sup>2</sup> The Advisory Committee on Medicines (ACM) was established in January 2017, to 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).

<sup>3</sup> The Australian Drug Evaluation Committee (ADEC) was formed in 1963 and given the role of providing independent, scientific advice on new drugs, within the policy framework of the time, to the Federal Government. ADEC was subsequently replaced by the ACPM in 2010.

have a 4-enopyranose uronate structure at the non-reducing end of their chain. 15 to 25% of the components have a 1,6-anhydro structure at the reducing end of their chain. Enoxaparin (Crusia-AFT) is comparable with similar products Lovenox and reference product Clexane (Sanofi Aventis) both of which are registered on the ARTG. The drug structure is shown in Figure 1, above.

### Active ingredient sameness

For the generic enoxaparin drug product, it was critical to demonstrate the sameness of the drug substance to the reference medicinal product based on the United States (US) Food and Drug Administration's (FDA) multiple point criteria for the approval of an enoxaparin sodium Abbreviated New Drug Application (ANDA).<sup>4</sup> The multiple point criteria include the following:

- Equivalence of physicochemical properties
- Equivalence of heparin source material and mode of depolymerisation
- Equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species
- Equivalence in biological and biochemical assays
- Equivalence of in vivo pharmacodynamic (PD) profile.

In addition, to comply with Australian requirements for biosimilars, a comparability exercise was carried out according to the 'Guideline on Similar Biological Medicinal Products'.<sup>5</sup>

The comparability exercise was designed to detect of any physicochemical or functional differences between the active substance in the generic product versus the active substance present in the reference medicinal product.

A comparability testing comparing both Clexane (EU reference product) and Lovenox (US reference product) with enoxaparin sodium manufactured by Rovi<sup>6</sup> has been performed in parallel. This parallel study forms a bridge between the EU sourced and US sourced product. In initial experiments, no significant differences were detected between the EU and US sourced material. Thus, studies were completed with Lovenox.

The EMA's '*Guideline on non-clinical and clinical development of similar biological medicinal products containing low molecular-weight-heparins using complex mixtures*' allows waiving clinical efficacy studies if similar efficacy of the biosimilar and the reference product can be convincingly deduced from the comparison of their physicochemical characteristics, biological activity/potency and PD fingerprint profiles.<sup>7</sup> Enoxaparin is a particularly well characterised product whose properties are indistinguishable from those of the innovator products Clexane and Lovenox. Base purely on quality grounds there are no objections to registration of this product.

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<sup>4</sup> Established by the FDA response to Citizen Petition, Docket No. FDA-2003-P-0273.

<sup>5</sup> EMA/CHMP/437/04: Guideline on Similar Biological Medicinal Products

<sup>6</sup> AFT is the Australian sponsor. Rovi is the drug manufacturer (and sponsor in the EU).

<sup>7</sup> EMEA/CHMP/BMWP/118264/2007 Rev. 1: Guideline on non-clinical and clinical development of similar biological medicinal products containing low molecular-weight-heparins using complex mixtures

### Stability (active substance)

Stability tests have been conducted under accelerated conditions, intermediate conditions and long term conditions according to the International Conference on Harmonisation (ICH) Q1A (R2) guidelines.<sup>8</sup>

The data from these studies showed no trends indicating detriment to the drug substance.

The real time data submitted support the proposed shelf life.

### Drug product

Enoxaparin is a white or almost white hygroscopic powder, freely soluble in water. It is clear in solution and has a pH of 5.5 to 7.5 and an osmolality 259 mOsm/kg for the 100 mg/mL strength and 410 mOsm/kg for the 150 mg/ml strength. It is presented in a sterile solution with water for injection as its excipient.

Specifications for all presentations of Crusia-AFT are provided by the sponsor.

All analytical procedures are validated. Both release and shelf life specifications are provided in the table below.

### Stability (drug product)

Stability tests have been conducted for each presentation (0.2 mL, 0.4 mL, 0.6 mL, 0.8 mL and 1.0 mL pre-filled syringes) of enoxaparin sodium 100 mg/mL solution for injection in pre-filled syringe and for three batches (production scale size) for each presentation (0.8 mL and 1.0 mL pre-filled syringes) of enoxaparin sodium 150 mg/mL solution for injection in pre-filled syringe, under accelerated conditions, intermediate conditions and long term conditions according to the ICH Q1A (R2) guideline.<sup>8</sup>

The finished product batches are of the same formulation and are packaged in the same container closure system as proposed for marketing. The manufacturing process and controls were the same as will be applied to industrial production batches.

Stability studies have been performed on each individual strength and container size of the finished product.

Based on the results and according with the Decision Tree for Data Evaluation for Shelf Life in the ICH Q1E guideline, the sponsor proposes a shelf life of 24 months at 25°C/60% relative humidity for the 150 mg/mL presentations and 36 months at 25°C/60% relative humidity for 100mg/mL presentations.<sup>9</sup> This is acceptable and in line with the shelf life of the existing heparin products Clexane and Lovenox.

### Quality summary and conclusions

There are no objections on quality grounds to the approval of:

- Crusia-AFT Enoxaparin sodium 20 mg/0.2 mL, 40 mg/0.4 mL, 60 mg/0.6 mL, 80 mg/0.8 mL and 100 mg/1 mL injection syringe; and
- Crusia-AFT Forte Enoxaparin sodium 120 mg/0.8 mL and 150 mg/1 mL injection syringe.

The product is a biosimilar that is demonstrably similar to Clexane and Lovenox on the basis of quality including formulation.

<sup>8</sup> ICH Q1A (R2): Harmonised tripartite guideline on stability testing of new drug substances and products.

<sup>9</sup> ICH Q1E: Harmonised tripartite guideline on the evaluation for stability data.

A comparability testing regime comparing both Clexane (EU reference product) and Lovenox (US reference product) with enoxaparin sodium manufactured by Rovi has been performed in parallel. This parallel study is designed to form a bridge between the EU sourced and US sourced product. In initial experiments, no significant differences were detected between the EU and US sourced material. Thus, studies were completed with Lovenox.

Extensive characterisation using state of the art techniques has demonstrated as follows:

- Equivalence of physicochemical properties
- Equivalence of heparin source material and mode of depolymerisation
- Equivalence in disaccharide building blocks, fragment mapping, and sequence of oligosaccharide species
- Equivalence in biological and biochemical assays.

In addition, to comply with Australian requirements for biosimilars, a comparability exercise was carried out according to the 'Guideline on similar biological medicinal products'.<sup>5</sup>

The collective data confirm the structure of the product is compliant with the monograph 'Enoxaparin Sodium' in the European Pharmacopoeia (Ph. Eur.) Eighth Edition.<sup>10</sup>

The specifications are mostly based on the Ph. Eur. monographs for Low Molecular Mass Heparins (0828);<sup>11</sup> and Enoxaparin Sodium (1097);<sup>10</sup> plus the following additional methods: Mass-average relative molecular mass percentage, Benzyl alcohol, Nitrogen, Loss on drying, Anti-Factor Xa and Anti-Factor IIa assays. The batch analysis data support the specifications.

The manufacturing processes of heparin sodium as well as of enoxaparin sodium have been validated for their respective capabilities in inactivating viral agents as recommended in ICH Q5A.<sup>12</sup> Sufficient evidence has been provided to date to demonstrate that the risks related to adventitious agents in the manufacturing of Crusia-AFT and Crusia-AFT Forte have been managed to an acceptable level.

One issue that requires consideration relates to comparability studies and whether there is a need for a bridging study using an Australian product (Clexane or Lovenox) on quality grounds. In an email dated 1 December 2016, the sponsor provided evidence to support the fact that the reference medicines (from the EU, specifically Spain) used in the comparability studies for Crusia-AFT are representative of the product registered on the ARTG. This includes the following (summarised):

- Clexane from Spain and Clexane supplied in Australia are from the same manufacturing site in France.
- The formulations of the drug product in Australia and Spain, are identical, being comprised of enoxaparin sodium (active pharmaceutical ingredient) and water for injections. This implies that there are no peculiar formulation issues specific to Australian Clexane.
- All strengths of the product that are registered in Australia are also available in Spain, as evidenced by the use of all strengths in the comparability studies. Clexane is supplied in identical dose forms in both Australia and Spain, that is, a solution for

<sup>10</sup>European Pharmacopoeia 8.0 volume II, Enoxaparin sodium monograph 1097, (2014), Council of Europe.

<sup>11</sup>European Pharmacopoeia 8.0 volume II, Heparins, low-molecular-mass monograph 0828, (2014), Council of Europe.

<sup>12</sup>ICH Q5A (R1) Harmonised tripartite guideline on viral safety evaluation of biotechnology products derived from cell lines of human or animal origin

injection in pre-filled syringes, as evidenced by the public ARTG summaries, and the details within the Spanish leaflets provided.

In addition to these, the evaluator considers that (consistent with the TGA's guidance on the regulation of biosimilar medicines) the company also carried out extensive comparability using Lovenox (US), Clexane Spain and Crusia.<sup>13</sup> This ensures that the breadth of the reference medicines is extensive through the use of products obtained from the major global biological medicines markets (US and EU).

These pieces of evidence indicated that the risk associated with differences (if any) that could be between EU Clexane and Australian Clexane on quality grounds is very minimal and does not warrant conducting additional physicochemical bridging studies.

Overall the quality data suggest that enoxaparin sodium (Crusia-AFT) is acceptable for registration on the ARTG.

### **Proposed conditions of registration**

#### ***Batch release testing***

1. It is a condition of registration that all batches of Crusia AFT imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
2. It is a condition of registration that each batch of Crusia-AFT 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.

The sponsor must supply:

- a. Certificates of Analysis of all active ingredient (drug substance) and final product.
- b. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
- c. Evidence of the maintenance of registered storage conditions during transport to Australia.
- d. Six vials of each batch for testing by the TGA Laboratories Branch together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

## **III. Nonclinical findings**

### **Introduction**

Nonclinical data consisted of comparative pharmacokinetic (PK) data, using PD parameters as surrogates for drug concentrations, and comparative immunogenicity data. The commercial batch of Crusia-AFT was used in all studies.

Comparative in vitro pharmacology studies were submitted in Quality part of the dossier.

The current TGA adopted EMA guideline recommends the conduct of comparative in vitro and in vivo pharmacology studies and a comparative repeat-dose toxicity study with an

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<sup>13</sup> Regulation of biosimilar medicines; version 2.0. TGA guidance document; December 2015.

assessment of local tolerance.<sup>14</sup> Therefore, the submitted nonclinical dossier does not fully comply with the current TGA adopted guideline due to the absence of a repeat-dose toxicity study. In January 2013, the EMA published a draft revision of the guideline cited above.<sup>15</sup> It is stated in this draft guideline that separate repeat-dose toxicity studies are generally not required. This appears to be based on the link between in vitro and in vivo pharmacodynamics effects and that dose-limiting toxicity with low molecular weight heparins is closely related to the pharmacological action of the product; in vivo toxicity studies are unlikely to add significantly to the risk assessment.<sup>16</sup> The presence of impurities may alter the toxicity profile of a biosimilar enoxaparin from that of the reference product. The absence of a comparative toxicity study is acceptable in this case, provided that:

- Adequate similarity is shown in the submitted pharmacology studies (quality and nonclinical data)
- Quality data demonstrate that the active substances are not significantly different from each other using physicochemical techniques
- Quality data demonstrate that Crusia-AFT contains similar types and levels of impurities to the reference product
- Adequate comparability is shown in an adequately conducted and robust in vivo pharmacodynamic study in human subjects (clinical data).

The submitted comparative PD/PK study used the US reference product (Lovenox) rather than the Australian reference product (Clexane) as the comparator. Provided the quality and the clinical evaluators consider the two reference products comparable, this is not considered to be a concern.<sup>13</sup>

## Pharmacology

No in vitro pharmacology studies were submitted for nonclinical evaluation. In vitro studies (anti-FXa, anti-FIIa and thrombin time) were evaluated by the quality evaluator. It is stated in the quality data submitted that Crusia-AFT had similar anti-Factor Xa activity to Lovenox and Clexane but a slightly lower (14 to 20%) anti-Factor IIa activity than the two reference products, resulting in an altered anti-FXa to anti-FIIa activity ratio. The in vivo or clinical relevance of this lower activity is unknown. Similar results were reported for Crusia-AFT, Lovenox and Clexane in the thrombin time assay. Comparative in vivo pharmacodynamic studies were conducted in rabbits following SC administration. This species is considered an appropriate animal model to assess the pharmacology of enoxaparin, as it has previously been shown to be a pharmacologically responsive species. Appropriate end points were assessed; anti-FXa activity, anti-FIIa activity, tissue factor pathway inhibitor (TFPI) and activated partial thromboplastin time (APTT). Bioequivalence between Lovenox and Crusia-AFT was demonstrated with respect to anti-FXa activity (discussed below). Similar profiles (versus time) between Lovenox and Crusia-AFT were observed with respect to anti-FIIa activity, APTT and TFPI. Therefore, there are no obvious differences in pharmacological action in rabbits between Crusia-AFT and Lovenox, the US reference product.

<sup>14</sup> EMEA/CHMP/BMWP/118264/2007: Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins.

<sup>15</sup> EMEA/CHMP/BMWP/118264/2007 Rev. 1: Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins. Draft.

<sup>16</sup> Revised EMA biosimilars guidelines: The impact on development requirements, a nonclinical perspective. White paper, September 2013.

No animal studies were submitted to support the use of Crusia-AFT for the proposed indications. While PD endpoints were examined in a non-disease animal model, this does not necessarily equate to efficacy. This is not a major deficiency (in terms of the nonclinical evaluation) but the inclusion of such studies would have aided in an assessment of efficacy for the proposed indications and could have been used to confirm that the pharmacological end points assessed in normal animals correlated with clinical efficacy. Therefore, no comment can be made from a nonclinical perspective to support the use of Crusia-AFT for any of the indications.

## Pharmacokinetics

Exposure to enoxaparin was assessed based on pharmacological endpoints (anti-FXa and anti-FIIa) which is considered acceptable based on current guidelines. In an appropriately powered study, bioequivalence (based on a 90% confidence interval for the ratio of Crusia-AFT and Lovenox exposures within an acceptance interval of 80 to 125%) was achieved for exposure (area under the curve (AUC) and maximum plasma concentrations ( $C_{max}$ )) to anti-FXa activity in rabbits following SC administration.<sup>17</sup> Bioequivalence based on anti-FIIa activity was not assessed by the sponsor. Bioequivalence for this activity should have been assessed to determine if the in vitro findings of comparatively lower anti-FIIa activity in Crusia-AFT was obvious in vivo. The time to peak plasma levels of inhibitory activity and the elimination half life were similar.

## Toxicity

Two immunogenicity studies were submitted; an in vivo study in rats and an in vitro study using human peripheral blood mononuclear cells (PBMC). These studies were appropriately comparative in nature, comparing the effects of Crusia-AFT with both Clexane and Lovenox.

A potential risk with enoxaparin (currently registered and biosimilars) is HIT, a thrombotic disorder caused by the binding of antibodies to complexes formed by heparin or LMWHs, such as enoxaparin, with the endogenous chemokine, PF4. In rats, there was no significant difference between test items in terms of seroconversion (the number of animals having heparin PF4 antibodies or titres), platelet activation or aggregation and there was no evidence of thrombocytopenia in any of the treated animals. However, seroconversion appeared to be similar in the negative control group (40% seroconversion rate; confirmed in two separate assays) to that of the enoxaparin-treated groups. The study report cited a paper suggesting that anti-heparin/PF4 antibodies can occur in apparently naïve subjects.<sup>18</sup> While this phenomenon may be accepted, the unexpectedly high number of animals in the control group having apparently spontaneously produced antibodies (40% compared with a spontaneous rate of 4.3% in the cited paper, albeit in a different species (humans)) and the fact that the animals did not apparently have anti-heparin/PF4 antibodies in the pre-study test (Day 0), indicate it is more likely that these animals were exposed to a heparin like compound (such as enoxaparin) during the study.

If this is the case, it sheds doubt on the conduct of the study and its data. Little weight can be placed on the findings in this study given the high seroconversion rate in the negative control group.

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<sup>17</sup> CPMP/EWP/QWP/1401/98 Rev. 1/Corr: Guideline on the Investigation of Bioequivalence. FDA Draft Guidance on Enoxaparin Sodium. October 2011.

<sup>18</sup> Hursting, M et al. (2010) Platelet factor 4/heparin antibodies in blood bank donors. *Am J Clin Pathol* 134: 774- 780.



The absence of an adequately conducted in vivo immunogenicity study in animals is not considered a deficiency for this application as the predictivity of animal studies for the evaluation of immunogenicity in humans is considered low and comparative immunogenicity studies in animals are generally not required for biosimilar products.<sup>19</sup>

A publication by the FDA suggests that comparative immunomodulatory studies should be conducted for enoxaparin biosimilars, citing two papers.<sup>20,21,22</sup> Enoxaparin has been shown to alter the extent of lipopolysaccharide (LPS) induced monocyte activation. In the in vitro study submitted, the effect of Crusia-AFT, Lovenox and Clexane on human PBMC was examined, with assays used to assess activation of different cells of the immune system. There was no meaningful activation (based on tumour necrosis factor alpha (TNF $\alpha$ ), interleukin 1 beta (IL-1 $\beta$ ) and interferon gamma (IFN- $\gamma$ ) release and the distribution of CD3+CD69+, CD3+CD25+, and CD3+HLA DR+ cells) by any of the test items, suggesting there are no contaminants/impurities in Crusia-AFT that would apparently activate immune cells in the blood. However, this study does not fully address the immunomodulatory issue raised in the above FDA publication. According to the papers cited in the FDA publication, enoxaparin alters the LPS induced activation of immune cells, and enoxaparin alone does not induce TNF $\alpha$  release. LPS induction was not performed in the submitted study. Therefore, a relevant comparison of the immunomodulatory activity of Clexane, Lovenox and Crusia-AFT has not been appropriately performed.

Another issue raised in the FDA publication above is that impurities may affect the avidity of enoxaparin binding to and forming complexes with PF4, as well as the charge and size of the resulting complexes. No studies were submitted in nonclinical data to characterise the affinity of Crusia-AFT for PF4 or the size and charge of enoxaparin-PF4 complexes. In response to a TGA request for further information, the sponsor submitted data assessing these factors. These data have been evaluated by the quality evaluator.

Nonetheless, the in vitro studies alone are unlikely to be sufficiently predictive of the in vivo situation.<sup>23</sup>

Therefore, any differences in immunogenicity, effects on the immune system or risks of HIT between Crusia-AFT and the Australian reference product Clexane cannot be addressed by the submitted nonclinical data.

## Pregnancy classification

The sponsor has proposed Australian Pregnancy Category C, which is consistent with the Australian Pregnancy Category for the reference product Clexane and is therefore considered acceptable.<sup>24</sup>

## Local tolerance

No studies were submitted, which is considered acceptable for this product.

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<sup>19</sup> EMEA/CHMP/BMWP/42832/2005 Rev1: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues.

<sup>20</sup> Lee, S et al. Scientific considerations in the review and approval of generic enoxaparin in the United States (2013). *Nature Biotech.* 31: 220-226.

<sup>21</sup> Heinzelmann, M et al. Heparin and enoxaparin enhance endotoxin-induced tumor necrosis factor- $\alpha$  production in human monocytes (1999). *Ann. Surg.* 229: 542-550.

<sup>22</sup> Hochart, H et al. Concentration-dependent roles for heparin in modifying lipopolysaccharide-induced activation of mononuclear cells in whole blood (2008). *Thromb. Haemost.* 99: 570-575.

<sup>23</sup> Suvarna, S et al. Determinants of PF4/heparin immunogenicity (2007). *Blood* 110: 4253-4260.

<sup>24</sup> TGA 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. Accompanying texts should be consulted for further details.

## Nonclinical summary and conclusions

- The submitted nonclinical dossier consisted of comparative PK studies (using PD markers as surrogates for assessing exposure to enoxaparin) and comparative immunogenicity studies.
- In the PD/PK studies in rabbits, no meaningful differences were observed in anti-FXa, APTT or TFPI activities. Bioequivalence between the US reference product, Lovenox and Crusia-AFT was demonstrated with respect to anti-FXa activity. Bioequivalence based on anti-FIIa activity was not assessed. This should have been considered given the differences between the two products observed in the in vitro studies submitted in data for quality evaluation.
- No animal efficacy studies were submitted to support the use of Crusia-AFT for the proposed indications.
- Due to either the conduct of the study or the design of the study, any differences in immunogenicity, effects on the immune system or risks of HIT between Crusia-AFT and the Australian reference product Clexane, cannot be addressed by the submitted immunogenicity studies.
- Provided adequate data are available in the quality and clinical dossiers to address the comparability of the US and Australian reference products and the comparability of the Australian reference product and the proposed biosimilar Crusia-AFT with respect to efficacy and immunogenicity, there are no objections on nonclinical grounds to the registration of Crusia-AFT.

## IV. Clinical findings

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

### Introduction

#### Clinical rationale

The sponsor states that Crusia-AFT has been developed to align with Clexane and Lovenox, both products with enoxaparin sodium as their active ingredient. The sponsor states that, in accordance with current scientific thinking and the TGA adopted EU guideline;<sup>25</sup> similarity between the biosimilar and the reference product (Lovenox (USA)) has been established in a randomised, double blind, 2 way, crossover pharmacodynamic bioequivalence study in healthy volunteers (Study ROV-RO20-2011-01). In addition, 2 nonclinical bioavailability studies have been performed in rabbits in order to establish bioequivalence of the absorption profiles of the biosimilar and the reference product. These clinical and nonclinical studies were performed using Lovenox marketed in the US as the reference product. In order to support registration in Europe and other territories where Lovenox is not registered, the sponsor states that an extensive state of the art analytical comparability exercise was performed to bridge Crusia-AFT, Lovenox (USA) and Clexane (Spain). In accordance with TGA guidelines, the sponsor considers Clexane (Spain) to be the Australian reference medicine.<sup>13</sup>

The sponsor indicates that the development of the proposed product (enoxaparin sodium solution for injection) is based on the published available data on the qualitative and

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<sup>25</sup> EMA/CHMP/437/04 Rev. 1: Guideline on similar biological medicinal products (2014).

quantitative composition of the reference medicinal product (Lovenox/Clexane). The sponsor states that the similarity between the proposed product and the reference product has been demonstrated by the in vitro 3 way state of the art comparability exercise (the sponsor's proposed enoxaparin sodium drug product, Lovenox (USA), and Clexane (Spain)). The data indicate that all the steps of the manufacturing process take place in Spain, with an alternative manufacturer (also in Spain) for the secondary packaging. Both manufacturing sites are subcontracted manufacturing facilities of Rovi.

### **Guidance**

There are currently no enoxaparin biosimilar medicines on the ARTG. The relevant TGA guidelines relating to the clinical evaluation of the submission include:

- Regulation of biosimilar medicines (Version 2.0, December 2015)
- EMEA/CHMP/BMWP/118264/2007: Guideline on non-clinical and clinical development of similar biological medicinal products containing low molecular weight heparins
- EMEA/CHMP/BMWP/42832/2005/Rev 1: Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substances: non-clinical and clinical issues
- EMEA/CHMP/BMWP/14327/2006: Guideline on immunogenicity assessment of biotechnology derived therapeutic proteins.

The key TGA adopted clinical guideline relating to the submission is considered to be the product specific guideline for biosimilar LMWH products.<sup>14</sup> The guideline provides nonclinical and clinical requirements for LMWH products claimed to be similar biological medicinal products to already marketed LMWHs. The guideline states that the major burden of demonstrating that two LMWHs are similar biological medicinal products is on a clinical trial, due to the high heterogeneity of LMWH, incomplete understanding of the mode of action of the product, and uncertainty about whether the pharmacodynamic markers are representative of the clinical outcome.

There is a draft revised EMA guideline relating to the nonclinical and clinical development of biosimilar LMWH products.<sup>15</sup> This draft revised guideline was released for consultation by the CHMP on 13 January 2013. The end of consultation (deadline for comments) for the guideline was 31 July 2013. The EMA has not released an overview of comments received on the draft guideline. Nearly three years has now elapsed since the end of the consultation period. The revised guideline has not yet been adopted by either the TGA or the EMA.

The clinical evaluation of the submission has been undertaken in the light of the TGA adopted LMWH biosimilar guideline.<sup>14</sup> The TGA has not yet adopted the revised LMWH biosimilar guideline nor has it rescinded the adopted guideline.<sup>15</sup> Therefore, it is reasonable to infer that the adopted guideline still reflect the TGA's current thinking on the clinical requirements for submissions to register a LMWH product claimed to be biosimilar to the Australian marketed product. While sponsors are not legally required to comply with TGA adopted guidelines, it is expected that they will adequately justify any deviations from the guidelines.

### **Contents of the clinical dossier**

The submission consisted of an abbreviated clinical dossier consisting of one single dose PD bioequivalence study (Study ROV-RO20-2011-01) in healthy volunteers comparing the enoxaparin sodium product proposed for registration and the enoxaparin sodium product marketed in the US (Lovenox). No other clinical studies were submitted.

In addition, the following were submitted: An Introduction; Quality Overall Summary; Nonclinical Overview; Clinical Overview; Nonclinical Written Summary; Summary of Biopharmaceutics and Associated Analytical Methods.

### **Paediatric data**

No paediatric data were submitted. The sponsor states that no paediatric data have been submitted to the EU. The sponsor indicates that the submission of paediatric data is not a requirement for similar biological medicinal products in the EU. The sponsor's decision not to submit paediatric data is considered to be acceptable.

### **Good clinical practice**

The submitted PD bioequivalence Study ROV-RO20-2011-01 was conducted according to the ICH guidelines for Good Clinical Practice.

### **Pharmacokinetics**

There were no studies providing conventional PK data.

The TGA adopted LMWH biosimilar guideline states that:

*'Due to the heterogeneity of LMWHs conventional pharmacokinetic studies cannot be performed. Instead, the absorption and elimination characteristics of LMWHs should be compared by determining pharmacodynamic activities (including anti-FXa and anti-FIIa), as surrogate markers for their circulating concentrations. In addition other pharmacodynamic tests such as Tissue Factor Pathway Inhibitor (TFPI) activity, as well as the ratio of anti-FXa and anti-FIIa activity should be compared. Assessment of these PD parameters will provide a fingerprint of the polysaccharidic profile'.<sup>14</sup>*

### **Pharmacodynamics**

#### **Studies providing pharmacodynamic data**

The clinical data included Study ROV-RO20-2011-01, a single dose (100 mg SC), PD bioequivalence study in healthy volunteers comparing the test product (enoxaparin sodium Rovi injection 100 mg/mL) with the reference product (US marketed, Lovenox 100 mg/mL). The submission included an addendum to the final study report, which provided post hoc analyses of the PD and AE data from the study. The submitted bioequivalence study has been fully evaluated. The study is summarised below in Table 1.

**Table 1. Study ROV-R020-2011-01 Pharmacodynamic bioequivalence study**

Objective	Design	Treatment	Subjects	Objective
To determine the PD bioequivalence of the test and reference products.	Single dose, randomised, double blind, 2 way crossover. Duration approximately 6 weeks, including 30 day screening period.	Test: enoxaparin sodium Rovi (100 mg/mL), 100 mg SC. Reference: Lovenox (100 mg/mL), 100 mg SC; US marketed.	HV n = 42; 25 male, 17 female; mean age 32.4 years (19, 45 years).	Demonstrate PD BE of the test and reference formulations based on anti-Xa and anti-IIa activity.

### Evaluator's conclusions on pharmacodynamics

A brief summary of the evaluator's conclusions is provided below. Please see Attachment 2 for a more in depth copy of the evaluator's conclusions on pharmacodynamics.

Study ROV-R020-2011-01 in healthy volunteers satisfactorily demonstrated that the reference product (Rovi enoxaparin sodium 100 mg/mL; 100 mg SC) and the test product (Lovenox enoxaparin sodium; 100 mg SC) were bioequivalent, based on the pre-specified statistical analysis of the PD parameters for anti-FXa activity which were the area under the effect curve from dosing to time of last sample ( $AUEC_{0-t}$ ), the area under the effect curve from dosing to infinity ( $AUEC_{0-inf}$ ) and maximal anti-FXa concentration ( $anti-FXa_{max}$ ).

The bioequivalence of the 2 products was supported by the pre-specified statistical analysis of the PD parameters for anti-FIIa activity of  $AUEC_{0-t}$  and the maximum anti-FIIa concentration ( $anti-FIIa_{max}$ ), but the data for  $AUEC_{0-inf}$  were not included in the statistical analysis due to the small number of subjects in the two treatment groups. The PD bioequivalence analyses of the baseline adjusted TFPI activity and the ratio of area under the effect curves ( $R_{AUEC}$ ) supported the PD bioequivalence analyses of anti-FXa and anti-FIIa activities. The post hoc analyses of the PD parameters using the more stringent criterion of a 95% CI were consistent with the pre-specified analyses using a 90% CI with the 80 to 125% PD bioequivalence interval.

Clinical limitations identified by the clinical evaluator from the study provided included:

- the absence of PD bioequivalence studies using the Australian reference product and no studies bridging the data for Lovenox (US) and Clexane (EU)
- no IV PD equivalence study, and the sponsor's justification for not producing a study was considered unsatisfactory because anti-FIIa activity cannot be predicted from SC data.
- no adequate justification was provided for the 80 to 125% PD bioequivalence intervals in the submitted PD studies.

### Dosage selection for the pivotal studies

No pivotal Phase III efficacy and safety studies were submitted.

### Efficacy

The TGA adopted, LMWH biosimilar guideline states:

*'Since a clear correlation between surrogate PD parameters (anti FXa or anti FIIa) and clinical outcome has not been established, a similar biological medicinal product containing LMWH should show equivalent efficacy and safety to a reference product approved in the EU. This therapeutic equivalence should be demonstrated in at least one adequately powered, randomised, double-blind, parallel group clinical trial. In theory, this could be done either in the setting of prevention of venous or arterial thromboembolism, or in the setting of treatment of venous thromboembolism. However, the most sensitive model to detect potential differences in efficacy between the new LMWH and the reference product should be selected'.<sup>14</sup>*

The guideline recommends demonstration of efficacy in the prevention of venous thromboembolism (VTE) in patients undergoing surgery with a high VTE risk. The guideline states:

*'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'.<sup>14</sup>*

In pre-submission correspondence, the TGA requested the sponsor to provide a 'therapeutic equivalence study (adequately powered, randomised, double blind, parallel group clinical trial with pre-specified equivalence margins) in the most sensitive model to detect potential differences in efficacy between the proposed enoxaparin product and the reference product. Preferably, the trial should be in patients in the setting of prevention of venous thromboembolism in patients undergoing major orthopaedic surgery with high VTE risk such as hip surgery'. This request is consistent with the TGA adopted LMWH biosimilar guideline.<sup>14</sup>

The sponsor did not comply with the TGA's request for a therapeutic equivalence study. No clinical efficacy and safety studies were submitted. The sponsor's response to the TGA's request is provided below.

'As stated in the TGA-adopted, EU Guideline on similar biological medicinal products:

*'In specific circumstances, a confirmatory clinical trial may not be necessary. This requires 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, it requires that the impurity profile and the nature of excipients of the biosimilar itself do not give rise to concern. It is recommended to discuss such simplified approaches with Regulatory Authorities'.<sup>14</sup>*

In this case, the manufacturer of the proposed product enoxaparin sodium has discussed with EMA the necessity of a therapeutic equivalence study and has been advised in the scientific advice that, 'The Committee for Medicinal Products for Human Use (CHMP) believes that it could indeed be acceptable to waive a pre-approval Phase III efficacy/safety trial'.

Because the analytical tools for the characterisation of complex molecules such as enoxaparin have greatly improved since the approval of the TGA adopted EU guideline on LMWH, deriving data from only PK/PD trials should be considered acceptable provided that the analysis of important molecule characteristics does not reveal differences which would contradict an assumption of biosimilarity and biosimilarity can convincingly be established based on nonclinical studies and clinical PD studies as well.<sup>14</sup>

The sponsor comments that the manufacturer discussed with the EMA whether a therapeutic equivalence study was necessary, and received advice from the CHMP that it might be possible to waive the requirement for a pre-approval Phase III efficacy/safety trial. In the opinion of the manufacturer, a confirmatory clinical efficacy and safety study would not provide any additional data to support similarity to that already obtained from

the 'comprehensive physiochemical characterisation, the nonclinical comparability studies and the Phase I healthy volunteer study'. The manufacturer comments that, 'preliminary analysis of the biosimilar version of enoxaparin sodium Rovi has showed similarity to the original drugs, Clexane and Lovenox. All of them demonstrate sameness (1) in weight-average molecular weight and weight distribution, (2) in proton ( $^1\text{H}$ ) nuclear magnetic resonance (NMR) spectra and signals areas, (3) in heteronuclear single quantum coherence (HSQC) NMR spectra and monosaccharide compositional analysis by HSQC NMR and (4) in values of in vitro anti-FXa and anti-FIIa activities both drug substance and drug product'. In further support of a waiver from the CHMP, the manufacturer referred to the outcome of the study in healthy volunteers demonstrating bioequivalence of the two enoxaparin products based on PD outcomes (Study ROV-RO20-2011-01), and the correlation between anti-Xa activity and clinical outcomes established in the literature.

The manufacturer acknowledged to the CHMP that a confirmatory therapeutic clinical equivalence trial *'could potentially overcome some of the uncertainties that enoxaparin sodium Rovi is biosimilar to Clexane'*. However, the manufacturer outlined the difficulties in conducting a suitably powered therapeutic equivalence study comparing the incidence of venous thromboembolic events between the two enoxaparin products. These included, no well established consensus regarding the equivalence margin, large number of patients ( $n = 1,260$ ) required to adequately power the study based on a relative risk delta of 1.33, and the use of invasive venography ('gold standard') to detect outcomes of proximal and distal deep vein thrombosis (DVT). The manufacturer stated that a study of the required size would take years to recruit, *'especially when there is a lack of interest by investigators to take part in biosimilar trials'*. The sponsor commented that a multinational, multisite study of *'such long duration [...] will be a real challenge for any sponsor. Moreover, given the variability of standard of care and methods of assessment across countries which could also change of the years, data integrity could be compromised. Therefore, one may question the scientific value of such a study and whether it is ethical to conduct such a study'*.

The sponsor's comments relating to the difficulties of undertaking a suitable therapeutic equivalence study are unconvincing. The challenges in undertaking an appropriately designed study are not insurmountable. As regards the sponsor's comments regarding the scientific value and ethics of conducting a therapeutic equivalence study, it is considered that one would have to be certain that, based on the totality of the submitted data, the two products were biosimilar in order to scientifically and ethically justify not undertaking such a study. The sponsor has not demonstrated a clear correlation between the surrogate PD markers (anti-Xa and anti-IIa) and clinical outcomes. Therefore, it is considered that a clinical study is required to establish the therapeutic equivalence of the two products and to provide reassurance that the safety data are comparable.

In its response to the manufacturer, the CHMP *'acknowledged that analytical tools for characterisation of complex molecules such as enoxaparin have greatly improved'* and stated that it believed *'that it could indeed be acceptable to waive a pre-approval Phase III efficacy/safety trial'*. However, *'such a scenario would only be acceptable if (1) comparisons on 'Chemistry, Manufacturing and Controls' (CMC) level are performed with state-of-the-art and analysis of important molecule characteristics does not reveal differences which would contradict an assumption of biosimilarity, and (2) biosimilarity can convincingly be established based on nonclinical studies and clinical PD studies as well. In this context, it has to be clearly stated that the recommendation to conduct a Phase III trial is not meant as a 'rescue' of failure to show similarity in early development phases'*.

The problem with the CHMP's criteria to waive the requirement to submit a Phase III efficacy and safety study relates to the previously discussed lack of a demonstrated correlation between the PD parameters and clinical outcomes. Therefore, it is considered that even if the CHMP criteria were satisfied this would not remove the requirement for a

Phase III clinical study to be submitted demonstrating the therapeutic equivalence of the 2 enoxaparin sodium formulations.

## **Safety**

### **Studies providing safety data**

No Phase III clinical efficacy and safety studies were submitted. The only clinical safety data in the submission related to the single dose bioequivalence study in healthy volunteers (Study ROV-R020-2011-01).

### **Patient exposure**

In Study ROV-R020-2011-01, all 42 subjects (healthy volunteers) received a single 100 mg SC dose of the proposed enoxaparin product (Rovi) and the reference product (Lovenox, USA).

### **Safety issues with the potential for major regulatory impact**

See the clinical evaluator's conclusions on safety below.

### **Post-marketing data**

No post-marketing safety data relating to the proposed enoxaparin product were submitted, as at the time of the application Crusia had not been approved for marketing in any country.

### **Evaluator's conclusions on safety**

No post-marketing safety data relating to the proposed enoxaparin product were submitted, as at the time of the application Crusia had not been approved for marketing in any country. The clinical safety data provided in the submission are limited to the single dose data in healthy volunteers from the PD bioequivalence Study ROV-R020-2011-01. In this study, the safety data indicated that both enoxaparin products were well tolerated when administered to a small number of healthy subjects. However, no meaningful conclusions regarding the clinical safety of the proposed enoxaparin sodium product can be drawn from Study ROV-R20-2011 for the following reasons:

1. Based on the 'rule of three's' the number of subjects (n = 42) is too low to reliably identify adverse drug reactions associated with the proposed product occurring with an incidence of less than 7%.
2. There were no single dose safety data in patients.
3. There were no repeat dose safety data in either healthy volunteers or patients.

Overall, no assessment of the clinical safety of the proposed enoxaparin sodium product can be made from the submitted clinical data.

The TGA adopted LMWH biosimilar guidelines state:

*'Even if the efficacy is shown to be comparable, the similar biological medicinal product may exhibit a difference in the safety profile. Pre-licensing safety data should be obtained in a number of patients sufficient to determine the adverse effect profiles of the test medicinal product. Care should be given to compare the type, frequency and severity of the adverse reactions between the similar biological medicinal product and the reference products. Usually, comparative safety data from the*



*efficacy trial will be sufficient to provide an adequate pre-marketing safety database'.<sup>14</sup>*

The guidelines also state:

*'For the detection of the immune-mediated type of Heparin-induced Thrombocytopenia (HIT Type II) monitoring of platelet count and an adequate diagnostic procedure in patients developing thrombocytopenia and/or thromboembolism (HITT) during the trial has to be performed'.<sup>14</sup>*

In pre-submission correspondence, the TGA asked the sponsor to provide 'comparative clinical safety data between the proposed product and the reference product, which could be provided from the previous therapeutic equivalence study.' The submission did not include the requested clinical safety data. The sponsor's justification for not submitting the requested follows:

*'The incidence of bleeding of LMWH in general and enoxaparin in particular is between 0.5% and 5% during clinical trial for prevention of thromboprophylaxis of patients undergoing hip or knee arthroplasty and it depends on several factors (e.g. standardisation of bleeding, hospital setting, patients involved in clinical trials), so that in many cases clinical trials were underpowered to find differences between those anticoagulants used.<sup>26</sup> That is the case of the study to evaluate the comparative effect of two enoxaparins (Sanofi-Aventis branded enoxaparin versus Eurofarma enoxaparin, a generic version) as prophylaxis for VTE following major abdominal surgery, where no statistically significant differences between the two groups were detected.<sup>27</sup>*

*The incidence of HIT is estimated at 0.2 to 0.4%, although it depends on several factors: individuals (platelet counts, previous exposition to heparin/LMWH), type of heparin/LMWH, type of patient (surgical, medical), kind of intervention (prevention or treatment of DVT/pulmonary embolism).<sup>28</sup> HIT is understood to be a result of a non-specific oligosaccharide interaction with endogenous chemokine PF4. These interactions are largely dependent on oligosaccharide molecular weights and charge densities.<sup>29</sup>*

*Rauova et al., demonstrated that the formation of PF4-heparin complexes is dependent on heparin polymer length.<sup>30</sup> Analytical comparative studies to quantify these complexes constitute supporting evidence of similarity. Qualitative and quantitative characterisation of impurities, as well as the non-clinical immunogenicity study performed by the sponsor with the proposed product enoxaparin sodium, Clexane and Lovenox, provide further assurance that the risk of immunogenicity of the biosimilar product is comparable to the reference product.*

*Moreover, the sponsor considers it not necessary to assess, in a clinical study, the incidence of HIT associated with the proposed product enoxaparin sodium because it has been shown that the proposed product has similar quality as the reference enoxaparin, for example similar disaccharide building blocks and sequence of*

<sup>26</sup> Dahl O et al. A critical appraisal of bleeding events reported in venous thromboembolism prevention trials of patients undergoing hip and knee arthroplasty. *J Thromb Haemos* 2010;8: 1966-75.

<sup>27</sup> Gomes M, et al. Generic versus branded enoxaparin in the prevention of venous thromboembolism following major abdominal surgery: report of an exploratory clinical trial. *Clin Appl Thromb Hemost* 2011; 17(6): 633-9.

<sup>28</sup> Kelton J and Warkentin T. Heparin-induced thrombocytopenia: a historical perspective. *Blood* 2008; 112: 2607-16.

<sup>29</sup> Newman P et al. Heparin-induced thrombocytopenia: IgG binding to PF4-heparin complexes in the fluid phase and cross-reactivity with low molecular weight heparin and heparinoid. *Thromb Haemost* 1998; 80: 292-7.

<sup>30</sup> Rauova L, et al. Ultralarge complexes of PF4 and heparin are central to the pathogenesis of heparin-induced thrombocytopenia. *Blood* 2005;105:131-8.

*oligosaccharide, and hence a similar propensity for PF4 complex formation, as well as similar incidence of HIT.*

*Furthermore, in the submitted bioequivalence Study ROV-RO20-2011-01, there were no unexpected safety findings in the 42 healthy adult subjects participating in the single-dose crossover biopharmaceutical study. No serious adverse effects (AEs) were reported. Enoxaparin has a well-established safety and tolerability profile, as described in published literature. The data do not indicate a higher frequency or more severe AEs with the proposed product enoxaparin sodium compared with the reference product’.*

The sponsor’s justification for a waiver is not supported for the following reasons:

1. As previously discussed, the sponsor’s justification for undertaking a therapeutic equivalence study is not supported.
2. In Dahl et al., (2010) the authors conclude that randomised ‘VTE prevention trials report markedly different rates of major bleeding despite similar patient populations and doses and durations of anticoagulant prophylaxis and were underpowered to detect modest differences in patient-important bleeding events. Standardization of bleeding definitions and reporting seems desirable’.<sup>26</sup> There is nothing in the conclusions of Dahl et al., (2010) relating to the author’s appraisal of the literature that would preclude the sponsor from undertaking a comparative safety study of the proposed enoxaparin product and Clexane (Australia).
3. In Gomes et al., (2011) the authors compared the effect of two enoxaparin products (Sanofi-Aventis branded enoxaparin versus Eurofarma enoxaparin, a generic version) as prophylaxis for VTE following major abdominal surgery.<sup>27</sup> The study randomised 200 patients in a 1:1 ratio to either 40 mg of branded enoxaparin or generic enoxaparin once daily for 7 to 10 days post-operatively as prophylaxis for VTE following major abdominal surgery. No statistically significant differences between the 2 enoxaparin groups were detected. In all, 2 patients in the branded enoxaparin group experienced DVT (2.1%) compared to no patients in the generic group. The authors conclude that ‘this exploratory trial suggests that the generic LMWH is probably as safe and effective as the branded enoxaparin (Lovenox, Brazil) in the prophylaxis of VTE in this population’. There is nothing in the conclusions of Gomes et al., (2011) relating to their exploratory trial that would preclude the sponsor from undertaking a comparative safety study of the proposed enoxaparin product and Clexane (Australia).
4. The sponsor refers to a number of matters relating to the association between treatment with enoxaparin and immune-mediated heparin induced thrombocytopenia (HIT Type II), including the physicochemical similarities of the proposed and reference products and the results of the nonclinical immunogenicity study. The sponsor appears to be of the opinion that the risk of immunogenicity of the proposed and reference products is comparable, due to the similar physicochemical properties of the two products and the data from the nonclinical immunogenicity study. The sponsor also appears to be of the opinion that the proposed and reference products have a similar propensity for PF4 complex formation as well as a similar incidence of HIT Type II, due to the similar disaccharide building block sequence for the oligosaccharides of the two products. The assessment of the nonclinical immunogenicity study is a matter for the nonclinical evaluator and the assessment of the disaccharide and oligosaccharide characteristics of the two products is a matter for the quality evaluator.
5. While it is acknowledged that the incidence of HIT Type II associated with enoxaparin is low, this does not preclude a safety study of the proposed enoxaparin product and Clexane (Australia) being undertaken. It is not a requirement that a comparative

safety study be specifically powered to detect HIT Type II. However, the study could reasonably include comparative assessment of AEs of thrombocytopenia and platelet counts. Information relating to the incidence of HIT Type II and other severe but uncommon immunogenic events (for example anaphylaxis and anaphylactoid reactions) associated with the proposed enoxaparin product is only likely to emerge from post-marketing pharmacovigilance.

6. It is considered that the safety data from the single dose PD bioequivalence Study ROV-RO20-2011-01 cannot be used as a surrogate for a clinical safety study comparing the proposed enoxaparin product and Clexane (Australia) [see the 3 reasons given at the start of the evaluator's conclusions on clinical safety, above].
7. There has been a published report of a patient in the USA developing two life-threatening haemorrhages within 4 months of initiation of treatment with a generic enoxaparin product, while there had been with no complications with 4 years previous treatment with branded enoxaparin.<sup>31</sup> There has been a reported communication identifying four cases of enoxaparin induced skin necrosis in the initial 18 months after switching from branded to generic enoxaparin.<sup>32</sup> The authors commented that they had not observed any cases of this condition for several years raising a '*concern of a greater risk of heparin-induced skin necrosis with the generic formulation*'. While the number of reported AEs associated with a generic enoxaparin following switching from a branded enoxaparin is low, the occurrences point towards the need to undertake comparative clinical safety studies when evaluating generic and branded enoxaparin products.

## First Round Benefit-Risk Assessment

### First round assessment of benefits

It is not possible to assess the benefits of Crusia-AFT and Crusia-AFT Forte based on the submitted data. The submission did not include a therapeutic equivalence study comparing the efficacy and safety of the proposed enoxaparin product with the Australian enoxaparin reference product (Clexane). Furthermore, there were no clinical studies exploring the PD effects of switching from Crusia to Clexane or vice versa. The sponsor seeks a waiver from the requirement to submit a therapeutic equivalence study. However, it is recommended that the justification for a waiver be rejected. It is considered that the sponsor has not satisfactorily demonstrated a clear correlation between surrogate PD parameters (anti-FXa and anti-FIIa) and clinical outcomes. Therefore, the PD bioequivalence data from the single dose study in healthy volunteers comparing the proposed enoxaparin product with the US enoxaparin reference product (Lovenox) cannot be extrapolated to patients with the clinical conditions.

### First round assessment of risks

It is not possible to assess the risks of Crusia-AFT and Crusia-AFT Forte based on the submitted data. The submission did not include clinical efficacy data in patients with any of the clinical conditions for which registration of Crusia-AFT and Crusia-AFT Forte are being sought. The sponsor justified the absence of therapeutic equivalence studies on the basis that it considered that the comparative molecular analysis data, nonclinical PD data and clinical PD bioequivalence data supported the essential similarity of Crusia and Clexane. Therefore, the sponsor argued that a bridging therapeutic equivalence study

<sup>31</sup> Kaffenberger B and Bekaii-Saab T. Clinical and Applied Thrombosis/Hemostasis. 2012;18(1):104-106.

<sup>32</sup> Gucalp A et al. Skin necrosis induced by generic enoxaparin. American Journal of Hematology. Letter to the editor. Published online 24 January 2013.

comparing the two products administered SC for the prevention of VTE in patients undergoing surgery with high VTE risk (for example, major orthopaedic surgery) was not required. Consequently, the sponsor considered that no other clinical studies for other indications supporting the clinical efficacy and safety of Crusia administered by SC injection were required. In addition, the sponsor considered that the PD bioavailability of Crusia following IV administration could be estimated from the comparative PD bioequivalence study of Crusia following SC administration. Therefore, a therapeutic equivalence study comparing Crusia and Clexane administered as an initial IV dose for the treatment of acute STEMI, in conjunction with a fibrinolytic agent was not required.

However, it is considered that the sponsor should submit a clinical therapeutic equivalence study comparing Crusia and Clexane administered SC for the prevention of VTE in patients undergoing surgery with high VTE risk (for example, major orthopaedic surgery). The sponsor has not demonstrated a clear correlation between surrogate PD parameters (anti-FXa and anti-FIIa) and clinical outcome. If comparable efficacy and safety of Crusia and Clexane administered SC for the prevention of VTE had been demonstrated in surgical patients at high risk of the condition, then the sponsor would have been in a position to justify extrapolation of the results of this study to other indications. In the absence of a bridging study, there are no clinical data supporting the efficacy and safety of Crusia for any of the proposed indications for which the product is to be administered by SC injection. In addition, as previously argued in [the Clinical Evaluation Report (see Attachment 2)], the PD bioequivalence of Crusia and Clexane following IV administration based on anti-FIIa activity cannot be predicted from the SC data. Therefore, it is considered that a therapeutic equivalence study comparing Crusia and Clexane administered as an initial IV dose for the treatment of acute STEMI, in conjunction with a fibrinolytic agent, is required to support approval for this indication.

It is considered that the safety data from the single-dose study in healthy volunteers comparing the proposed enoxaparin product with the US enoxaparin reference product (Lovenox) cannot be meaningfully extrapolated to patients with the medical conditions of interest. Comparative safety data from a submitted efficacy trial would have been sufficient to provide an adequate pre-marketing safety database (LMWH biosimilar guidelines).<sup>14</sup> However, the sponsor elected not to submit such a study and the justification for a waiver is considered to be unsatisfactory. The sponsor's justification for a waiver for submitting clinical safety data has been examined and is considered to be unsatisfactory.

Other risks that have not been adequately addressed in the submission relate to the absence of PK/PD bioequivalence data relating to the low dose of Crusia proposed for prophylaxis (that is 20 mg), the absence of PK/PD bioequivalence data relating to the higher strength of Crusia (that is, 150 mg/mL), the absence of a satisfactory justification for the 80% to 125% PD equivalence interval used in Study ROV-RO20-2011-01, and the lack of any immunogenicity data from a therapeutic clinical efficacy and safety study.

### **First round assessment of benefit-risk balance**

As it is not possible to assess the benefits or risks of Crusia-AFT and Crusia-AFT Forte based on the submitted data, it is not possible to assess the benefit-risk balance of the products for the proposed usage. Therefore, for regulatory purposes the benefit-risk balance of Crusia for the proposed indications is considered to be unfavourable.

### **First Round Recommendation Regarding Authorisation**

It is recommended that the application to register Crusia-AFT and Crusia-AFT Forte be rejected for the following reasons:

1. No clinical efficacy data relating to any of the proposed indications have been submitted. The sponsor's justification for not submitting at least one adequately powered, randomised, double blind, parallel group clinical trial establishing therapeutic equivalence of the proposed enoxaparin sodium product with the Australian registered reference product (Clexane) is considered to be unsatisfactory. It is considered that efficacy in the target patient populations for the proposed indications cannot be inferred from the pharmacodynamic bioequivalence data from the single dose study in 42 healthy volunteers (Study ROV-RO20-2011-01). It is considered that the sponsor has not satisfactorily established a correlation between surrogate PD parameters (anti-FXa and anti-FIIa) and clinical outcome. The absence of a clinical therapeutic equivalence study precludes the known efficacy and safety data for Clexane being safely extrapolated to Crusia. The sponsor's justification for not providing a therapeutic equivalence study is considered to be unsatisfactory for the reasons provided and discussed under Section: Pharmacodynamics (see Attachment 2).
2. No clinical safety data relating to any of the proposed indications have been submitted. Comparative safety data from an efficacy trial would have been sufficient to provide an adequate pre-marketing safety database. However, the sponsor elected not to submit an efficacy trial. The sponsor's justification for not submitting clinical safety data is considered to be unsatisfactory for the reasons provided [see Attachment 2 for further details].
3. Other clinical limitations of the submitted data include:
  - a. No pharmacodynamic bioequivalence studies comparing the proposed enoxaparin sodium product with the Australian reference product (Clexane) were submitted. No clinical studies were submitted bridging the data for Lovenox (US) used as the reference product in Study RO-RO20-2011-01 to Clexane (Australia). Therefore, there are no clinical data establishing the PD bioequivalence of the proposed formulation (Crusia) with the Australian reference product (Clexane). This raises doubts about the relevance of the submitted PK/PD bioequivalence Study ROV-RO20-2011-02 to Australian clinical practice.
  - b. No single dose intravenous (IV) pharmacokinetic bioequivalence study in healthy subjects comparing the proposed enoxaparin sodium product to the Australian reference product (Clexane) was submitted. The sponsor's justification for a waiver of the requirement for such a study is considered to be inadequate. The PD bioequivalence of Crusia and Clexane following IV administration based on anti-FIIa activity cannot be predicted from the SC data.
  - c. No adequate justification has been provided for selecting 80 to 125% as the PD bioequivalence interval in Study ROV-RO20-2011-01. The sponsor's justification was based on the bioequivalence guideline relating to conventional chemical entities.<sup>17</sup> This guideline specifies the use of plasma drug concentrations (that is  $C_{max}$ , and AUC) to establish bioequivalence rather than PD outcomes. Furthermore, this guideline expressly states that its scope is limited to chemical entities.
  - d. No adequate justification has been provided for not submitting a PD bioequivalence study with the 150 mg/mL strengths of Crusia and Clexane 150 mg/mL. Consequently, no conclusions can be made about the PD bioequivalence of Crusia and Clexane presented in the higher strength formulations (that is, 150 mg/mL).
  - e. No low dose, single dose, SC pharmacodynamic bioequivalence study in healthy volunteers comparing the proposed enoxaparin sodium product to the Australian

reference product (Clexane) was submitted. Consequently, no conclusions can be made about the PD bioequivalence of Crusia and Clexane at the clinically relevant lower prophylactic SC dose of 20 mg.

## Clinical Questions

The clinical evaluator had the following questions for the sponsor:

1. What randomisation method was used to assign patients to treatment sequence AB or BA in Study ROV-RO20-2011-01?
2. What population was the healthy subjects participating in Study ROV-RO20-2011-01 drawn from?
3. The sponsor is requested to provide a formal justification for not undertaking a SC, single dose PD bioequivalence study in healthy volunteers comparing the proposed product with the Australian reference product (Clexane) at a dose of 20 mg (that is, a low dose consistent with the use of enoxaparin for prophylaxis).
4. The sponsor's is requested to submit a justification addressing the relevant criteria in the 'Justification for not submitting biopharmaceutic data (15.9)' in the 'Australian Regulatory Guidelines for Prescription Medicines (ARGMP)' for not submitting pharmacodynamic bioequivalence studies for the proposed enoxaparin product at strengths other than 100 mg/mL.

## Second Round Evaluation of clinical data submitted in response to questions

For details of the sponsor's responses and the evaluation of these responses, please see Attachment 2.

## Second Round Benefit-Risk Assessment

### Second round assessment of benefits

After consideration of the responses to clinical questions and the additional PD equivalence Study ROV-RO20-2015-01 provided by the sponsor in its response to TGA questions, it is still not possible to assess the benefits of Crusia-AFT and Crusia-AFT Forte for the proposed usage. Neither the original submission nor the sponsor's response included a therapeutic equivalence study comparing the efficacy and safety of the proposed enoxaparin product with the Australian enoxaparin reference product (Clexane). Furthermore, there were no clinical studies exploring the PD effects of switching from Crusia to Clexane or vice versa. The sponsor seeks a waiver from the requirement to submit a therapeutic equivalence study. However, it is recommended that the justification for a waiver be rejected. It is considered that the sponsor has not satisfactorily demonstrated a clear correlation between surrogate PD parameters (anti-FXa and anti-FIIa) and clinical outcomes. Therefore, the PD bioequivalence data from the 2 single dose studies in healthy volunteers comparing the proposed enoxaparin product with the US enoxaparin reference product (Lovenox) and with the EU reference product (Clexane) cannot be extrapolated to patients with the clinical conditions proposed for approval.

## Second round assessment of risks

After consideration of the responses to clinical questions and the additional PD equivalence Study ROV-RO20-2015-01 provided by the sponsor in its response to TGA questions, it is still not possible to assess the benefits of Crusia-AFT and Crusia-AFT Forte for the proposed usage. Neither the original submission nor the sponsor's response included clinical efficacy data in patients with any of the clinical conditions for which registration of Crusia-AFT and Crusia-AFT Forte are being sought.

The sponsor justified the absence of therapeutic equivalence studies on the basis that it considered that the comparative molecular analysis data, nonclinical PD data and clinical PD bioequivalence data supported the essential similarity of Crusia and Clexane. Therefore, the sponsor argued that a bridging therapeutic equivalence study comparing the two products administered SC for the prevention of VTE in patients undergoing surgery with high VTE risk (that is, major orthopaedic surgery) was not required. Consequently, the sponsor considered that no other clinical studies for other indications supporting the clinical efficacy and safety of Crusia administered by SC injection were required. In addition, the sponsor considered that the PD bioavailability of Crusia following IV administration could be estimated from the comparative PD bioequivalence study of Crusia following SC administration. Therefore, a therapeutic equivalence study comparing Crusia and Clexane administered as an initial IV dose for the treatment of acute STEMI, in conjunction with a fibrinolytic agent was not required.

However, it is considered that the sponsor should submit a clinical therapeutic equivalence study comparing Crusia and Clexane administered SC for the prevention of VTE in patients undergoing surgery with high VTE risk (for example, major orthopaedic surgery). The sponsor has not demonstrated a clear correlation between surrogate PD parameters (anti-FXa and anti-FIIa) and clinical outcome. If comparable efficacy and safety of Crusia and Clexane administered SC for the prevention of VTE had been demonstrated in surgical patients at high risk of the condition, then the sponsor would have been in a position to justify extrapolation of the results of this study to other indications. In the absence of a bridging study, there are no clinical data supporting the efficacy and safety of Crusia for any of the proposed indications for which the product is to be administered by SC injection. In addition, as previously argued in this document, the PD bioequivalence of Crusia and Clexane following IV administration based on anti-IIa activity cannot be predicted from the SC data. Therefore, it is considered that a therapeutic equivalence study comparing Crusia and Clexane administered as an initial IV dose for the treatment of acute STEMI, in conjunction with a fibrinolytic agent, is required to support approval for this indication.

It is considered that the safety data from the single dose PD equivalence studies in healthy volunteers comparing the proposed enoxaparin product with the US enoxaparin reference product (Lovenox) and the EU enoxaparin reference product (Clexane) cannot be meaningfully extrapolated to patients with the medical conditions of interest. Comparative safety data from a submitted efficacy trial would have been sufficient to provide an adequate pre-marketing safety database as per LMWH biosimilar guidelines.<sup>14</sup> However, the sponsor elected not to submit such a study and the justification for a waiver from the requirement to submit clinical safety data is considered to be unsatisfactory.

Other risks that have not been adequately addressed in the submission relate to the absence of a satisfactory justification for the 80% to 125% PD equivalence interval used in Studies ROV-RO20-2011-01 and ROV-RO20-2015-01, and the lack of any immunogenicity data for Crusia-AFT or Crusia-AFT Forte from a therapeutic clinical efficacy and safety study.

## Second round assessment of the benefit-risk balance

As it is not possible to assess the benefits or risks of Crusia-AFT and Crusia-AFT Forte based on the submitted data and the additional data provided with the sponsor's response to the first round clinical evaluation report, it is not possible to assess the benefit-risk balance of the products for the proposed usage. Therefore, for regulatory purposes the benefit-risk balance of Crusia for the proposed indications is considered to be unfavourable.

## V. Pharmacovigilance findings

### Risk management plan

The sponsor submitted a Risk Management Plan: EU-RMP version 01 dated 31 July 2014 (Data lock point (DLP) 31 July 2014) and Australian Specific Annex (ASA) version 01 dated 10 February 2016 (DLP 10 February) which was reviewed by the RMP evaluator.

### Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown below in Table 2.

**Table 2. Sponsor's summary of the ongoing safety concerns**

Summary of safety concerns	
Important identified risks	Bleeding Immune mediated thrombocytopenia Anaphylactoid and anaphylactic reactions
Important potential risks	Liver injury Hyperkalaemia <sup>1</sup> Fetal death <sup>1</sup> Prosthetic heart valve thrombosis <sup>1</sup> Neuraxial haematoma <sup>1</sup> Skin and subcutaneous disorders <sup>1</sup> Osteoporosis following long term therapy <sup>1</sup>
Missing information	Safety profile in patients with hepatic impairment Safety profile in paediatric patients <sup>1</sup> Safety profile in obese patients (BMI > 30) <sup>1</sup> Safety profile in pregnant and lactating women
Other risks	Risks associated with brand switching <sup>1</sup>

1. Refers to newly added concerns in the updated ASA; BMI = Body mass index.

### Pharmacovigilance plan

No additional pharmacovigilance activities are proposed.



### Risk minimisation activities

No additional risk minimisation activities are proposed.

### Reconciliation of issues outlined in the RMP report

The sponsor did not respond directly to the recommendations in the first round RMP evaluation report. Instead, it has provided an updated EU-RMP with the ASA with the sponsor's response to TGA questions and requests for additional information. The RMP evaluator's recommendations and response to how they have been addressed in the updated EU-RMP and ASA are shown below in Table 3.

**Table 3. RMP recommendations and evaluation of changes following the submission of an updated RMP and ASA**

First round RMP recommendations and evaluation of changes following submission of an updated RMP and ASA
<p><b>Recommendation 1:</b> Any safety concerns identified by the clinical or nonclinical evaluators that impact on the safety specifications should be addressed in a revised RMP.</p>
<p>RMP evaluator comment: The clinical and nonclinical evaluators are satisfied with the safety specification.</p>
<p><b>Recommendation 2:</b> The following safety concerns have also been related to the use of enoxaparin. The sponsor should provide justification to why they are not related to Crusia-AFT enoxaparin or add them to the ASA as important potential risks:</p> <p>a) Hyperkalaemia; b) Foetal death; c) Prosthetic heart valve thrombosis; d) Neuraxial haematoma; e) Skin and subcutaneous disorders; and f) Osteoporosis following long term therapy.</p>
<p>RMP evaluator comment: The sponsor has added the above safety concerns in the updated RMP.</p>
<p><b>Recommendation 3:</b> It is noted that the clinical setting in which enoxaparin is used and the duration of treatment provide limited opportunities for brand switching. However, as a requirement for biosimilar medicines, the sponsor should assess the risk of different immunological response in patients who have previously used the reference products in the ASA. The risks associated with biosimilarity and predictable patterns of use, in particular, assessment of risks associated with the switching between the reference and the biosimilar products should be discussed.</p>
<p>RMP evaluator comment: The sponsor has added brand switching to the list of safety concerns in the ASA as 'other risks'. It has also addressed the risk under 'Potential for medical errors or other risks if applicable' in the updated ASA. This is acceptable.</p>
<p><b>Recommendation 4:</b> The sponsor should discuss how it plans to monitor the risks associated with brand switching in the ASA.</p>
<p>RMP evaluator comment: The sponsor has included in the draft PI that trade name of the administered medicine should be recorded in the patient's file to trace the use of specific brand agents. This is acceptable.</p>
<p><b>Recommendation 5:</b> The sponsor should assess the need for risk minimisation</p>

### First round RMP recommendations and evaluation of changes following submission of an updated RMP and ASA

activities to mitigate the risks associated with different clinical response following brand switching in the ASA.

RMP evaluator comment: The sponsor has proposed to mitigate brand switching through routine risk minimisation. This is acceptable at this stage.

#### Summary of recommendations

The sponsor has adequately addressed all issues raised in the first round RMP evaluation report.

#### Wording for conditions of registration

The suggested wording for registration is:

- Implement EU-RMP version 1.0; dated 8 April 2016; (DLP 8 April 2016) with Australian Specific Annex version 01; dated 26 October 2016 (DLP 26 October 2016) and any future updates as a condition of registration.

## VI. Overall conclusion and risk/benefit assessment

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

### Quality

The quality evaluation considered the sponsor has established similarity between its product and Clexane and has no objection to its approval.

Enoxaparin is presented in a sterile solution with water for injection as its excipient.

Enoxaparin is obtained by alkaline depolymerisation of the benzyl ester derivative of heparin for porcine mucosa.

The evaluator noted several steps in the manufacturing process, including the formation of a salt, the formation of an ester, a depolymerisation step and a purification step.

The sponsor undertook comparability studies with EU Clexane and US Lovenox. The following aspects were compared:

- *Higher order structure:* This was similar but not identical to Clexane and Lovenox, particularly with regards to amide bonds, carboxyl group, sulfation and alcohol groups. The Crusia-AFT product had a relatively higher percentage of molecular masses < 2000 Da and relatively less > 8000 Da. The quantitation of monosaccharides in Clexane, Lovenox and the proposed enoxaparin are not identical but the monosaccharides found in Clexane and Lovenox are also found in the proposed enoxaparin in quantities within the range of normal variation.
- *Disaccharides, including sulfation of disaccharides:* The quantitation of the disaccharides derived from digestion of enoxaparin showed statistically significant differences between the Clexane, Lovenox and Crusia-AFT. The sponsor considered these differences due to a difference in raw material heparin sodium. The depolymerisation step of manufacture produces 1,6 anhydro structures at the reducing end of the sugars. The content was  $21 \pm 0.6\%$  (range 20 to 22),  $20 \pm 0.7\%$

(range 19 to 21),  $21 \pm 1.0\%$  (range 21 to 22). The test and reference products (Clexane) had approximately 2 sulphates per disaccharide unit as required by the Ph.Eur./British Pharmacopoeia monographs, and were approximately equally sulphated.

- *Oligosaccharide fragment mapping*: This showed the products were similar but not identical.
- *Biological activity*: The potency, as measured by anti-FXa, anti-FIIa and AT III binding showed a similar but not identical binding.

The binding of all products to AT III were found to be similar, however this reflects the similarity of the anti-FXa activity.

- *Immunogenicity*: Residual lipidic impurities were not detected in Crusia nor in Clexane and the risk of residual amounts of nucleotidic and protein impurities were below the pharmacopoeial limits. [information redacted]. The sponsor and the evaluator concluded that the sponsor's product and Clexane are equivalent in their capacity to expose antigenic neoepitopes on PF4 to which PF4/heparin antibodies bind. Heparin induced platelet activation demonstrated no relevant difference between the reference products and the sponsor's product. The evaluator concluded that the test and reference products interact in the same way with PF4, leading to very similar and probably identical conformational changes in PF4. The evaluator also noted that immunogenicity in vivo did not correlate with large PF4/heparin complexes and near neutral surface charge as expected in a mouse model.
- *Stability*: The stability data supported a shelf life of 36 months with storage conditions of 'Store below 25°C (Do Not Freeze)'.

It is noted that there has been no direct comparison, such as a bridging study, to conclude the comparability of the Australian reference product with the EU Clexane. The sponsor has stated the two products are produced in a single manufacturing facility in France, the formulations in Australia and Spain are identical, being comprised of enoxaparin sodium (as active pharmaceutical ingredient) and water for injections, implying no peculiar formulation issues specific to Australian Clexane, that all strengths that are registered in Australia are available in Spain, and they are presented in identical dose forms. The evaluator has considered that for this particular biosimilar, given the closeness of its characteristics with the international reference products, a bridging study would not contribute to the comparability exercise in a meaningful way.

## Nonclinical

The nonclinical evaluator had no objection to the approval of the proposed biosimilar provided adequate data are available in [parts of the dossier other than nonclinical data] to address the comparability of the US and Australian reference products, and the comparability of the Australian reference product and the proposed biosimilar, Crusia-AFT, with respect to efficacy and immunogenicity.

A summary of the findings of the nonclinical evaluation is as follows:

- Comparative pharmacokinetic studies using pharmacodynamic markers as surrogates for assessing exposure to enoxaparin were conducted using the US reference product Lovenox rather than the Australian reference product Clexane.
- In rabbits, US Lovenox and Crusia-AFT had similar profiles for FIIa, aPTT and TFPI. This was a non-diseased animal model, and the evaluator noted the results do not equate with clinical efficacy. US Lovenox and Crusia-AFT were bioequivalent for anti-FXa activity but anti-FIIa activity was not assessed for bioequivalence. The

evaluator considered this should have been considered given the differences between the products observed in the in vitro studies submitted in for the quality evaluation.

- No repeat dose toxicity studies were submitted.
- No animal efficacy studies were submitted to support the use of Crusia-AFT for the proposed indications
- The Pregnancy Category C was considered acceptable.<sup>24</sup>
- Local toxicity studies were not submitted but this was considered acceptable.

Comparative immunogenicity studies:

- A rat study compared seroconversion of Crusia-AFT with Clexane and enoxaparin (development of anti-heparin/PF4 antibodies) of exposed and unexposed animals, however approximately 40% seroconverted in both groups, and the evaluator suggested '*little weight can be placed on the findings in this study given the high seroconversion rate in the negative control group*'. There was no significant difference for platelet activation or aggregation and there was no evidence of thrombocytopenia in any of the treated animals. The evaluator noted the low predictivity of animal studies for the evaluation of immunogenicity in humans.
- Enoxaparin has been shown to alter the extent of lipopolysaccharide induced monocyte activation. An in vitro study of the effect of US Lovenox, EU Clexane and Crusia-AFT on human monocytes did not show meaningful differences in activation of TNF $\alpha$ , IL- $\beta$ , IFN $\gamma$  release and the distribution of CD3+CD69+, CD3+CD25+ and CD3+HLA DR+ cells.
- The evaluator concluded that '*due to either the conduct of the study or the design of the study, any differences in immunogenicity, effects on the immune system or risks of HIT between Crusia-AFT, and the Australian reference product, Clexane, cannot be addressed by the submitted immunogenicity studies*'.

## Clinical

The clinical dossier contained two pharmacology studies in healthy volunteers. There were no clinical efficacy or safety/immunogenicity studies.

## Pharmacology

The sponsor provided two single dose studies to investigate the PD bioequivalence of Crusia-AFT with international reference products, one for US Lovenox and one for Clexane EU.

Study ROV-RO20-2011-01 was a randomised, double blind, single dose, 2 period, 2 sequence cross over study in 42 healthy adults aged 18 to 45 years to determine the PD bioequivalence and the safety and tolerability of Rovi enoxaparin (Crusia-AFT) and US Lovenox. Subjects had a mean age of 32.4 years, were mostly male (59.5%) and mostly White (81%) or Black/African American (16.7%). 36 subjects would have provided at least 80% power to conclude PD bioequivalence assuming the mean ratio of test to reference treatments was between 0.9 and 1.1 and the intra-subject coefficient of variation was less than 20%. All 42 subjects completed the study.

**Table 6. Study ROV-R020-2011-01 Anti-FXa, Anti-FIIa and TFPI**

Test	Anti-FXa	Anti-FIIa	TFPI
	Ratio (%) of geometric LS means test/reference (90% CI)	Ratio (%) of geometric LS means test/reference (90% CI)	Ratio (%) of geometric LS means test/reference (90% CI)
AUEC <sub>0-inf</sub>	103.3 (100.6, 106.0)		99.7 (94.3, 105.5)
AUEC <sub>0-t</sub>	103.3 (100.5, 106.1)	96.3 (90.5, 102.4)	102.3 (95.2, 109.9)
A <sub>max</sub>	101.1 (97.0, 105.5)	96.2 (91.1, 101.7)	97.0 (92.6, 101.7)

The ratio (%) of geometric least squares (LS) mean of test/reference and the 90% CI for the ratio of anti-FXa to anti-FIIa was 107.1 (100.2, 114.5).

Using 95% CI the sponsor demonstrated the PD parameters of interest were within the pre-specified bioequivalence limits of 80 to 125%.

At the second round, the sponsor provided an additional PD bioequivalence study using EU Clexane. Study ROV-R020-2015-01 was a single dose, randomised, double blind, 2 period, 2 sequence crossover trial of 46 healthy subjects aged 18 to 45 years that compared the proposed product (test) with EU Clexane (reference). Subjects were mostly male (72%), White (85%), with a median age of 25 years. A study including 40 subjects was considered to provide at least 80% power to conclude biosimilarity, assuming the geometric mean ratio of the test versus reference treatments was between 0.9 and 1.1 and the intrasubject CV was < 18%. 45 subjects completed the first sequence, and 43 completed the second. One withdrew because of an AE. A summary of study findings is shown in Table 7, below.

**Table 7. Study ROV-R020-2015-01 Anti-FXa, Anti-FIIa and TFPI**

Test	Anti-FXa		Anti-FIIa		TFPI	
	ratio (%) of geometric LS means test/reference (90% CI)	CV (%)	ratio (%) of geometric LS means test/reference (90% CI)	CV (%)	ratio (%) of geometric LS means test/reference (90% CI)	CV (%)
AUEC <sub>0-inf</sub>	104.2 (100, 108.6)	8.8			108.4 (102.1, 115.2)	7.9
AUEC <sub>0-t</sub>	103.8 (99.8, 108.0)	9.1	103.3 (94.7, 112.6)	30.5	105.9 (99.1, 113.1)	8.6
A <sub>max</sub>	101.1 (94.6, 105.9)	13.0	103.5 (94.7, 112.6)	20.2	104.1 (95.6, 113.4)	12.8

T<sub>max</sub> for anti-FXa for both treatments was 4.0 hours, and 4.5 hours for anti-FIIa.

Similar results were obtained from a sensitivity analysis conducted using patient data from those subjects with < 3 missing anti-FXa activities in the 2 to 6 hours post dose interval.

The ratio (%) of geometric LS means of test/reference and the 90% CI for the ratio of anti-FXa to anti-FIIa was 107 (87.9 to 114.5).

The sponsor provided a number of justifications for its approach to the characterising of the clinical comparability of its biosimilar with the international reference products:

- The sponsor provided a justification for the bioequivalence margins based on PK parameters and that for most medicines differences in systemic exposure of up to 20% are not clinically significant. However, a discussion of the relevance of these margins for the safety and efficacy of the product compared to the reference was not included.
- The sponsor provided its view of the correlation between PD parameters and clinical outcomes based equating anti-FXa with reported clinical outcomes from literature. The literature referenced was reviewed by the evaluator who was not convinced sufficiently robust evidence of the predictive value of the PD markers chosen for the PD studies for safety and efficacy had been presented. The substantial gap in the justification was anti-FIIa activity and its relationship to outcome in patients using enoxaparin.
- An acceptable justification for providing bioequivalence studies using the 100 mg strength only was provided on the basis of the linearity of anti-FXa activity for Clethane over the dose range from 20 to 100 mg, and the comment about the similarity of the PK profiles for the 100 mg/mL and 200 mg/mL dosing reported in the US Product Monograph for Lovenox.
- A justification for the absence of an IV PK/PD study was presented. The TGA adopted EU guidelines for similar LMWHs recommend an IV PK/PD study if the originator enoxaparin is also licenced for IV or intra-arterial use. The sponsor's justification was based on the anti-FXa ratio of SC/IV is 91% of the reference product, and has provided references to support this statement. The clinical evaluator on reviewing this evidence found variability in the reported absolute bioavailability of the anti-FIIa component. Bioavailability for anti-FIIa SC/IV 19% and the terminal half-life 275 minutes for SC and IV administration for a 40 mg dose was reported in Bara et al., (1985).<sup>33</sup> In Sanderink et al., (2002) the absolute bioavailability for anti-FXa following a 1.5 mg/kg dose of enoxaparin (SC and IV) in non-obese subjects was also higher than the absolute value for anti-FIIa (106% versus 85%, respectively).<sup>34</sup> The terminal half life of anti-FIIa was longer with SC administration of the biosimilar and Clethane (2.75 versus 1.46 hours) in Study ROV-RO20-2011-01 compared to 4.85 and 4.60 for anti-FXa suggesting some kind of difference in these products. The evaluator concluded bioequivalence for all activity of enoxaparin IV cannot be accurately predicted from the SC data.

The TGA obtained an expert opinion regarding the suitability of the bioequivalence margins in this submission. The conclusion was:

- The use of pharmacodynamics metric (anti-FXa and anti-FIIa activity) to investigate and compare the in vivo biosimilarity of enoxaparin is supported by guidance documents, peer reviewed publications and consensus statements
- There is no clear regulatory guidance on the statistical comparison of anti-FXa or anti-FIIa activity using the 90% confidence interval of log-transformed  $A_{UEC}$  and  $A_{max}$  ratio data. However, there are at least 2 excellent peer review publications that have used this approach in rigorous bioequivalence studies.

<sup>33</sup> Bara L et al., Comparative pharmacokinetics of a low molecular weight heparin (PK 10 169) and unfractionated heparin after intravenous and subcutaneous administration. *Thromb Res* 1985 Sep 1;39(5):631-6.

<sup>34</sup> Sanderink G et al., The pharmacokinetics and pharmacodynamics of enoxaparin in obese volunteers. *Clinical Pharmacology and Therapeutics* 2002, 72: 308-318.

- In summary, the use of the 90% confidence interval of the log-transformed  $A_{U_{EC}}$  and  $A_{max}$  ratio based in anti-FXa and/or anti-FIIa activity and comparison to the accepted bioequivalence criteria of 80% to 125% is appropriate to assess the in vivo biosimilarity of enoxaparin products.

### **Efficacy**

No clinical data comparing the biosimilar product to an Australian or international reference product were provided in the submission.

### **Safety**

The clinical safety of the proposed enoxaparin Crusia was provided through direct single dose exposure of 87 healthy volunteers from the two PD studies. AEs were experienced by 44 (51%) of subjects. Treatment emergent AEs using the Crusia product occurred in 31 subjects and when using the reference product in 27. Overall more AEs were reported in the Clexane comparison study for both the Crusia and Clexane products compared to the Lovenox comparison study. 11 treatment related adverse events were reported by the subjects while taking enoxaparin Rovi and 14 while taking the reference products. No deaths or serious adverse events occurred during the PD studies. There was one withdrawal due to a treatment emergent AE in the Clexane comparison study. No notable changes occurred to clinical laboratory and physical findings during the studies. No post-market data were submitted. There were no repeat dose safety data from healthy volunteers and no safety data were obtained from patients. At the time of submission there were no post-market safety data.

The sponsor has noted the infrequent complication rate reported for clinical trials of thromboprophylaxis reported in the literature from patients undergoing hip or knee arthroplasty, and a study comparing Sanofi-Aventis branded enoxaparin and another brand of Eurofarma enoxaparin in Brazil that showed no statistically significant differences in bleeding events. There are no specific clinical immunogenicity studies for this biosimilar enoxaparin product, which may be reasonable given the infrequent nature of HIT.

### **Clinical evaluator's recommendation**

The clinical evaluator recommended rejection for the requested indications:

*'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 clinical evaluator was primarily concerned about:

- no clinical efficacy data in support of any of the proposed indications

- no clinical safety data relating to any of the proposed indications.

Other clinical limitations included:

- the absence of PD bioequivalence studies using the Australian reference product and no studies bridging the data for Lovenox (US) and Clexane (EU)
- no IV PD equivalence study, and the sponsor's justification for not producing a study was considered unsatisfactory because anti-FIIa activity cannot be predicted from SC data.
- no adequate justification was provided for the 80 to 125% PD bioequivalence intervals in the submitted PD studies.

## Risk management plan

The TGA has accepted the EU-RMP (Version 01 dated 31 July 2014) with an updated ASA (Version 01 dated 27 October 2016). There were no outstanding issues.

## Risk-benefit analysis

### Delegate's considerations

#### *Discussion*

The sponsor has approached the comparability of its Crusia-AFT with Clexane by relying on the quality aspects of the submission to establish comparability. The quality data comparability exercise, nonclinical and clinical studies has been undertaken using overseas reference products. A bridging study is recommended in the TGA biosimilar guidelines to link the international product with the Australian product. The sponsor has taken an alternative approach and argued that the EU Clexane products data can be accepted for the Australian Clexane product based on a single site of manufacture, and similar components in the formulation. The sponsor has not (and may not be able to) provide assurance these products are released for supply to the exactly the same specifications in Australia and the EU and are therefore reasonably expected to be the same. The quality evaluator has found the sponsor's justification for not providing a bridging study to be acceptable in this case.

The quality evaluator found the physicochemical properties showed very good correlation with the EU Clexane and US Lovenox. Some differences in the disaccharide building blocks were attributed to a difference in the raw materials, but the similarity in 1,6 anhydro pyranose rings at the reducing end of the saccharide chains is considered evidence of its similarity of depolymerisation. The test and reference products were similar but not identical in their oligosaccharide fragment mapping. The quality tests for biological activity showed that while similar they were not identical. There was more difference in the anti-FIIa activity than other parameters tested. The range of activity in the batches tested was wider than the reference Clexane with more batches with lower activity. Additional batches were included in the analyses provided in response to questions were closer in activity to the reference product. Although both products comply with the specifications of the European Pharmacopoeia Enoxaparin monograph the Clexane product had a tighter range of anti-FIIa activity.

The in vivo PD profile was demonstrated in a healthy animal model and in 2 single dose PD studies, one to compare the test product to EU Clexane and another to compare it with US Lovenox. Compared with US Lovenox the PD parameters were within the pre-specified bioequivalence margins. These appear to be adapted from the PK equivalence margins for



bioequivalence. Expert advice provided to the TGA suggests these margins are acceptable. Higher inter-individual variability was found for anti-FIIa activity raising uncertainty about the predictability of clinical efficacy and safety of the biosimilar product. An unexpected increase in activity may have safety consequences. Nevertheless, the sponsor has demonstrated equivalence of activity in the human PD studies to within a tighter range than the pre-specified bioequivalence limits. No IV dosing studies were provided. The absolute bioavailability of the anti-FIIa activity is variable from the evidence presented, producing uncertainty about the comparable clinical efficacy and safety of Crusia when it is given by this route. No repeat dose PD studies were provided to demonstrate that accumulation is comparable. If different from the reference product, an understanding of the accumulation is most for its use in patients with chronic kidney disease. Although the half lives for activity were similar between the biosimilar and the reference products in single dose studies, small differences in the physicochemical structure may be important for clearance in renal disease.

Clinical data are an important part of the overall clinical comparability exercise. In pre-submission discussions with the TGA a therapeutic equivalence study was recommended to the sponsor. The absence of clinical data is the critical issue for this submission. Surrogate PD markers based on single-dose studies have been relied upon to provide support for the efficacy and safety of the enoxaparin biosimilar. While anti-FXa levels may be used to guide therapy for the individual patient in certain circumstances, the predictive value has not been demonstrated to be sufficiently precise that clinical outcomes can be predicted from the studies performed and clinical studies are not required. The sponsor's discussion did not take into account the role of anti-FIIa in outcome both for safety and efficacy of enoxaparin. This is difficult to predict because the role of anti-FIIa in the safety and efficacy of enoxaparin is not well characterised. The similarity of TFPI activity in the PD studies may provide some additional confidence in the results in the similarity of the anticoagulant of the biosimilar enoxaparin compared with the reference products however its predictive value for clinical outcomes is unclear. The Committee is requested to comment on the sensitivity and predictability of the biomarkers measured in the PD studies for detecting potential differences between these products.

The range of requested indications covers a broad category of patients including patients with established VTE, in whom the thrombogenic propensity of the disease differs. It is not clear whether the anticoagulant properties expected of the Crusia-AFT enoxaparin will be sufficiently similar to those of the reference product in all indications without the support of some clinical data derived from patients.

The human exposure is limited to healthy volunteers and provides very limited safety data. Clinical data are important to establish the equivalence of bleeding risk since it is not clear that the bleeding risk with enoxaparin is driven only by its anti-FXa and anti-FIIa activity. Although anti-FXa levels are used to guide therapy this measure insufficiently characterises the anticoagulant activity of enoxaparin given SC and IV to enable its use as a surrogate marker of safety and efficacy in the clinical comparability exercise.

Immunogenicity studies are of great importance in the absence of clinical data. Although some reassurance is provided by the studies conducted is not certain the sponsor has adequately addressed all aspects of immunogenicity and safety in the submission. The advice of the Committee is sought in this matter.

No study designed to investigate the PD, efficacy or safety aspects of switching to/from Crusia-AFT to/from Australian Clexane in patients was provided in the dossier. Given that this may occur if the product were to be registered such information may be useful.

For a biosimilar, clinical data can provide reassurance of the therapeutic equivalence of the products when used in patients where there may be differences between the registered product and the biosimilar. In this case there are no clinical data to provide such reassurance. The Delegate is unconvinced that the sponsor has sufficiently

demonstrated the clinical safety and efficacy of Crusia for all the proposed indications and routes of administration based on the studies provided.

### ***Indications***

The requested indications are consistent with the approved indications for the reference product, Clexane.

### ***Dose***

The proposed doses are consistent with the approved doses for the reference product, Clexane.

### ***Data deficiencies***

The principal data deficiency in this submission for a biosimilar product is clinical data, in particular safety and immunogenicity data. The sponsor has relied on laboratory findings, animal studies and pharmacodynamic studies in healthy volunteers to support its claims of biosimilarity with the reference product Clexane. There are no data on switching to/from Clexane.

### **Conditions of registration**

The following are proposed as conditions of registration:

1. Implement EU-RMP version 1.0; dated 8 April 2016; (DLP 8 April 2016) with Australian Specific Annex version 01; date 26 October 2016 (DLP 26 October 2016) and any future updates as a condition of registration.
2. It is a condition of registration that all batches of Crusia-AFT imported into/manufactured in Australia must comply with the product details and specifications approved during evaluation and detailed in the Certified Product Details (CPD).
3. It is a condition of registration that each batch of Crusia-AFT 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.

The sponsor must supply:

- a. Certificates of Analysis of all active ingredient (drug substance) and final product.
- b. Information on the number of doses to be released in Australia with accompanying expiry dates for the product and diluents (if included).
- c. Evidence of the maintenance of registered storage conditions during transport to Australia.
- d. Six vials of each batch for testing by the TGA Laboratories Branch together with any necessary standards, impurities and active pharmaceutical ingredients (with their Certificates of Analysis) required for method development and validation.

### **Summary of issues**

In order to establish similarity with Clexane the sponsor has conducted comparisons of physicochemical properties, in-vitro tests of PD and immunogenicity, and 2 single dose PD studies in healthy volunteers. No clinical safety or efficacy data from patients are included in this submission. The issues are as follows:

1. Whether an acceptable justification has been provided to allow extrapolation of the quality, nonclinical and clinical aspects of the submission to the Australian registered Clexane, in the absence of a bridging study.

2. Whether there is sufficient evidence of similarity (physicochemical and PD) to support the efficacy of Crusia for the proposed indications and routes of administration (including IV use).
3. Whether the safety and immunogenicity of Crusia have been adequately characterised.
4. Whether the efficacy, safety and immunogenicity can be extrapolated from Clexane to Crusia for all indications and routes of administration in the absence of specific intravenous PD studies and in the absence of direct evidence from clinical trial data.

**Proposed action**

The Delegate was not in a position to say, at this time, that the application for Crusia-AFT and Crusia-AFT Forte should be approved for registration.

**Questions for the sponsor**

1. What was the age of the product used in the immunogenicity studies, for example recently manufactured, at end of shelf life? If immunogenicity testing was not conducted with product at different stages of the shelf-life please explain why the sponsor considered that was not necessary.
2. Were the batches of Clexane used in the comparability study the same as those used in the PD study? If not, have the in vitro activity of anti-FXa, anti-FIIa and TFPI been measured for these batches? If so, please provide the results.

**Request for ACM advice**

The Advisory Committee on Medicines (ACM) is requested to provide advice on the following specific issues:

1. Does the committee concur with the quality evaluator's view about a bridging study to enable linkage between the Australian reference product Clexane and the internationally registered enoxaparin reference products?
2. The sponsor has conducted a detailed comparability study. Can the committee comment on whether the different anti-FIIa activity (as per the comparability study review [not included here], and Tables 4 and 5 shown above) is likely to be of clinical concern for the efficacy of Crusia-AFT, given there are no clinical studies to support the product.
3. What are the committee's views about the sensitivity and predictability of PD markers to detect potential differences in efficacy and safety between similar low molecular weight heparin products?
4. Has sufficient data been presented to allow extrapolation of the Clexane indications and routes of administration to Crusia?
5. The sponsor has conducted a number of immunogenicity studies but there are no clinical data regarding immunogenicity. Has a sufficiently broad range of assessments been undertaken? Has the sponsor adequately characterised the interaction of its LMWH with PF4?
6. Has sufficient data been presented to allow extrapolation of the safety, aside from immunogenicity of Clexane to Crusia?

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

## Response from sponsor

### *Response to Delegate's questions for the sponsor*

1. *'What was the age of the product used in the immunogenicity studies, for example recently manufactured, at end of shelf-life? If immunogenicity testing was not conducted with product at different stages of the shelf-life please explain why the sponsor considered that was not necessary.'*

The sponsor confirms that the immunogenicity studies were conducted with product at different stages of shelf life:

- Study S15/518-RV-PD (dated January 2016) used batches at different stages, from recently manufactured (6 months old) to the end of shelf life (3 years old).
  - Report number 1-2016 (dated May 15 to March 16) used batches from recently manufactured (4 months old) to the end of shelf life (3 years old).
  - IV-RODI04-003/01 (dated October 2015) used batches at different stages, from recently manufactured (8 months old) to the end of shelf life (3 years old).
  - Kymos Study Code S15/492-RV (dated October to November 2015) used batches at different stages, from recently manufactured (1 month old) to close to the end of shelf life (more than 2 years old).
  - S37677 (dated November to December 2012) used batches recently manufactured (4 to 9 months old).
  - VPT1266 (dated January 2013) used batches from 5 months old to 1 year old.
2. *'Were the batches of Clexane used in the comparability study the same as those used in the PD study? If not, have the in vitro activity of anti-FXa, anti-FIIa and TFPI been measured for these batches? If so, please provide the results.'*

The sponsor confirms that Clexane used in the PD study was included in the comparability study.

### *Response to the Delegate's Overview*

In response to the Delegate's Overview, the summary of issues and the application and evaluation as a whole, the sponsor wishes to put forward the following comments.

#### *Regulatory context*

The global context relating to the regulation of LMWHs has been dynamic in its change over the past decade. The first biosimilar of enoxaparin was approved by the FDA in the United States in 2010. Classified in the US as a generic medicine and submitted via the ANDA pathway, the approval was based on extensive in vitro and in vivo PD comparability data. Notably, the product was approved without clinical safety or efficacy data, signalling how far the FDA considered scientific and analytical methods had advanced since submissions made in the early to mid 2000s.

In the EU, enoxaparin and other LMWHs are classified as biosimilars and, according to the guideline on the nonclinical and clinical development of biosimilar LMWHs originally published in 2009, applications for such enoxaparin biosimilars required, in addition to in vitro and in vivo comparability data, at least one clinical trial demonstrating efficacy and safety.<sup>14</sup> However, in 2011, the EMA released a concept paper acknowledging that *'based on scientific and analytical progress, e.g. in the field of physicochemical characterisation...'* analytical data might substitute for clinical data in exceptional cases. A revised draft guideline was released for consultation in 2013.<sup>15</sup> The draft guideline allowed for the waiving of a dedicated efficacy trial if *'similar efficacy of the biosimilar and the reference product can be convincingly deduced from the comparison of their physicochemical*

*characteristics, biological activity/potency and PD fingerprint profiles, based on the use of highly sensitive and specific methods’.* This draft guideline represents the EMA’s scientific viewpoint in 2012, when the draft was agreed by the Biosimilar Medicinal Products Working Party.

While no further action was taken by the EMA on this guideline for a number of years, it is evident that the EMA and member states have been operating in accordance with this draft guideline, rather than the more restrictive 2009 guideline. This is evident from the Scientific Advice received from the EMA and detailed in our application to the TGA that dates from 2013. Furthermore, the European Public Assessment Report (EPAR) for the recently approved biosimilar enoxaparin by the EMA states that the sponsor of this biosimilar received similar advice regarding the waiving of clinical efficacy studies as early as May 2012.

In the EU, the first biosimilars of enoxaparin were approved by the EMA via the centralised procedure on 15 September 2016. These biosimilars (Inhixa and Thorinane) were approved based on the same development strategy undertaken for Crusia and presented to the TGA in this application for registration in Australia; that is, thorough and rigorous scientific comparability including both in vitro analysis and in vivo PD analysis, in addition to immunogenicity studies, comprehensive enough to provide evidence of essential similarity that negates a dedicated clinical efficacy study. The relevant EU guideline, in draft form, was revised again and adopted by the EMA in November 2016. Although it is set to come into effect in the EU in June 2017, it is clear that the EMA has actioned applications in line with the guideline already, prior to its official implementation.

It is clear that scientific opinion on these matters worldwide has shifted as advancements have been made in the field of analytical testing and that the original 2009 EU guideline no longer reflects current thinking. The strategy adopted for the development of Crusia was very much based on these advancements, in line with EU and US approaches, and consistent with international regulatory practice.

#### *Appropriateness of the biomarkers for efficacy*

The sponsor considers that the PD biomarkers used in the PD studies submitted in support of Crusia are, and have been for some time, widely accepted as appropriate markers for the pharmacological action of enoxaparin, as evidenced by both FDA and EU guidelines. Indeed, current EU scientific opinion considers that biomarkers such as anti-FXa, anti-FIIa and TFPI are considered more sensitive to detect potential differences between products than a therapeutic equivalence study. In the EPAR for the recently approved biosimilar enoxaparin Inhixa, the EMA states that:

*‘...the applicant claimed that PK/PD parameters such as anti-Xa, anti-IIa and TFPI activities are more sensitive to detect potential differences in efficacy than clinical equivalence. This was endorsed by the CHMP since these biomarkers are predictive indicators of the pharmacologic action of LMWH. Furthermore efficacy trials do not seem to have enough sensitivity or statistical power to detect differences in clinical endpoints, since they have never been able to detect differences between different LMWH with evident differences in PK/PD and anti-FXa activity’.<sup>35</sup>*

Indeed, the report goes on to confirm that:

*‘...there was no clinical efficacy study performed to support the biosimilarity claim. It was agreed that potential efficacy study would not be sensitive enough to reveal small differences between two similar enoxaparin-containing products showing a similar PD profile. From this perspective, a stringent comparative quality*

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<sup>35</sup> European Public Assessment Report (EPAR), Inhixa, 21 July 2016.

*documentation supported by a reduced (non-) clinical program was considered appropriate for showing equivalence of efficacy of LMWH.'*

This view was then officially confirmed in the newly adopted EU guideline, which plainly states, under the 'Clinical studies' section that: *'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.'*

This opinion is consistent with the Scientific Advice received by the applicant of Inhixa, and is consistent with the Scientific Advice received by Rovi for Crusia in Europe. It is also consistent with the views of the FDA on this matter. The approach of using such data to demonstrate similarity in the place of a clinical efficacy trial has been referenced in EU guidelines since 2009, and is also referred to in two overarching biosimilar EU guidelines adopted by the TGA, both of which state that in some certain cases a confirmatory clinical may not be.<sup>19</sup>

The sponsor believes that strong and convincing evidence demonstrating the physicochemical, functional and PD comparability between Crusia and the reference medicine has been submitted. It is this comparability exercise, that forms the basis of the entire biosimilar application. Indeed, the quality evaluator has stated in their report that overall the quality data (inclusive of the extensive comparability study) suggest that Crusia is acceptable for registration on the ARTG.

The sponsor considers that, given the aim of an efficacy trial for a biosimilar is not to demonstrate efficacy per se but to confirm comparable clinical performance of the biosimilar with the reference medicine, a clinical efficacy trial in the case of enoxaparin would be of little value given that it is known that efficacy trials have neither the sensitivity nor the statistical power to detect differences between different LMWHs classified as distinct entities (with known differences in PK/PD and anti-FXa activities). If such studies cannot detect differences between different LMWH entities, the sponsor does not consider this approach sensitive enough to detect potential differences between biosimilar and reference versions of the same entity. On the other hand, the state of the art in vitro comparative techniques employed in the comparability exercise in support of Crusia, in addition to the PD bioequivalence studies, have demonstrated sufficient sensitivity to detect such differences.

#### *LMWHs and anti-FIIa activity*

LMWHs are derived from UFH by chemical or enzymatic depolymerisation. LMWHs have reduced inhibitory activity against FIIa relative to FXa, have a more favourable benefit-to-risk ratio than heparin in animal models and when used to treat VTE, and have superior pharmacokinetic properties.

Like UFH, LMWHs produce their major anticoagulant effect by catalysing AT mediated inhibition of coagulation factors. The pentasaccharide sequence required for binding is found on less than one-third of LMWH molecules. Because only pentasaccharide-containing heparin chains composed of at least 18 saccharide units are of sufficient length to bridge AT to thrombin, 50% to 75% of LMWH chains are too short to catalyse thrombin inhibition. However, these chains are capable of promoting FXa inactivation by AT because this reaction does not require bridging.<sup>36,37</sup>

<sup>36</sup> Garcia, D et al., Parenteral anticoagulants. Antithrombotic therapy and prevention of thrombosis: 9th ed. American College of Chest Physicians evidence-based clinical practice guidelines (2012). Chest Journal, 141(2\_suppl), e24S-e43S.

<sup>37</sup> Liu, Z et al., Pharmacological effects and clinical applications of ultra low molecular weight heparins (2014). Drug discoveries & therapeutics, 8(1), 1-10.

LMWHs are typically administered in fixed or weight-adjusted doses for thromboprophylaxis and in weight adjusted doses for therapeutic purposes. Coagulation monitoring is not generally necessary, but some authorities suggest that monitoring be done in obese patients and in those with renal insufficiency. Monitoring may also be advisable when treatment doses of LMWH are given during pregnancy. Normally monitoring is not recommended for the majority of patients, but if monitoring is required, the anti-FXa level is the recommended test.<sup>38</sup> On the contrary, the measurement of anti-IIa activity has never been recommended for monitoring LMWHs.

Although thrombin inhibition seems essential for the antithrombotic activity of UFH and LMWHs, reduction of thrombosis is a global effect to which both anti-FIIa and anti-FXa activity contribute but to a different extent. From a clinical point of view, after SC administration of prophylactic or therapeutic doses of LMWHs, the anti-FIIa activity is rapidly eliminated, whereas the anti-FXa activity remains in plasma for a significantly longer period. Thus, the *in vivo* anticoagulant efficacy of LMWHs is related to some extent to their anti-FXa function, in addition to other actions such as release of TFPI.<sup>39</sup> Therefore, the efficacy of a single daily injection of LMWH in the prophylaxis of thrombosis is not logical in light of the short half life of anti-FIIa activity.<sup>40</sup>

The thrombin-dependent feed-back mechanism leading to the generation of additional thrombin plays an important role in the pathogenesis of pulmonary embolism. Most likely, the newly formed thrombin serves as a fibrin stabiliser via the enhancement of TAFI (thrombin activatable fibrinolysis inhibitor) and factor XIII activation. Accordingly, drugs with a high anti-FXa/anti-FIIa ratio, similarly to activated protein C, will prevent the formation of lysis-resistant fibrin by inhibiting the positive feedback activation of blood clotting, thereby allowing the endogenous fibrinolytic system to work more efficiently. Moreover, the inhibition of the clotting cascade at a higher level is safer than inhibition of thrombin activity.<sup>41</sup> This finding further supports the hypothesis that inhibition of thrombin is by itself a condition associated with a higher risk of haemorrhage.

Bara et al, evaluated the relationship between clinical outcomes (thromboembolic and bleeding events) and *ex vivo* anti-FXa and anti-FIIa activities, APTT and D-dimers in 440 patients undergoing total hip replacement and given prophylaxis once daily with a LMWH (221 patients received 4500 anti-FXa IU of tinzaparin; 219 patients received 4000 anti-FXa IU of enoxaparin) in a multicentre, double blind randomised study.<sup>42</sup> Although the injected dose of enoxaparin expressed in anti-FXa IU (4000) was slightly lower than that of tinzaparin (4500), mean plasma anti-FXa IU peak levels were significantly higher in patients receiving enoxaparin. In contrast, the amount of anti-FIIa IU given in the tinzaparin group was approximately twice that of enoxaparin and mean plasma anti-FIIa peaks were significantly higher, but lower than expected, in patients receiving tinzaparin. Interestingly, the mean anti-IIa activity for both drugs 12 hours after SC injection was comparable to that measured at the basal state before any heparin treatment. The authors pointed out that if anti-FIIa was a good marker of the antithrombotic activity, it was strange that its duration was < 12 hours when patients received a single injection daily, at

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<sup>38</sup> Garcia, *op. cit.*

<sup>39</sup> Gerotziafas, G., et al. (2007). Effect of the anti-factor Xa and anti-factor IIa activities of low-molecular-weight heparins upon the phases of thrombin generation. *Journal of Thrombosis and Haemostasis*, 5(5), 955-962.

<sup>40</sup> Samama, M et al., (1994). Mechanisms for the antithrombotic activity in man of low molecular weight heparins (LMWHs). *Haemostasis*, 24(2), 105-117.

<sup>41</sup> Momi, S., et al. (2001). Low molecular weight heparins prevent thrombin-induced thrombo-embolism in mice despite low anti-thrombin activity. Evidence that the inhibition of feed-back activation of thrombin generation confers safety advantages over direct thrombin inhibition. *Haematologica*, 86(3), 297-302

<sup>42</sup> Bara, L., et al. (1999). Occurrence of thrombosis and haemorrhage, relationship with anti-Xa, anti-IIa activities, and D-dimer plasma levels in patients receiving a low molecular weight heparin, enoxaparin or tinzaparin, to prevent deep vein thrombosis after hip surgery. *British Journal of Haematology*, 104(2), 230-240.

least in Europe. In contrast, a significant anti-FXa activity was persistent for both drugs 12 hours after injection.

On the other hand, Gray et al., have found that the molecular weight dependence of binding to PF4 is very similar to that for thrombin inhibition.<sup>43</sup> Therefore the molecules which are most effective in inhibiting thrombin are also most likely to be neutralised by PF4 in a situation where platelets are activated, whereas the molecules which have only anti-FXa activity are hardly affected by PF4.

Finally, it is worth noting that generic LMWH preparations are currently under development and some have been approved for clinical use in some countries. For instance, in Brazil 5 generic versions of enoxaparin are available. Glauser et al., made a careful analysis of the enoxaparin available for clinical use in that country.<sup>44</sup> 33 batches of the active ingredient of pharmaceutical grade enoxaparin and 70 of the final pharmaceutical product were obtained from 6 different suppliers. They were analysed for their chemical composition, molecular size distribution, in vitro anticoagulant activity, and clearly there were no differences between the generic versions of enoxaparin available for clinical use in Brazil and the original drug. Specifically, the anti-FIIa activity of the final pharmaceutical preparations of the original enoxaparin was 3.8 IU/mg<sup>-1</sup> and of the generic enoxaparin [products] range from 25.8 IU/mg<sup>-1</sup> to 28.3 IU/mg<sup>-1</sup> but the pharmacological effects on animal models of experimental thrombosis and bleeding were similar.

Therefore, it could be concluded that:

- LMWHs consist of a mixture of saccharide chains of different lengths and molecular weights and thus, have a reduced inhibitory activity against FIIa relative to FXa.
- After SC administration of prophylactic or therapeutic doses of LMWHs, the anti-FIIa activity is rapidly eliminated, whereas the anti-FXa activity remains in plasma for a significantly longer period.
- Routine monitoring is not generally recommended in patients while are under anticoagulation with LMWHs, except in some special clinical settings (for example renal impairment, pregnancy). In these cases, measurement of anti-FXa activity is the most widely recommended test for monitoring LMWHs.
- Although the antithrombotic properties of the LMWHs are due to different pleiotropic effects, the contribution of the anti-FIIa activity is very limited in terms of efficacy, especially for those LMWHs with higher anti-FXa/anti-FIIa ratios, such as enoxaparin; in fact, some investigations suggest that a greater inhibition of FIIa may increase the risk of bleeding and heparin-induce thrombocytopenia.

Nevertheless, the sponsor has undoubtedly shown in two single dose crossover trials that the anti-FIIa activity of Crusia is bioequivalent to that of Lovenox/Clexane. Specifically, the 95% confidence intervals of the ratios of the geometric LS means of the peak (94.7 to 112.6) and AUC (90.9 to 117.9) anti-FIIa activities of Crusia versus the European reference enoxaparin fell in a narrower interval than the prospectively defined interval 80 to 125%.

#### *Safety and immunogenicity*

In line with the EMA's current scientific opinion on these matters, the sponsor considers that it has provided sufficient assurance concerning the comparative safety and immunogenicity of this biosimilar. The approach, in line with Scientific Advice that EMA

<sup>43</sup> Gray, E et al., (2008). Heparin and low-molecular-weight heparin. *Thrombosis and Haemostasis*, 99(5), 807.

<sup>44</sup> Glauser, B et al., (2012). Structure and haemostatic effects of generic versions of enoxaparin available for clinical use in Brazil: similarity to the original drug. *Thrombosis and Haemostasis*, 107(2), 302-314.



has been providing for several years, has now been confirmed as acceptable to the EMA in the recently adopted guideline, where it states:

*'If immunogenicity is not evaluated in a clinical trial, the immunogenic potential of the biosimilar and the reference LMWH needs to be compared in appropriate non-clinical tests (...). 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 (e.g. 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 section 4 (Non-clinical studies) should be performed'.*

The approach has been further confirmed in the approval of biosimilars Inhixa/Thorinane by the EMA, and the discussion of such data in the relevant EPARs. The development of Crusia was conducted in accordance with this approach. Given that similar physicochemical and functional characteristics were demonstrated in the comparability exercise and pharmacodynamics profiles were shown to be comparable, safety studies were directed at further elucidation of the immunogenic potential.

The similarity of the results obtained in the abovementioned studies indicates that Crusia interacts with PF4 in the same way as Lovenox and Clexane, leading to similar conformational changes in PF4. Based on these data, the risk to induce anti-PF4/heparin antibodies has been shown to be comparable between brand name products and Crusia.

#### *Extrapolation of SC data to the IV route of administration*

Again in line with current scientific opinion, in order to waive a specific single dose IV PD equivalence study in healthy subjects, the same approach has been followed that: 1) was previously accepted by the CHMP in the Scientific Advice requested by the manufacturer (Rovi) (Procedure No.: EMEA/H/SA/2647 /1/2013/III); 2) is now endorsed by the EMA guidelines; and 3) is confirmed by the European Commission who recently granted the marketing authorisation of two biosimilar enoxaparin medicines without a dedicated IV PD equivalence study.

The premise behind this EMA endorsed approach is that SC administration covers both absorption and elimination, and SC PD data are considered to be more sensitive. The mean absolute bioavailability following SC administration of enoxaparin is estimated to be 91% or higher. Indeed, the EU Summary of Product Characteristics (SmPC) for Clexane (reviewed in December 2016 by the EMA), the US PI for Lovenox, and the recently approved EU SmPC for Inhixa/Thorinane biosimilars, all state that the absolute bioavailability after SC administration, based on anti-FXa activity, *'is approximately 100%'*. Thus, provided that similarity is demonstrated in a rigorous comparability exercise and through primary endpoints of a SC PD study, a dedicated IV study is considered to be unnecessary. This is plainly stated in the recently adopted EU guideline, which states that *'Since subcutaneous administration covers both absorption and elimination of LMWH, additional pharmacology studies for intravenous or intra-arterial use, if applicable, are not required'*. Further, the EMA clearly acted in accordance with this premise prior to this guideline, as evidenced by Scientific Advice received by Rovi, Scientific Advice received by the applicant of the recently approved Inhixa in the EU, and the approval itself of the Inhixa biosimilar without a dedicated IV PD study.

In summary, the sponsor is confident that the data provided for this biosimilar application for Crusia demonstrates strong evidence of comparative similarity using state of the art analytical techniques in line with current scientific opinion and regulatory guidance worldwide. Divergence from major regulatory authorities worldwide would have wider

implications on patient access to such biosimilars in this part of the world, and would contradict efforts that encourage development of these important medicines by fostering global regulatory harmonisation.

### Advisory Committee Considerations

The Advisory Committee on Medicines (ACM), taking into account the submitted evidence of efficacy, safety and quality, considered Crusia-AFT, solution for injection, containing 100 mg/1 mL and Crusia-AFT Forte, solution for injection, containing 150 mg/1 mL of enoxaparin sodium are of the opinion that there is an overall negative benefit–risk profile for the indications as follows:

*‘Crusia-AFT/Crusia-AFT Forte is indicated for:*

- *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)’.*

In making this recommendation the ACM noted that there were no clinical efficacy or safety data in support of any of the proposed indications, and no immunogenicity studies in vivo.

The ACM further noted that the TGA currently adopted EMA guideline on the evaluation of biosimilars requires clinical studies. The ACM acknowledged the new EMA guideline on non-clinical and clinical development of similar biological medicinal products containing LMWHs, due to come into effect in June 2017.

### Specific advice

The ACM advised the following in response to the Delegate’s specific questions on this submission:

1. *Does the committee concur with the quality evaluator’s view about a bridging study to enable linkage between the Australian reference product Clexane and the internationally registered enoxaparin reference products?*

The ACM advised that although a bridging study would have been definitive, it was acknowledged that the internationally registered enoxaparin reference products and the Australian reference product were manufactured in the same facility and therefore unlikely to have any formulation differences.

2. *The sponsor has conducted a detailed comparability study. Can the committee comment on whether the different anti-FIIa activity is likely to be of clinical concern for the efficacy of Crusia-AFT, given there are no clinical studies to support the product.*

The ACM advised that though there was variability in the reported absolute bioavailability of the anti-FIIa component, the anti-FIIa activity plays a relatively minor role. The LMWHs have a reduced inhibitory activity against FIIa relative to FXa.

3. *What are the committee's views about the sensitivity and predictability of PD markers to detect potential differences in efficacy and safety between similar low molecular weight heparin products?*

The ACM noted that the new EU guideline suggested that PK and PD parameters such as anti-FXa, anti-FIIa and TFPI activities may be more sensitive to detect potential differences in efficacy than clinical equivalence. The ACM noted that the TGA adopted EU guidelines for similar LMWHs recommend an IV PK/PD study if the originator enoxaparin is also licenced for IV use.

4. *Has sufficient data been presented to allow extrapolation of the Clexane indications and routes of administration to Crusia?*

The ACM noted anti-FIIa activity cannot easily be predicted from SC data, therefore the lack of an IV PD equivalence study raised concern about the safety of this route of administration for the Crusia products.

Although the sponsor makes a reasonable argument based on the good SC bioavailability and that anti-FIIa activity plays a relatively minor role, the ACM agreed with the clinical evaluator that a dedicated IV study is required.

5. *The sponsor has conducted a number of immunogenicity studies but there are no clinical data regarding immunogenicity. Has a sufficiently broad range of assessments been undertaken? Has the sponsor adequately characterised the interaction of its LMWH with PF4?*

The ACM noted that while there were nonclinical immunogenicity studies undertaken. The ACM advised that there were no human immunogenicity studies using Crusia products to clarify the immunogenic potential in humans.

6. *Has sufficient data been presented to allow extrapolation of the safety, aside from immunogenicity of Clexane to Crusia?*

The ACM advised that there was not enough sufficient clinical efficacy or safety data to allow extrapolation of the safety, aside from immunogenicity of Clexane to Crusia.

## **Outcome**

The sponsor withdrew this application on the 6 April 2017, before the TGA had reached a decision.

## **Attachment 1. Extract from the Clinical Evaluation Report**

## **Therapeutic Goods Administration**

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