Public Assessment Report

Decentralised Procedure

Ghemaxan 10,000 IU (100 mg)/1 mL solution for injection in pre-filled syringes

Ghemaxan 15,000 IU (150 mg)/1 mL solution for injection in pre-filled syringes

Ghemaxan 2,000 IU (20 mg)/0.2 mL solution for injection in pre-filled syringes

Ghemaxan 4,000 IU (40 mg)/0.4 mL solution for injection in pre-filled syringes

Ghemaxan 6,000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes

Ghemaxan 8,000 IU (80 mg)/0.8 mL solution for injection in pre-filled syringes

Ghemaxan 12,000 IU (120 mg)/0.8 mL solution for injection in pre-filled syringes

(Enoxaparin sodium)

Procedure No: UK/H/5798/001-007/DC

UK Licence No: PL 04465/0009-10 & 0014-18

Chemi S.p.A.
LAY SUMMARY

Ghemaxan 10,000 IU (100 mg)/1 mL solution for injection in pre-filled syringes
Ghemaxan 15,000 IU (150 mg)/1 mL solution for injection in pre-filled syringes
Ghemaxan 2,000 IU (20 mg)/0.2 mL solution for injection in pre-filled syringes
Ghemaxan 4,000 IU (40 mg)/0.4 mL solution for injection in pre-filled syringes
Ghemaxan 6,000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes
Ghemaxan 8,000 IU (80 mg)/0.8 mL solution for injection in pre-filled syringes
Ghemaxan 12,000 IU (120 mg)/0.8 mL solution for injection in pre-filled syringes

This is a summary of the Public Assessment Report (PAR) for Ghemaxan 10,000 IU (100 mg)/1 mL solution for injection in pre-filled syringes (PL 04465/0009; UK/H/5798/001/DC), Ghemaxan 15,000 IU (150 mg)/1 mL solution for injection in pre-filled syringes (PL 04465/0010; UK/H/5798/002/DC), Ghemaxan 2,000 IU (20 mg)/0.2 mL solution for injection in pre-filled syringes (PL 04465/0014; UK/H/5798/003/DC), Ghemaxan 4,000 IU (40 mg)/0.4 mL solution for injection in pre-filled syringes (PL 04465/0015; UK/H/5798/004/DC), Ghemaxan 6,000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes (PL 04465/0016; UK/H/5798/005/DC), Ghemaxan 8,000 IU (80 mg)/0.8 mL solution for injection in pre-filled syringes (PL 04465/0017; UK/H/5798/006/DC) and Ghemaxan 12,000 IU (120 mg)/0.8 mL solution for injection in pre-filled syringes (PL 04465/0018; UK/H/5798/007/DC). It explains how the applications were assessed and their authorisation recommended, as well as the conditions of use. It is not intended to provide practical advice on how to use this medicine.

The products may be collectively referred to as ‘Ghemaxan’ throughout the remainder of this public assessment report (PAR).

For practical information about using Ghemaxan, patients should read the package leaflets or contact their doctor or pharmacist.

What is Ghemaxan and what is it used for?
Ghemaxan is a ‘similar biological’ medicine (biosimilar). This means that Ghemaxan is similar to a biological ‘reference’ medicine already authorised in the European Union (EU) called Clexane Syringes 2,000 IU (20 mg)/0.2 mL solution for injection, Clexane Syringes 4,000 IU (40 mg)/0.4 mL solution for injection, Clexane Syringes 6,000 IU (60 mg)/0.6 mL solution for injection, Clexane Syringes 8,000 IU (80 mg)/0.8 mL solution for injection, Clexane Syringes 10,000 IU (100 mg)/1 mL solution for injection (Aventis Pharma Limited; PL 04425/0187) and Clexane Forte Syringes 12,000 IU (120 mg)/0.8 mL solution for injection and Clexane Forte Syringes 15,000 IU (150 mg)/1 mL solution for injection (Aventis Pharma Limited; PL 04425/0185). The biological reference products may be collectively referred to as Clexane Syringes throughout the remainder of this PAR.

Ghemaxan can be used to:
- treat blood clots in the blood
- stop blood clots forming in the blood in the following situations:
  - Before and after an operation
  - When the patient has an acute illness and faces a period of limited mobility
  - When the patient has unstable angina (a condition when not enough blood gets to the heart)
  - After a heart attack
- stop blood clots forming in the tubes of the patient’s dialysis machine (used for people with severe kidney problems)
How does Ghemaxan work?
This medicine contains the active substance, enoxaparin sodium, which is a low molecular weight heparin (LMWH). It works in two ways:
1. by stopping existing blood clots from getting bigger. This helps the body to break them down and stop them causing the patient harm.
2. by stopping blood clots forming in the blood.

How is Ghemaxan used?
The pharmaceutical form of this medicine is a solution for injection and the route of administration is usually by injection beneath the skin (subcutaneous). This medicine can also be given by injection into a vein (intravenous) or through the arterial line of a dialysis circuit.

The patient should always use this medicine exactly as their doctor or pharmacist has told them. The patient should check with their doctor or pharmacist if they are not sure.

Having this medicine
- The patient’s doctor or nurse will normally give them Ghemaxan. This is because it needs to be given as an injection.
- When the patient goes home, they may need to continue to use Ghemaxan and give it to themselves (see instructions below on how to do this in the package leaflet).
- Ghemaxan is usually given by injection beneath the skin (subcutaneous).
- Ghemaxan can be given by injection into a vein (intravenous) after certain types of heart attack or operation.
- Ghemaxan can be added to the tube leaving the body (arterial line) at the start of the dialysis session.
Ghemaxan should not be injected into a muscle.

How much will be given to the patient
- The patient’s doctor will decide how much Ghemaxan to give them. The amount will depend on the reason it is being used.
- If the patient has problems with their kidneys, they may be given a smaller amount of Ghemaxan.

1) Treating blood clots in the blood
- The usual dose is 150 IU (1.5 mg) for every kilogram of body weight each day or 100 IU (1 mg) for every kilogram of body weight twice a day.
- The patient’s doctor will decide how long they should receive Ghemaxan.

2) Stopping blood clots forming in the blood in the following situations:
a) Operation or periods of limited mobility due to an illness
- The dose will depend on how likely the patient is to develop a clot. The patient will be given 2,000 IU (20 mg) or 4,000 IU (40 mg) of Ghemaxan each day.
- If the patient is going to have an operation, their first injection will usually be given 2 hours or 12 hours before their operation.
- If the patient has restricted mobility due to illness, they will normally be given 4,000 IU (40 mg) of Ghemaxan each day.
- The patient’s doctor will decide how long they should receive Ghemaxan.

b) After a heart attack
Ghemaxan can be used for two different types of heart attack called STEMI (ST-segment elevation myocardial infarction) or non STEMI (NSTEMI). The amount of Ghemaxan given to the patient will depend on their age and the kind of heart attack they have had.
PAR: Ghemaxan 100 mg/1.0ml, 150 mg/1.0 ml, 20 mg/0.2ml, 40 mg/0.4 ml, 60 mg/0.6 ml, 80 mg/0.8 ml & 120 mg/0.8 ml solution for injection in pre-filled syringe UK/5798/001-007/DC

NSTEMI type of heart attack:
- The usual amount is 100 IU (1 mg) for every kilogram of weight, every 12 hours.
- The patient’s doctor will normally ask them to take aspirin (acetylsalicylic acid) as well.
- The patient’s doctor will decide how long they should receive Ghemaxan.

STEMI type of heart attack if the patient is under 75 years old:
- An initial dose of 3,000 IU (30 mg) of Ghemaxan will be given as an injection into the vein.
- At the same time, the patient will also be given Ghemaxan as an injection beneath the skin (subcutaneous injection). The usual dose is 100 IU (1 mg) for every kilogram of body weight, every 12 hours.
- The patient’s doctor will normally ask them to take aspirin (acetylsalicylic acid) as well.
- The patient’s doctor will decide how long they should receive Ghemaxan.

STEMI type of heart attack if the patient is aged 75 years or older:
- The usual dose is 75 IU (0.75 mg) for every kilogram of body weight.
- The maximum amount of Ghemaxan given for the first two injections is 7,500 IU (75 mg).
- The patient’s doctor will decide how long they should receive Ghemaxan.

For patients having an operation called Percutaneous Coronary Intervention (PCI):
Depending on when the patient was last given Ghemaxan, their doctor may decide to give an additional dose of Ghemaxan before a PCI operation. This is by injection into the vein.

3) Stopping blood clots from forming in the tubes of the patient’s dialysis machine:
- The usual dose is 100 IU (1 mg) for every kilogram of body weight.
- Ghemaxan is added to the tube leaving the body (arterial line) at the start of the dialysis session. This amount is usually enough for a 4-hour session. However, the patient’s doctor may give them a further dose of 50 IU to 100 IU (0.5 to 1 mg) for every kilogram of body weight, if necessary.

Section 3 of the package leaflet can be consulted for detailed information on dosing recommendations, the route of administration, instructions on use of the syringe and the duration of treatment.

This medicine can only be obtained with a prescription.

What benefits of Ghemaxan have been shown in studies?
As Ghemaxan is a similar biological medicine of Clexane Syringes (Aventis Pharma Limited), studies have been limited to determine whether Ghemaxan is equivalent to the reference medicine Clexane Syringes (Aventis Pharma Limited).

What are the possible side effects of Ghemaxan?
Because Ghemaxan is a similar biological medicine, the possible side effects are taken as being the same as those of the reference medicine.

For the full list of all side effects reported with Ghemaxan, section 4 of the package leaflet can be consulted.

For the full list of restrictions, see the package leaflet.

Why is Ghemaxan approved?
It was concluded that, in accordance with EU requirements, Ghemaxan has been shown to have comparable quality and to be equivalent to Clexane Syringes (Aventis Pharma Limited). Therefore, the MHRA decided, as for Clexane Syringes (Aventis Pharma Limited), that the benefits of Ghemaxan are greater than their risks and recommended that they be approved for use.
What measures are being taken to ensure the safe and effective use of Ghemaxan?
A risk management plan (RMP) has been developed to ensure that Ghemaxan is used as safely as possible. Based on this plan, safety information has been included in the Summaries of Product Characteristics (SmPCs) and the package leaflets for Ghemaxan including the appropriate precautions to be followed by healthcare professionals and patients.

This medicinal product is a ‘black triangle’ product which is denoted by the following symbol ▼. This indicates that Ghemaxan is subject to additional monitoring and it will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

Known side effects are continuously monitored. Furthermore, new safety signals reported by patients/healthcare professionals will be monitored/reviewed continuously.

Other information about Ghemaxan
The UK, Belgium, Germany, Denmark, Greece, Spain, Finland, Italy, Netherlands and Norway agreed to grant Marketing Authorisations for Ghemaxan on 08 March 2018. Marketing Authorisations were granted in the UK to Chemi S.p.A on 05 April 2018.

The full PAR for Ghemaxan follows this summary.

For more information about treatment with Ghemaxan, read the package leaflet, or contact your doctor or pharmacist.

This summary was last updated in May 2018.
SCIENTIFIC DISCUSSION

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Scientific Discussion

I INTRODUCTION

Based on the review of the data on quality, safety and efficacy, the member states considered that the applications for Ghemaxan (PL 04465/0009-10 & 0014-18; UK/H/5798/001-007/DC) could be approved. Ghemaxan pre-filled syringes are Prescription Only Medicines (POM) indicated in adults for:

- Prophylaxis of venous thromboembolic disease in moderate and high-risk surgical patients, in particular those undergoing orthopaedic or general surgery including cancer surgery.
- Prophylaxis of venous thromboembolic disease in medical patients with an acute illness (such as acute heart failure, respiratory insufficiency, severe infections or rheumatic diseases) and reduced mobility at increased risk of venous thromboembolism.
- Treatment of deep vein thrombosis (DVT) and pulmonary embolism (PE), excluding PE likely to require thrombolytic therapy or surgery.
- Prevention of thrombus formation in the extracorporeal circulation during haemodialysis.
- Acute coronary syndrome:
  - Treatment of unstable angina and non ST-segment elevation myocardial infarction (NSTEMI), in combination with oral acetylsalicylic acid.
  - Treatment of acute ST-segment elevation myocardial infarction (STEMI) including patients to be managed medically or with subsequent percutaneous coronary intervention (PCI).

These applications were submitted using the Decentralised Procedure (DCP), with the UK as Reference Member State (RMS) and Belgium, Germany, Denmark, Greece, Spain, Finland, Italy, Netherlands and Norway as Concerned Member States (CMS). The applications for Ghemaxan were submitted under Article 10(4) of Directive 2001/83/EC, as amended, as similar biological applications (biosimilars). The reference biological product for these applications is Lovenox 4,000 UI anti-Xa/0.4 ml solution injectable en seringue préremplie which was first authorised in France to the marketing authorisation holder (MAH) Sanofi-Aventis France on 17 March 1993. The equivalent UK reference biological products are Clexane Syringes and Clexane Forte Syringes which were first authorised to May and Baker Limited on 22 October 1990 (Clexane Syringes; PL 00012/0196) and 16 December 1999 (Clexane Forte Syringes; PL 00012/0339) and underwent changes of ownership procedures to the current MAH Aventis Pharma Limited on 30 January 2009 (PL 04425/0187) and 27 August 2009 (PL 04425/0185) respectively. The reference biological product used in the bioequivalence study has been taken from the UK market (Clexane Syringes [Aventis Pharma Limited; PL 04425/0187]). This is acceptable.

Enoxaparin is a LMWH with a mean molecular weight of approximately 4,500 daltons, in which the antithrombotic and anticoagulant activities of standard heparin have been dissociated. The drug substance is the sodium salt.

In the *in vitro* purified system, enoxaparin sodium has a high anti-Xa activity (approximately 100 IU/mg) and low anti-IIa or anti-thrombin activity (approximately 28 IU/mg), with a ratio between 3.3 and 5.3. These anticoagulant activities are mediated through anti-thrombin III (ATIII), resulting in anti-thrombotic activities in humans.

Beyond its anti-Xa/IIa activity, further anti-thrombotic and anti-inflammatory properties of enoxaparin have been identified in healthy subjects and patients, as well as in non-clinical models. These include ATIII-dependent inhibition of other coagulation factors, such as factor VIIa, induction of endogenous Tissue Factor Pathway Inhibitor (TFPI) release, as well as a reduced release of von Willebrand factor (vWF) from the vascular endothelium into the blood circulation. These factors are known to contribute to the overall anti-thrombotic effect of enoxaparin sodium.
When used as prophylactic treatment, enoxaparin sodium does not significantly affect the aPTT. When used as curative treatment, aPTT can be prolonged by 1.5-2.2 times the control time at peak activity.

The original Committee for Medicinal Products for Human use (CHMP) guidance on non-clinical and clinical development of similar biological medicinal products containing LMWHs dates from 2009 (Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight heparins: EMEA/CHMP/BMWP/118264/2007; 19 March 2009).

A revision to this guideline was pending at the time of initial assessment and has now been finalised (Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight heparins: EMEA/CHMP/BMWP/118264/2007 Rev. 1; 10 November 2016). This has some significant changes. Notably, the original guideline required a comparative clinical trial demonstrating similar efficacy and safety of the biosimilar versus the reference LMWH in the prevention of venous thromboembolism (VTE) in patients undergoing major orthopaedic surgery, with extrapolation to the other indications if clinically justified. In the revised guideline, this can be waived if similarity is demonstrated in physicochemical, functional and pharmacodynamic comparisons. On this basis, several other biosimilar enoxaparin products have been approved via the centralised and decentralised procedures.

Scientific advice for the applications was given by MHRA on 15 August 2013 and 14 September 2017. This guidance has generally been followed.

The non-clinical studies conducted by the applicant in support of these applications are stated to have been conducted in accordance with Good Laboratory Practice (GLP).

One pilot study and one pharmacodynamic equivalence study (pivotal) were submitted to support these applications. The pharmacodynamic equivalence study compared the applicant’s test product Ghemaxan 8,000 IU (80 mg)/0.8 mL solution for injection in pre-filled syringes with the biological reference product Clexane Syringes 8,000 IU (80 mg)/0.8 ml solution for injection (Aventis Pharma Limited; PL 04425/0187). It is stated that both the pilot and pivotal study were conducted in accordance with Good Clinical Practice (GCP).

The RMS has been assured that acceptable standards of Good Manufacturing Practice (GMP) are in place at all sites responsible for the manufacture, assembly and batch release of this product.

For manufacturing sites within the Community, the RMS has accepted copies of current manufacturing authorisations issued by inspection services of the competent authorities as certification that acceptable standards of GMP are in place at those sites.

For manufacturing sites outside the Community, the RMS has accepted copies of current GMP Certificates of satisfactory inspection summary reports, ‘close-out letters’ or ‘exchange of information’ issued by the inspection services of the competent authorities (or those countries with which the EEA has a Mutual Recognition Agreement for their own territories) as certification that acceptable standards of GMP are in place at those non-Community sites.

The UK, Belgium, Germany, Denmark, Greece, Spain, Finland, Italy, Netherlands and Norway considered that the applications could be approved at the end of procedure (Day 210) on 08 March 2018. After a subsequent national phase, Marketing Authorisations were granted in the UK to Chemi S.p.A on 05 April 2018.
QUALITY ASPECTS

II.1 Introduction

Ghemaxan 10,000 IU (100 mg)/1 mL solution for injection in pre-filled syringes:
Each pre-filled syringe contains enoxaparin sodium 10,000 IU anti-Xa activity (equivalent to 100 mg) in 1 mL water for injections.

The finished product is packaged in a 1 mL Type I glass pre-filled syringe with staked needle and needle shield (synthetic polyisoprene rubber) closed with elastomeric plunger stopper (chlorobutyl rubber) and plunger rod. The syringe is equipped with a needle shield system and is available in pack sizes of 2, 6 and 10 pre-filled syringes. Not all pack sizes may be marketed.

Ghemaxan 15,000 IU (150 mg)/1 mL solution for injection in pre-filled syringes
Each pre-filled syringe contains enoxaparin sodium 15,000 IU anti-Xa activity (equivalent to 150 mg) in 1 mL water for injections.

The finished product is packaged in a 1.0 mL Type I glass pre-filled syringe with staked needle and needle shield (synthetic polyisoprene rubber) closed with elastomeric plunger stopper (chlorobutyl rubber) and plunger rod. The syringe is equipped with a needle shield system and is available in pack sizes of 2, 6 and 10 pre-filled syringes. Not all pack sizes may be marketed.

Ghemaxan 2,000 IU (20 mg)/0.2 mL solution for injection in pre-filled syringes:
Each pre-filled syringe contains enoxaparin sodium 2,000 IU anti-Xa activity (equivalent to 20 mg) in 0.2 mL water for injections.

The finished product is packaged in a 0.5 mL Type I glass pre-filled syringe with staked needle and needle shield (synthetic polyisoprene rubber) closed with elastomeric plunger stopper (chlorobutyl rubber) and plunger rod. The syringe is equipped with a needle shield system and is available in pack sizes of 2, 6 and 10 pre-filled syringes. Not all pack sizes may be marketed.

Ghemaxan 4,000 IU (40 mg)/0.4 mL solution for injection in pre-filled syringes:
Each pre-filled syringe contains enoxaparin sodium 4,000 IU anti-Xa activity (equivalent to 40 mg) in 0.4 mL water for injections.

The finished product is packaged in a 0.5 mL Type I glass pre-filled syringe with staked needle and needle shield (synthetic polyisoprene rubber) closed with elastomeric plunger stopper (chlorobutyl rubber) and plunger rod. The syringe is equipped with a needle shield system and is available in pack sizes of 2, 6 and 10 pre-filled syringes. Not all pack sizes may be marketed.

Ghemaxan 6,000 IU (60 mg)/0.6 mL solution for injection in pre-filled syringes:
Each pre-filled syringe contains enoxaparin sodium 6,000 IU anti-Xa activity (equivalent to 60 mg) in 0.6 mL water for injections.

The finished product is packaged in a 1 mL Type I glass pre-filled syringe with staked needle and needle shield (synthetic polyisoprene rubber) closed with elastomeric plunger stopper (chlorobutyl rubber) and plunger rod. The syringe is equipped with a needle shield system and is available in pack sizes of 2, 6 and 10 graduated pre-filled syringes. Not all pack sizes may be marketed.

Ghemaxan 8,000 IU (80 mg)/0.8 mL solution for injection in pre-filled syringes:
Each pre-filled syringe contains enoxaparin sodium 8,000 IU anti-Xa activity (equivalent to 80 mg) in 0.8 mL water for injections.

The finished product is packaged in a 1 mL Type I glass pre-filled syringe with staked needle and needle shield (synthetic polyisoprene rubber) closed with elastomeric plunger stopper (chlorobutyl rubber) and
plunger rod. The syringe is equipped with a needle shield system and available in pack sizes of 2, 6 and 10 graduated pre-filled syringes. Not all pack sizes may be marketed.

**Ghemaxan 12,000 IU (120 mg)/0.8 mL solution for injection in pre-filled syringes:**
Each pre-filled syringe contains enoxaparin sodium 12,000 IU anti-Xa activity (equivalent to 120 mg) in 0.8 mL water for injections.

The finished product is packaged in a 1 mL Type I glass pre-filled syringe with staked needle and needle shield (synthetic polyisoprene rubber) closed with elastomeric plunger stopper (chlorobutyl rubber) and plunger rod. The syringe is equipped with a needle shield system and is available in pack sizes of 2, 6 and 10 graduated pre-filled syringes. Not all pack sizes may be marketed.

Water for Injections is the only excipient in the finished product.

Satisfactory specifications and Certificates of Analysis for the primary packaging materials have been provided. All primary packaging complies with current European regulations concerning materials in contact with foodstuffs.

**II.2 DRUG SUBSTANCE**
INN: Enoxaparin sodium
Structure:
Enoxaparin sodium consists of fragments of the glycosaminoglycan heparin, having the following structural formula:

![Structural formula of Enoxaparin sodium](image)

where: \( R = H \) or \( SO_3Na \), \( R' = H \) or \( SO_3Na \) or \( COCH_3 \), \( R_2 = H \) and \( R_3 = CO_2Na \) or \( R_2 = CO_2Na \) and \( R_3 = H \)

Enoxaparin sodium is the sodium salt of a low-molecular-mass heparin that is obtained by alkaline depolymerisation of the benzyl ester derivative of heparin from porcine intestinal mucosa. Enoxaparin consists of a complex set of oligosaccharides that have not yet been completely characterised. Based on current knowledge, the majority of the components have a 4-enopyranose uronate structure at the non-reducing end of their chain. 15 per cent to 25 per cent of the components have a 1,6-anhydro structure at the reducing end of their chain.

The basic structure is that of heparin, with a series of disaccharide units formed from a uronic acid (glucuronic or iduronic) and a glucosamine, substituted in various ways. The most represented disaccharide unit of both enoxaparin sodium and heparin sodium is \( 4-\alpha-L\text{-iduronic acid-2-O-sulfate-}\alpha-(1\rightarrow4)-D\text{-glucosamine-N,6-sulfate} \), with extensive sulfation at position 6 of the amino sugar and at position 2 of the iduronic acid. Some of the amino sugar residues are N-acetylated instead of N-sulfated, and iduronic acid residues are occasionally nonsulfated.
Enoxaparin sodium complies with the monograph Low-molecular-mass heparins (0828) with the modifications and additional requirements below.

The mass-average relative molecular mass ranges between 3800 and 5000, with a characteristic value of about 4500.

The degree of sulfatation is about 2 per disaccharide unit.
The potency is not less than 90 IU and not more than 125 IU of anti-factor Xa activity per milligram, calculated with reference to the dried substance. The anti-factor IIa activity is not less than 20.0 IU and not more than 35.0 IU per milligram, calculated with reference to the dried substance. The ratio of anti-factor Xa activity to anti-factor IIa activity is between 3.3 and 5.3.

Enoxaparin is produced by alkaline depolymerisation of benzyl ester derivatives of heparin from porcine intestinal mucosa under conditions that yield a product complying with the structural requirements stated above.

Molecular formula: As shown above by the structural formula, the molecule does not have a defined molecular formula
Relative Molecular Mass: As shown above by the structural formula, the molecule does not have a defined molecular mass
Appearance: Practically white, hygroscopic powder
Solubility: Very soluble in water

Enoxaparin sodium is the subject of a European Pharmacopoeia monograph

Synthesis of the active substance from the designated starting material has been adequately described and appropriate in-process controls and intermediate specifications are applied. Satisfactory control of the starting material (pooled porcine intestinal mucosa) has been demonstrated and appropriate specifications supported by relevant Certificates of Analysis are in place for all reagents.

Appropriate proof-of-structure data have been supplied for the active substance. Potential known impurities have been identified and characterised.

An appropriate specification is provided for the active substance. Analytical methods have been appropriately validated and are satisfactory for ensuring compliance with the relevant specifications.

Batch analysis data are provided that comply with the proposed specification.

Satisfactory Certificates of Analysis have been provided for all working standards used.

Suitable specifications have been provided for all packaging used. The primary packaging has been shown to comply with current guidelines concerning contact with food.

Stability data have been generated which support a five-year shelf life when stored in the proposed packaging.
II.3 MEDICINAL PRODUCT

Pharmaceutical Development
The objective of the development programme was to formulate a safe, efficacious, solution for injection in two strengths of 100 mg/mL and 150 mg/mL enoxaparin sodium in pre-filled syringes (preservative-free; various fill volumes) that are biosimilar to the biological reference product Clexane Syringes (Aventis Pharma Limited). Suitable pharmaceutical development data have been provided for these applications.

Biosimilarity assessment and comparability studies have sufficiently demonstrated that the proposed product can be considered similar to the biological reference product from a quality perspective (refer to ‘Comparability assessment (biosimilarity)’ section below).

The active substance, enoxaparin sodium is derived from pooled porcine intestinal mucosae, the other excipient, water for injections, is not derived from animal or human origin. The applicant has confirmed that the pooled porcine intestinal mucosae are derived from pigs that fulfil the requirements for the health of animals suitable for human consumption and all stages of product and sourcing are subject to a suitable quality management system. The manufacturer has provided a declaration that the starting materials used for the manufacture of the medicinal product comply with the “Note for Guidance on Minimizing the Risk of Transmitting Animal Spongiform Encephalopathy Agents via Medicinal Products” (EMA/410/01 rev.3) and that neither the starting material used in the medicinal product nor the manufacturing process adopted to manufacture the product are potential sources of contamination by agents causing animal spongiform encephalopathy.

This product does not contain or consist of genetically modified organisms (GMO).

Manufacturing Process
Satisfactory batch formulae have been provided for the manufacture of the products, along with an appropriate description of the manufacturing process. The manufacturing process has been validated at the commercial-scale batch size and has shown satisfactory results.

Control of Finished Products
The finished product specifications are acceptable. Test methods have been described that have been validated adequately. Batch data have been provided that comply with the release specifications. Certificates of Analysis have been provided for all working standards used.

Stability of the Products
Finished product stability studies were performed in accordance with current guidelines on batches of finished product in the packaging proposed for marketing. The data from these studies support a shelf life of 36 months with the storage conditions ‘Do not freeze.’ This medicinal product is for single use only. Discard any unused product.

Suitable post-approval stability commitments have been provided to continue stability testing on batches of finished product.

Comparability assessment (biosimilarity)
The pharmaceutical form of the proposed enoxaparin sodium injection products is identical to the pharmaceutical form of the reference product Clexane i.e. ready-to-use pre-filled syringes. The formulation has been based on the listed product information of the reference product Clexane; the active substance and water for injections make up the formulation.

Enoxaparin sodium is obtained by alkaline depolymerisation of the benzyl ester derivative of heparin from porcine intestinal mucosa and as such is subject to characteristic structural modifications arising from the effects of the depolymerization reaction. Characteristic modifications to the structure such as
partial transformation of glucosamines into mannosamines, formation of 1,6-anydro derivatives and 2,3 epoxide residues with subsequent conversion to galacturonic acid and the change in the proportion of the sulfated and non-sulfated residues make enoxaparin a structurally difficult molecule to characterise.

No single technique or parameter is adequate to fully characterise the enoxaparin sodium molecule as part of a biosimilarity exercise against the reference product and therefore the applicant has followed an appropriate step-wise approach to establish biosimilarity as per relevant EU guidelines i.e. demonstration of high similarity with respect to:
- starting material (tissue type and species) and mode of depolymerisation
- molecular weight distribution and overall chemical composition
- disaccharide building blocks, fragment mapping profiles and sequences of selected unfragmented oligosaccharides
- biological and biochemical assays

An extensive (side-by-side) comparability exercise has been undertaken to demonstrate that the biosimilar enoxaparin candidate has "a highly similar" quality profile compared to the reference medicinal product. The biosimilarity comparisons have involved analysis and comparison of a broad range of physicochemical / structural properties in addition to those parameters included in the Ph. Eur. monograph and tests such as UV spectral analysis and free sulphate/carboxylate ratio. The types of studies performed and the parameters investigated are considered appropriate for the assessment of the biosimilarity of Enoxaparin sodium products and are in line with current EU guidelines.

Comparisons of test and reference enoxaparin formulations have also examined the effect of the drug product age at the time of testing.

Sufficient information regarding the starting material, pooled porcine intestinal mucosa, has been provided. An extensive biosimilarity study that encompasses comparison of heparin source material and mode of depolymerisation, physico-chemical properties, structural comparisons (similarity of oligosaccharides sequence, similarity of oligosaccharide fragments, similarity of disaccharide building blocks and similarity of affinity components) and in-vitro biological (clotting test - activated partial thromboplastin time (aPTT)) and biochemical activity (inhibition of coagulation factors Xa (anti-FXa) and IIa (anti-FIIa)) has been carried out. The large amount of data from these extensive studies was considered to acceptably support the applicant’s claim of biosimilarity between Ghemaxan and Clexane drug products.

II.4 Discussion on chemical, pharmaceutical and biological aspects
It is recommended that Marketing Authorisations are granted for these applications, from a quality point of view.
II NON-CLINICAL ASPECTS

III.1 Introduction

The applicant provided an overview which was based on non-clinical studies conducted by the applicant and data from published literature. These studies are summarised below. The non-clinical overview was written by an appropriately qualified person and is satisfactory, providing an appropriate review of the relevant non-clinical pharmacology, pharmacokinetics and toxicology.

For the statistical assessments conducted on the in vivo and in vitro parameters studied, the applicant showed that in general the 95% confidence interval analysis confirmed the essential similarity between the Ghemaxan and reference products and that in a few instances slight deviation from the 80-125% range was seen which did not change the overall conclusion that is based on a number of different equivalence criteria and scientific considerations. Thus, the confidence interval demonstrated that the proposed and reference products did not differ by an important degree.

III.2 Pharmacology

In vitro studies were conducted to compare the anti-FXa activity, anti-FIIa activity and ratio of anti-Xa to anti-Ila obtained with the proposed Ghemaxan product and Clexane UK reference product. In this study, 6 lots of Clexane and 10 lots of Ghemaxan solution for injection were tested using validated analytical methods in compliance with current British Pharmacopoeia (BP) and European Pharmacopoeia (Ph. Eur.) monographs. All lots of Clexane or Ghemaxan used were comparable and compliant with the BP and EU monographs and therefore considered to be similar.

An in vitro study was conducted to evaluate the kinetics of fibrin formation induced by the addition of thrombin to human plasma in the presence of different amounts of Ghemaxan and Clexane. The results indicated that there was no statistical difference between the average IC50 of the two products. Five Ghemaxan lots were within the Clexane range whereas one batch fell outside this range but was not statistically different to the nearest Clexane lot. Thus, based on these criteria, the fibrinokinetic activities of the two enoxaparin products were considered to be similar.

A series of studies were conducted in rats to compare the in vivo pharmacodynamics profiles of Ghemaxan and Clexane. The parameters measured included anti-FXa activity, anti-FIIa activity, tissue factor pathway inhibitor (TFPI) activity, activated thrombin activatable fibrinolysis inhibitor (TAFIa) inhibitory activity and thrombin generation inhibitory activity.

In the study conducted in rats to evaluate the anti-FXa and anti-FIIa activities of Ghemaxan compared with Clexane, statistical analysis indicated that there was no significant difference between the average AUCs of the two products nor was there any difference when the average values of each parameter were considered at various time points up to 24 hours. Furthermore, the value of each parameter for a given lot at each time point was not statistically different from any of the other lots. Therefore, it was concluded that the two products showed a similar pharmacodynamic activity in vivo.

A study was conducted in rats to measure the effect of Ghemaxan and Clexane on thrombin generation. Rats were subcutaneously administered Ghemaxan or Clexane at 3000 anti-FX U/Kg. Thrombin was rapidly reduced by the enoxaparins after 30 minutes and reached the lowest value at 2 hours returning to basal values within 18 hours. The profiles of thrombin levels were similar in all animal groups as were the respective AUC(0-24 h). Statistical analyses indicated similar inhibitory activity by the two enoxaparins.
TFPI has inhibitory effects on the coagulation cascade. A study was conducted to determine the TFPI activity in plasma samples of rats subcutaneously administered Ghemaxan and Clexane at 3000 anti FX U/Kg. As measured by a two-step colorimetric assay, both enoxaparins induced TFPI mobilisation average values of approximately 8 U/ml, compared to the pre-dose value of 6.8 U/ml; and decreased to basal values after 7 hours. The levels of TFPI and AUC0-24hrs for the two enoxaparins were also similar.

Further studies were conducted to investigate differences between Ghemaxan and Clexane. A study was conducted to compare the trace amounts of deoxyribonucleic acid (DNA) in Ghemaxan drug product compared to that in the Clexane reference product. Six representative Ghemaxan-DP batches were tested and found to contain less protein traces than the Clexane reference product. It was also demonstrated that the Ghemaxan and Clexane batches tested were similar in that they were both ribonucleic acid (RNA) free.

The fatty acids content in the Clexane and Ghemaxan samples was also determined. No quantifiable trace amounts of palmitic acid, stearic acid, oleic acid and linoleic acid, the 4 most abundant fatty acids present in the porcine fatty tissue (the porcine intestinal mucosa is the source of crude heparin used to manufacture enoxaparin) were detected in both products. The absence of significant differences between Clexane and Ghemaxan batches was also confirmed by a qualitative comparison on the content of 17 different fatty acids present in a standard mixture.

In another study, leachables (alkyl alcohols and phthalates) were detected in Clexane solution but not the Ghemaxan tested. Clexane also contained larger amounts of boron, aluminium, zinc and tungsten than Ghemaxan although levels of these components were below the limit of acceptability for elemental impurities as stipulated in ICH Q3D guidance.

Studies were conducted to evaluate the thermodynamic parameters of human platelet factor 4-enoxaparin complexes (to assess direct measurement of the heat generated or absorbed from the interaction between molecules) of batches of Ghemaxan and Clexane. The affinity, enthalpy and stoichiometry of aged and freshly produced batches of Ghemaxan and Clexane were measured. No significant differences in the parameters measured between Ghemaxan and the reference product were detected.

Using flow cytometry, the size of human platelet factor 4-enoxaparin complexes was measured. The method was specific and sensitive to changes in size of the complexes formed at various platelet factor 4 (PF4) to heparin ratios (PHRs) and to small changes among reference product batches. The structure of the complexes was studied at 9 PHRs by measuring their size distribution, the average diameter and the width of distribution. There was no significant difference in complexes between the two products. The complexes of the 6 batches of Ghemaxan were compliant with the defined acceptance criteria at all PHRs.

A study was conducted to compare the immunoreactivity of the complexes formed by Ghemaxan or Clexane when bound to human PF4. Nine heparin-induced thrombocytopenia-positive human plasma samples were used and the presence of antibodies to the complex measured using an internally developed enzyme-linked immunosorbent assay. Six batches each of Ghemaxan and Clexane were used in the study and complexes were made at 3 different PF4 to heparin ratios. The reactivity of each plasma sample was measured at 7 different serial dilutions and expressed as antibody titer (IC50). The evaluation of similarity between the two enoxaparins was based on three criteria. The two products were considered to be similar since their average titres were not statistically different at all PHRs. There were 116 out of 162 cases (6 batches x 3 PHRs x 9 plasmas) where Ghemaxan values fell within the min-max range of Clexane and in the remaining 46 cases where Ghemaxan was outside the min-max range, there was no statistically significant difference with the nearest Clexane batch.
In response to questions raised, additional non-clinical studies were conducted. To further assess the risk of immunogenicity, the potential immunomodulatory effects of the impurities present in enoxaparin were studied in vitro and in vivo. The in vitro assay measured the effect of the impurities on IgM production by splenocyte preparations and the in vivo assay measured the effect of the impurities on antigen (e.g. ovalbumin) specific immunoglobulin G (IgG) production in mice. In general, the Ghemaxan and Clexane products induced the same type of immunoglobulin M (IgM) and IgG responses. In addition, there was no effect of aging on the enoxaparin product used in the immunogenicity studies. Apart from occasional differences, statistical comparisons indicated that the Ghemaxan and Clexane products were shown to be similar.

In mice immunised with complexes made at three different enoxaparin to PF4 ratios, and seroconversion followed for 80 days, the immunogenicity of the Ghemaxan and Lovenox (Clexane equivalent in the US) were comparable.

The proposed SmPCs for Ghemaxan are in line with those for the originator products.

### III.3 Pharmacokinetics

Due to the heterogeneity of LMWHs, the pharmacokinetic assessments were determined indirectly with the pharmacodynamic evaluations (see ‘III.2 Pharmacology’ section above). Conventional non-clinical absorption, distribution, metabolism and excretion data are not requested for biosimilar applications and were not provided by the applicant. This is in accordance with the guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins (EMEA/CHMP/BMWP/118264/2007).

### III.4 Toxicology

Toxicology studies conducted to demonstrate biosimilarity are not generally required for LMWH biosimilar applications and were not presented by the applicant. This is in accordance with the guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins (EMEA/CHMP/BMWP/118264/2007).

### III.5 Ecotoxicity/Environmental Risk Assessment (ERA)

An environmental risk assessment of Ghemaxan was not conducted. In accordance with the guideline on the environmental risk assessment for medicinal products for human use (EMEA/CHMP/SWP/4447/00 corr. 1) proteins are exempted because they are unlikely to result in significant risk to the environment.

### III.6 Discussion of the non-clinical aspects

It was recommended that Marketing Authorisations are granted, from a non-clinical point of view. The CHMP concluded that the submitted non-clinical data support biosimilarity of the candidate product to the reference product.

### IV. CLINICAL ASPECTS

#### IV.1 Introduction

Enoxaparin binds to antithrombin III and accelerates antithrombin III activity, preferentially inhibiting the coagulation activity of factors Xa and IIa. The anticoagulant effect of enoxaparin is directly correlated with its inhibition of factor Xa activity. Factor Xa catalyses the conversion of prothrombin to thrombin; inhibition of this process by enoxaparin results in decreased thrombin concentration and the prevention of fibrin clot formation. Anti-Xa activity is used to monitor response to treatment with, and in vitro potency of, the LMWHs, including enoxaparin.

The accurate determination of enoxaparin in blood or target tissues is difficult to achieve as LMWHs are mainly composed of glycosaminoglycans, which are normally present in biological tissues. AntiXa and anti-IIa activities are accepted pharmacodynamic surrogates to determine the pharmacokinetic properties
and bioavailability of the LMWHs.

The toxicology, and pharmacodynamic properties, efficacy and safety profile of enoxaparin are well established.

The clinical overview is acceptable. The applicant has not performed any patient trials, the efficacy and safety discussion is restricted to published data with the innovator. As such it is an adequate review of the literature.

The applicant considers that no additional patient studies are required given:

- Bioequivalence of Clexane and Ghemaxan has been shown in healthy volunteers, on the basis of pharmacodynamic (PD) parameters
- Comparability of physicochemical characteristics, biological activity/potency and PD fingerprint profiles, based on the use of highly sensitive and specific methods.
- Comparability of in vitro and in vivo tests, fibrinokinetic analysis of clot formation and the comparable immunoreactivity.

The applicant considers that the pharmacological activity of Ghemaxan and Clexane can be expected to be the same, and that as the PD parameters compared are relevant to the coagulation cascade in both venous and arterial thromboembolism, Ghemaxan will have a similar efficacy profile in all the indications for which Clexane/Lovenox is currently approved. This is accepted. Demonstration of similarity after subcutaneous administration also supports similarity after i.v. administration, as enoxaparin is rapidly and almost completely absorbed after subcutaneous injection with a bioavailability close to 100%.

Additional non-clinical data were submitted within the procedure to assess the comparative immunogenicity between the Ghemaxan and innovator products, on the basis of the immune response in mice to the administration of enoxaparin/PF4 complexes, and on IgM production in a murine lymphocyte model. In general, the Ghemaxan and Clexane products induced the same type of IgM and IgG responses. In addition, there was no effect of ageing on the enoxaparin product used in the immunogenicity studies.

The applicant directly determined the affinity of their product versus Clexane for platelet factor 4, they were comparable. The average diameters and distribution of complexes containing different enoxaparin to PF4 molar ratios were the same for the two preparations, and the immunoreactivity of complexes prepared at different PF4 to enoxaparin molar ratios measured in HIT-positive human plasmas was comparable for both enoxaparins. Further, human plasma samples were taken from 9 subjects who had received heparin and had positive HIT antibodies. The resulting complexes with hPF4 made by Ghemaxan and Clexane were found to be of the same size and immunologically to react to the same extent.

In US post-marketing data for Ghemaxan, no reports of HIT were received for the period September 1st 2014 – August 31st 2016, corresponding to a rough estimate of over 3 million patients exposed. Although a downward reporting bias is likely as HIT is well established for enoxaparin, these figures do give some reassurance.

In general, for currently marketed LMWH products the relative risk of HIT in patients is accepted to be significantly lower than with UFH. There are however scarce data on the relative risk of HIT between enoxaparin and other LMWH. The applicant submitted a single pharmacodynamic equivalence study in healthy volunteers, from which no relevant information on the comparability of safety between test and
reference medicinal products could be derived - although the applicant's additional post-marketing and non-clinical data offer some reassurance.

The physical composition of the antigen, in particular size and charge, is thought to be an important determinant of HIT, and also the presence of impurities may affect the interaction of the LMWH with PF4. To support the available non-clinical and clinical evidence, further reassurance was sought from the biosimilar comparability exercise to conclude that any differences in immunogenicity between the proposed product and Lovenox are not clinically significant. Following responses to questions, the quality assessor concludes that the biosimilar comparability data are acceptable.

**IV.2 Pharmacokinetics**

The accurate determination of enoxaparin in blood or target tissues is difficult to achieve as LMWHs are mainly composed of glycosaminoglycans, which are normally present in biological tissues. AntiXa and anti-lla activities are accepted pharmacodynamic surrogates to determine the pharmacokinetic properties and bioavailability of the LMWHs (refer to ‘IV.3 Pharmacodynamics’ section below).

**IV.3 Pharmacodynamics**

The applicant has submitted a pivotal, cross-over study in comparison to Clexane, with a preceding pilot study. These studies are summarised below:

**PILOT STUDY**

This was a pilot, open-label study in subjects to evaluate the pharmacodynamics of enoxaparin following subcutaneous administration of 80 mg Clexane, on 2 different occasions, in healthy adult subjects. This study was conducted in order to examine the within-subject variability of Clexane in PD parameters, and subsequently the design of the pivotal PD study in healthy volunteers. Each subject received 2 s.c. doses of 80 mg Clexane over 2 Treatment Periods (1 dose/period). The results are reflected in the power calculation for the main study.

**PIVOTAL STUDY (pharmacodynamic equivalence study)**

An open-label, randomised, single-dose, 2-way crossover study to determine the comparative bioavailability of enoxaparin sodium of the test product Ghemaxan 8,000 IU (80 mg)/0.8 mL solution for injection in pre-filled syringes (Chemi S.p.A) with the reference product Clexane Syringes 8,000 IU (80 mg)/0.8 ml solution for injection (Aventis Pharma Limited) in healthy adult subjects under fasting conditions.

Following an overnight fast, subjects were administered a single dose (80 mg/0.8 ml) of test or reference product via subcutaneous injection (s.c). Blood samples were collected pre-dose and up to and including, 36 hours after each administration for the measurement of PD markers anti-FIIa, anti-FXa, thrombin/FIIa generation, TFPI, TAFi activity and TAFI antigen. The washout period between the treatment phases was 7 days between each dose administration for male subjects and female subjects of non-child bearing potential. Fertile women were in the same menstrual cycle phase (i.e. follicular phase or luteal phase) when they received test and reference product, therefore each dosing day for female subjects of child bearing potential was separated by a washout of approximately 28 days.

Individual plasma anti-FIIa, anti-FXa, thrombin/FIIa generation, TFPI, TAFi activity and TAFI antigen activity/concentration-time data were listed by treatment. Individual and mean activity/concentration-time data were also plotted by treatment on both linear and semi-logarithmic scales.

The PK parameters/end-points, were derived from plasma anti-FIIa, anti-FXa, thrombin/FIIa generation and TFPI, activity/concentration-time data. For the calculations, values below the limit of quantification (BLQ) were assigned a value of zero and the actual time of sample collection was used in the calculations. In addition, the ratio of anti-FXa/anti-FIIa activity was calculated for each PK parameter.
Derived PK end-points were listed and summarised using descriptive statistics by treatment. It was not possible to derive PK parameters from plasma TAFI activity and TAFI antigen concentration.

Following logarithmic transformation, $C_{\text{max}}$, $C_{\text{min}}$ (for thrombin/FIIa generation), $\text{AUC}_{0-t}$ and $\text{AUC}_{0-\text{inf}}$ values were subjected to an analysis of variance (ANOVA), including fixed effects for sequence, period, treatment and subject nested within sequence.

Point estimates and 95 % confidence intervals (CI) were constructed for the contrasts between treatments using the residual mean square error obtained from the ANOVA. The point and interval estimates were back-transformed to give estimates of the ratios of the geometric least squares means (LSmean) and corresponding 95 % CI. In addition, estimated geometric means were produced for each treatment.

Pharmacodynamic equivalence was achieved if the 95 % CI for geometric mean $C_{\text{max}}$ and $\text{AUC}_{0-t}$ lay between 80.00 % and 125.00 %, for both the primary endpoints Anti-FXa and anti-thrombin/factor IIa (anti-FIIa):

An assessment of $T_{\text{max}}$ and $T_{\text{min}}$ (for thrombin/FIIa generation) was performed. In addition, a 95 % non-parametric CI was constructed for the median difference in $T_{\text{max}}$.

**Results**

**Table: Summary of statistical analysis of baseline adjusted anti-FIIa activity following administration of Ghemaxan (test product) and Clexane (reference product)**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TEST IMP: Chemi Enoxaparin (80 mg/0.8 mL)</th>
<th>REFERENCE IMP: Clexane (80 mg/0.8 mL)</th>
<th>Test vs Reference</th>
<th>CV% from ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>$C_{\text{max}}$ (IU/mL)</td>
<td>Geometric LSMean</td>
<td>0.111</td>
<td>Geometric LSMean</td>
<td>0.121</td>
</tr>
<tr>
<td>$\text{AUC}_{0-t}$ (h.IU/mL)</td>
<td>0.887</td>
<td>0.954</td>
<td>93.00 (86.86 – 99.58)</td>
<td>16.0</td>
</tr>
<tr>
<td>$\text{AUC}_{0-\text{inf}}$ (h.IU/mL)</td>
<td>1.007</td>
<td>1.087</td>
<td>92.68 (86.30 – 99.54)</td>
<td>14.7</td>
</tr>
<tr>
<td>$T_{\text{max}}$ (h)</td>
<td>Median</td>
<td>4.0</td>
<td>Median</td>
<td>4.0</td>
</tr>
</tbody>
</table>

Results obtained using a fixed effects ANOVA with fixed effects for sequence, period, treatment and subject nested within sequence (excl. $T_{\text{max}}$).

$T_{\text{max}}$ results obtained using the method of Campbell and Gardner and the[a] Wilcoxon Matched Pairs test.

ANOVA = analysis of variance, N/a = not applicable.
Table: Summary of statistical analysis of anti FXa activity following administration of Ghemaxan (test product) and Clexane (reference product)

<table>
<thead>
<tr>
<th>Parameter</th>
<th>TEST IMP: Chemi Enoxaparin (80 mg/0.8 ml)</th>
<th>REFERENCE IMP: Clexane (80 mg/0.8 ml)</th>
<th>Test vs. Reference</th>
<th>CV% from ANOVA</th>
</tr>
</thead>
<tbody>
<tr>
<td>C_{max} (IU/ml)</td>
<td>0.840</td>
<td>0.845</td>
<td>Geometric LS Mean</td>
<td>7.5</td>
</tr>
<tr>
<td>AUC_{0-t} (h.IU/ml)</td>
<td>9.484</td>
<td>9.218</td>
<td>Geometric LS Mean</td>
<td>5.1</td>
</tr>
<tr>
<td>AUC_{0-inf} (h.IU/ml)</td>
<td>10.142</td>
<td>9.728</td>
<td>Geometric LS Mean</td>
<td>5.8</td>
</tr>
<tr>
<td>Median</td>
<td>Median</td>
<td>Medial</td>
<td>Geometric LS Mean</td>
<td>N/a</td>
</tr>
<tr>
<td>T_{max} (h)</td>
<td>4.0</td>
<td>4.0</td>
<td>Median Difference</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>(95% C.I.)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>99.42 (96.28 – 102.65)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>102.89 (100.67 – 105.15)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>104.26 (101.68 – 106.90)</td>
<td></td>
</tr>
</tbody>
</table>

Results obtained using a fixed effects ANOVA with fixed effects for sequence, period, treatment and subject nested within sequence (excl. T_{max}). T_{max} results obtained using the method of Campbell and Gardner and the[a] Wilcoxon Matched Pairs test. ANOVA = analysis of variance

Figure: Mean Activity-Time Profiles for Anti-FIIa Activity - Linear Scale
PAR: Ghemaxan 100 mg/1.0ml, 150 mg/1.0 ml, 20 mg/0.2ml, 40 mg/0.4 ml, 60 mg/0.6 ml, 80 mg/0.8 ml & 120 mg/0.8 ml solution for injection in pre-filled syringe
UK/5798/001-007/DC

Figure: Mean Activity-Time Profiles for Anti-FXa Activity - Linear Scale

According to the predefined criteria, Ghemaxan was bioequivalent to the reference product on the basis of primary endpoints $C_{\text{max}}$ and AUC$_0$-$t$, for both anti-FIIa and anti-FXa activity. There was also no significant difference in $T_{\text{max}}$ for anti-FIIa or anti-FXa activity.

There were measurable levels of anti-FIIa activity in some subjects pre-dose on several occasions with values ranging from 4.85% - 18.42% of the corresponding treatment period $C_{\text{max}}$. This is expected given endogenous anti-FIIa activity, so all subjects were included in the PK calculations as appropriate. Given that the baseline levels of anti-FIIa were as high as 18% of $C_{\text{max}}$ in some subjects, the applicant repeated the analyses, correcting for baseline levels.

Measurable pre-dose values were also seen for secondary endpoints of thrombin/FIIa generation and TFPI activity. For the co-primary endpoint of anti-FXa activity data all pre-dose values were BLQ.

For Anti FIIa activity, the majority of subjects had AUC %ex that was $\leq$ 20%, this occurred in some subjects receiving test product and in some subjects receiving reference product. For Anti FXa activity, all subjects exhibited AUC%ex that was $\leq$ 20%.

The results in the primary endpoints were supported by results in the ratio of Anti-FXa/Anti-FIIa Activity, and in the thrombin/FIIa generation assay.

Given the inverted shape of the thrombin/FIIa generation plasma concentration-time curves, $C_{\text{max}}$ and AUC were not reported, however the mean concentration-time profiles were comparable for test and reference products, with comparable $C_{\text{min}}$ and $T_{\text{min}}$. AUC 0-inf is not meaningful because after 12 hours the values are less than baseline, because of biological rebound effects. However, looking at values to 12 hours, the graphs are near identical.
PAR: Ghemaxan 100 mg/1.0ml, 150 mg/1.0 ml, 20 mg/0.2ml, 40 mg/0.4 ml, 60 mg/0.6 ml, 80 mg/0.8 ml & 120 mg/0.8 ml solution for injection in pre-filled syringe

UK/5798/001-007/DC

It was not possible to derive PK parameters for TAFI activity or antigen as there was little difference in either value across the 0 - 36 hour sampling period, for both test and reference product.

**Pharmacodynamic conclusions**

The 95% confidence intervals of the test/reference ratio for AUC\(0-t\) and C\(max\) values for both anti-FIIa (baseline adjusted) and anti-FXa activity lie within the acceptable limits of 80.00% to 125.00%, in line with the guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev 1/Corr**). Thus, the data support the claim that the applicant’s test product Ghemaxan 8,000 IU (80 mg)/0.8 mL solution for injection in pre-filled syringes (Chemi S.p.A) is considered pharmacodynamically bioequivalent to the reference product Clexane Syringes 8,000 IU (80 mg)/0.8 ml solution for injection (Aventis Pharma Limited).

There was also no significant difference in T\(max\) for anti-FIIa or anti-FXa activity.

**IV.4 Clinical Efficacy**

The clinical efficacy of enoxaparin sodium is well-known. No new efficacy data are presented and none are required for applications of this type. The applicant cross-refers to the literature with the reference product.

**IV.5 Clinical Safety**

No new safety data were submitted and none are required for applications of this type. The applicant cross-refers to the literature with the reference product.

No new or unexpected safety issues arose during the pharmacodynamic equivalence study.

**IV.6 Risk Management Plan (RMP)**

The marketing authorisation holder (MAH) has submitted a risk management plan (RMP), in accordance with the requirements of Directive 2001/83/EC as amended, describing the pharmacovigilance activities and interventions designed to identify, characterise, prevent or minimise risks relating to Ghemaxan.

A summary of safety concerns and planned risk minimisation activities, as approved in the RMP, are listed below:
Summary of safety concerns:

<table>
<thead>
<tr>
<th>Important identified risks</th>
<th>Heparin-induced thrombocytopenia (HIT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Important identified risks</td>
<td>Anaphylactic/anaphylactoid reactions</td>
</tr>
<tr>
<td>Important identified risks</td>
<td>Haemorrhages</td>
</tr>
<tr>
<td>Important identified risks</td>
<td>Hyperkalaemia</td>
</tr>
<tr>
<td>Important identified risks</td>
<td>Liver injury</td>
</tr>
</tbody>
</table>

| Important potential risks                       | Valve thrombosis in patients with prosthetic heart valves |
| Important potential risks                       | Medication errors                        |
| Important potential risks                       | Osteoporosis                              |
| Important potential risks                       | Use in severe renal impairment           |

| Important potential risks                       | Use in paediatric patients              |
| Important potential risks                       | Use in patients with hepatic impairment |
| Important potential risks                       | Use during pregnancy                    |
| Important potential risks                       | Use during lactation                    |
| Important potential risks                       | Use in obese patients (BMI > 30 kg/m²)   |
| Important potential risks                       | Use in patients with end stage renal disease (creatinine clearance <15 mL/min) |
Summary table of pharmacovigilance activities and risk minimisation activities by safety concern:

<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Risk minimisation measures</th>
<th>Pharmacovigilance activities</th>
</tr>
</thead>
</table>
| Heparin-induced thrombocytopenia (HIT) (identified) | Routine risk minimisation measures:  
Listed in SmPC section 4.3  
Warning in SmPC section 4.4  
Discussed in SmPC section 4.8  
A questionnaire of HIT for HCPs (Annex 4) is proposed to collect important follow up data on this condition. |                                                                                             |
| Anaphylactic/anaphylactoid reactions (identified) | Routine risk minimisation measures:  
Listed in SmPC section 4.8 | None                                                                                        |
| Haemorrhages (identified) | Routine risk minimisation measures:  
Warning in SmPC section 4.4  
Warning in SmPC section 4.5  
Discussed in SmPC section 4.8 | None                                                                                        |
| Hyperkalaemia (identified) | Routine risk minimisation measures:  
Warning in SmPC section 4.4  
Listed in SmPC section 4.8 | None                                                                                        |
| Liver injury (identified) | Routine risk minimisation measures:  
Listed in SmPC section 4.8 | None                                                                                        |
<table>
<thead>
<tr>
<th>Safety concern</th>
<th>Risk minimisation measures</th>
<th>Pharmacovigilance activities</th>
</tr>
</thead>
<tbody>
<tr>
<td>Valve thrombosis in patients with prosthetic heart valves (potential)</td>
<td>Routine risk minimisation measures:</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td><strong>Warning in SmPC section 4.4</strong></td>
<td></td>
</tr>
<tr>
<td>Medication error (potential)</td>
<td>Routine risk minimisation measures:</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td><strong>Discussed in SmPC section 4.2</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Discussed in SmPC section 6.6</strong></td>
<td></td>
</tr>
<tr>
<td>Osteoporosis (potential)</td>
<td>Routine risk minimisation measures:</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td><strong>Listed in SmPC section 4.8</strong></td>
<td></td>
</tr>
<tr>
<td>Use in severe renal impairment (potential)</td>
<td>Routine risk minimisation measures:</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td><strong>Discussed in SmPC section 4.2</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Warning in SmPC section 4.4</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Discussed in SmPC section 5.2</strong></td>
<td></td>
</tr>
<tr>
<td>Use in paediatric patients (missing information)</td>
<td>Routine risk minimisation measures:</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td><strong>Discussed in SmPC section 4.2</strong></td>
<td></td>
</tr>
<tr>
<td>Use in patients with hepatic impairment (missing information)</td>
<td>Routine risk minimisation measures:</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td><strong>Discussed in SmPC section 4.2</strong></td>
<td></td>
</tr>
<tr>
<td></td>
<td><strong>Warning in SmPC section 4.4</strong></td>
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</tr>
<tr>
<td></td>
<td><strong>Discussed in SmPC section 5.2</strong></td>
<td></td>
</tr>
<tr>
<td>Use during pregnancy (missing information)</td>
<td>Routine risk minimisation measures:</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td><strong>Discussed in SmPC section 4.6</strong></td>
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<tr>
<td></td>
<td><strong>Discussed in SmPC section 5.3</strong></td>
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<tr>
<td>Use during lactation (missing information)</td>
<td>Routine risk minimisation measures:</td>
<td>None</td>
</tr>
<tr>
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<td><strong>Discussed in SmPC section 4.6</strong></td>
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<tr>
<td>Use in obese patients (BMI &gt; 30 kg/m²) (missing information)</td>
<td>Routine risk minimisation measures:</td>
<td>None</td>
</tr>
<tr>
<td></td>
<td><strong>Discussed in SmPC section 4.6</strong></td>
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</tr>
</tbody>
</table>
IV.7 Discussion of the clinical aspects
It is recommended that Marketing Authorisations are granted, from a clinical point of view.

V. USER CONSULTATION
The package leaflet has been evaluated via a user consultation study in accordance with the requirements of Articles 59(3) and 61(1) of Directive 2001/83/EC. The language used for the purpose of user testing the PIL was English.

The results show that the package leaflet meets the criteria for readability as set out in the Guideline on the readability of the label and package leaflet of medicinal products for human use.

VI. OVERALL CONCLUSION, BENEFIT/RISK ASSESSMENT AND RECOMMENDATION
The efficacy and safety profile of enoxaparin is well known; the originator was first authorised in the EU in 1987 and has been widely used. Pharmacodynamic equivalence in man between the test and reference products was shown. Whether a dedicated clinical efficacy/safety trial in patients may be waived in this case takes into account the comparison to the reference product in terms of physicochemical characteristics and pharmacological activity, impurity profile, nature of excipients and immunogenicity evaluations.

Taking into account the latest CHMP guidance on low molecular-weight-heparins, and following satisfactory responses to all non-clinical and quality questions, it is agreed that a clinical efficacy/safety trial is not required.

The benefit/risk is therefore considered to be positive and the grant of Marketing Authorisations is, therefore, recommended.
Summary of Product Characteristics (SmPC), Patient Information Leaflet (PIL) and Labels
In accordance with Directive 2010/84/EU the Summaries of Product Characteristics (SmPC) and Patient Information Leaflets (PIL) for products granted Marketing Authorisations at a national level are available on the MHRA website.

The approved labelling for this medicine is presented below:
PAR: Ghemaxan 100 mg/1.0ml, 150 mg/1.0 ml, 20 mg/0.2ml, 40 mg/0.4 ml, 60 mg/0.6 ml, 80 mg/0.8 ml & 120 mg/0.8 ml solution for injection in pre-filled syringe

UK/5798/001-007/DC
PAR: Ghemaxan 100 mg/1.0ml, 150 mg/1.0 ml, 20 mg/0.2ml, 40 mg/0.4 ml, 60 mg/0.6 ml, 80 mg/0.8 ml & 120 mg/0.8 ml solution for injection in pre-filled syringe

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UK/5798/001-007/DC
Annex 1 - Table of content of the PAR update for MRP and DCP

Steps Taken After The Initial Procedure With An Influence On The Public Assessment Report

<table>
<thead>
<tr>
<th>Scope</th>
<th>Procedure number</th>
<th>Product information affected</th>
<th>Date of start of the procedure</th>
<th>Date of end of procedure</th>
<th>Approval/ non approval</th>
<th>Assessment report attached Y/N (version)</th>
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