Public Assessment Report

Decentralised Procedure

Heparin 5,000 I.U./ml, solution for injection

UK/H/6053/001/DC

UK licence no: PL 41947/0016

ELC GROUP SRO
LAY SUMMARY

This is a summary of the Public Assessment Report (PAR) for Heparin 5,000 I.U./ml solution for injection (PL 41947/0016; UK/H/6053/001/DC). This report will refer to Heparin 5,000 IU per ml solution for injection, as Heparin, from this instance onward. It explains how heparin was assessed and explains why authorisation was recommended, as well stating the conditions for its use. It is not intended to provide practical advice on how to use this product.

For practical information about using heparin, patients should read the Patient Information Leaflet (PIL) or contact their doctor or pharmacist.

What is Heparin and what is it used for?
Heparin belongs to a group of medicines called anticoagulants. Heparin prevents blood clotting. It is used to treat and prevent:
- blood clots in leg veins (deep vein thrombosis)
- blood clots in the lung (pulmonary embolism)

as well as for the:
- treatment of chest pains resulting from disease of the heart arteries (unstable angina pectoris)
- treatment of severe blockages affecting arteries in the legs (acute peripheral arterial occlusion)
- prevention of blood clots in the heart following a heart attack (mural thrombosis)

It is also used during heart and lung operations, and during kidney dialysis.

The doses required vary depending on the condition, full details can be found in the PIL or Summary of Product Characteristics (SmPC).

Each vial with 5 ml solution for injection contains 25,000 I.U. of heparin sodium. The other ingredients are benzyl alcohol, sodium hydroxide, hydrochloric acid and water for injections.

The product is supplied as a pack of 10 vials of Heparin 5,000 I.U./ml

How does Heparin work?
Heparin contains the active substance, heparin sodium, which prevents the formation of blood clots.

How is Heparin used?
Heparin is only administered by qualified healthcare professionals. The dose will be given into a vein either all at once or over a longer period of time (usually via a drip). The amount injected all at once into a vein should not be greater than 15ml.

Alternatively, heparin can be injected underneath the skin.

The doses required to treat vary depending on the condition full details can be found in the PIL or SmPC.

Heparin injection must not be given to premature or newborn babies, and there are no specific dosing recommendations in children.
What benefits of Heparin have been shown in studies?
As heparin is a well-known active substance and its use in the licensed indications is well-established, the applicant has presented data from the scientific literature. The literature provided confirmed the efficacy and safety of heparin for use in the licensed indications.

What are the possible side effects of Heparin?
It is important to lookout for severe allergic reactions; heparin can cause a severe allergic reaction with wheezing, difficulty breathing, a blue tinge to the lips, fever, chills, swelling of the eyes and lips, and shock. If the signs of allergic reaction are present, the treatment must be stopped and your doctor or nurse told immediately.

It is also important to look out for the below signs that you are bleeding more easily:
- unusual bruising or purple spots on your skin
- unusual bleeding from your gums
- unusual nose bleeds
- blood in your urine (which may cause this to go dark)
- black, tarry-looking stools
- bleeding that will not stop from any operation site or other injury

If unusual bleeding is suspected the doctor or nurse must be told immediately as heparin treatment may need to be stopped.

For information about side effects that may occur with using heparin, please refer to the PIL or the SmPC available on the Medicines and Healthcare products Regulatory Agency (MHRA) website.

Why is Heparin approved?
The MHRA concluded that, in accordance with EU requirements, the benefits of heparin outweigh the identified risks and recommended that the product be approved for use.

What measures are being taken to ensure the safe and effective use of Heparin?
A Risk Management Plan (RMP) has been developed to ensure that Heparin is used as safely as possible. Based on this plan, safety information has been included in the SmPC and the PIL for these products, including the appropriate precautions to be followed by healthcare professionals and patients.

Known side effects are continuously monitored. Furthermore new safety signals reported by patients and healthcare professionals will be monitored and reviewed continuously as well.

Other information about Heparin
Following the completion of a decentralised procedure a marketing authorisation was granted in the UK on 27th May 2016 (PL 41947/0016).

For more information about treatment with heparin, read the PIL or contact your doctor or pharmacist.

This summary was last updated in June 2016.
TABLE OF CONTENTS

I   Introduction                      Page 5
II  Quality aspects                  Page 7
III Non-clinical aspects            Page 8
IV  Clinical aspects                Page 9
V   User consultation               Page 13
VI  Overall conclusion, benefit/risk assessment and recommendation Page 13

Table of content of the PAR update for MRP and DCP Page 17
I INTRODUCTION

This is an application made under Article 10(a) of Directive 2001/83/EC as amended, also known as a “well-established use” application. It was submitted by decentralised procedure (UK/H/6053/001/DC), with the UK as Reference Member State (RMS). During the procedure the company withdrew the application from one CMS. The end of procedure (Day 210) was on 01 May 2016.

Heparin is a highly sulfated glycosaminoglycan polymer of varying chain size (molecular weight from 3 to 30 kDa) that is widely used as an injectable anticoagulant (though its physiological role in the body remains unknown). Pharmaceutical-grade heparin is extracted from the mucosa of pig intestines or cattle lungs.

Heparin binds to the enzyme inhibitor antithrombin III causing a conformational change that results in its activation that then inactivates thrombin and other proteases involved in blood clotting, most notably factor Xa. The rate of inactivation of these proteases by antithrombin III can increase by up to 1000-fold following binding of heparin.

Heparin is indicated in the following situations:
- Prophylaxis of deep vein thrombosis and pulmonary embolism
- Treatment of deep vein thrombosis, pulmonary embolism, unstable angina pectoris and acute peripheral arterial occlusion
- Prophylaxis of mural thrombosis following myocardial infarction
- For extracorporeal circulation and haemodialysis

A venous thrombus is a blood clot that forms within a vein. Venous thrombi are caused mainly by a combination of venous stasis, hypercoagulability and alterations in the blood vessel wall. A common type of venous thrombosis is a deep vein thrombosis, which is a blood clot in the deep veins of the leg. When a blood clot breaks loose and travels in the blood, this is called a venous thromboembolism. If the thrombus breaks off, i.e. embolises and flows towards the lungs, it can become a life-threatening (i.e. pulmonary embolism, a blood clot in the lungs). The overall incidence of venous thromboembolism is about 30 per 100,000 person years. Risk factors for venous thromboembolism include old age, major surgery, cancers, immobilisation, pregnancy, a family history and pro-inflammatory states.

Evidence supports the use of heparin in people following surgery who have a high risk of thrombosis to reduce the risk of a deep vein thrombosis. The effect of prophylaxis on pulmonary emboli or overall mortality, however, is not known.

No new non-clinical studies have been conducted. Since a literature review has been presented, it is not known whether the studies cited were conducted in accordance with the Good Laboratory Practice (GLP) regulations. No new clinical studies have been submitted.

The quality, non-clinical and clinical expert reports have been written by appropriately qualified persons.

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

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

Regarding the statement on GMP for the active substance a statement/declaration is provided from the manufacturer(s) responsible for manufacture of the finished product and batch release situated in the EU.

Following the decentralised procedure, the product licence was approved in the UK on 27 May 2016 (PL 41947/0016).

II QUALITY ASPECTS
II.1 Introduction
This is a decentralised application made under Article 10(a) well-established use application of amended directive 2001/83/EC for heparin sodium.

Other ingredients consist of the pharmaceutical excipients
Benzyl alcohol
Sodium chloride
Sodium hydroxide
Hydrochloric acid
Water for injections

With the exception of the active substance, which is derived from porcine intestinal mucosa, none of the excipients are derived from animal or human origin.

The product is supplied as 10 vials, each containing 5 ml of product. Each vial contains 25,000 I.U. of the active substance, heparin sodium.

II.2 DRUG SUBSTANCE
The active ingredient is heparin sodium.

Heparin sodium is a natural copolymer of animal origin, consisting of a repetitive fundamental disaccharide (uronic acid - glucosamine) with different degree of sulphation. The sulphated polysaccharide is present in animal organs, such as intestine and lung, linked to polypeptidic components according to the sequence HEPARIN-GAL-GAL-XYL-SER in the form of polyglycan having a molecular mass between 160,000 and 200,000 Daltons (were GAL = galactose, XYL = xylose, SER = serine). Thus heparin is obtained from animal organs by extraction in presence of a proteolytic enzyme. A proteolytic enzymatic hydrolysis give the formation of products with molecular mass included in a range 10,000 – 20,000 Daltons. The product is described in the Ph. Eur. Heparin Sodium <0333>.

In the original submission, the starting material for the drug substance is correctly identified as porcine intestinal mucosa.

Only healthy Chinese pigs less than 1 year old, under veterinary supervision are used to supply crude heparin. The abattoirs are certified and are dedicated solely to the slaughter of pigs. Each of the drug substance manufacturers has been independently audited. The drug product manufacturer has issued a declaration from a suitably qualified person (QP) at the finished product manufacturer/batch release site of GMP compliance for each active substance supplier. The active substance suppliers have quality management systems in place to audit the suppliers of the crude heparin.
In China, crude heparin suppliers are not inspected by Chinese pharmaceutical inspectorate for GMP compliance, but are controlled under the food industry so a QP declaration cannot be applied. The crude heparin suppliers are regularly audited, qualified and validated by each of the three heparin sodium purified suppliers. The purified heparin sodium suppliers have developed a quality system with internal standard operational procedures to validate the crude heparin suppliers. The pharmaceutical responsibility of the applicant extends from the heparin sodium purified manufacturers until the release of the finished product.

A comparability study comparing the manufacturing processes, batches of crude heparin and batches of purified heparin and it’s properties e.g. ratio anti-factor Xa activity to anti-factor IIa activity, molar ratio of sulphate ion to carboxylate ions and molecular mass distribution revealed no differences. Though slightly different manufacturing processes are used to produce purified heparin sodium the resulting active substance is not significantly different.

The specification each of the active substance manufacturers’ applies to the crude heparin is appropriate. The test applied by each of the manufacturers to detect ruminant-derived heparin is adequate to control non-porcine material. The purification processes used are sufficient to inactivate any potential viral contamination of the drug substance. The heparin sodium produced by each of the three manufacturers complies with the requirements of the current European Pharmacopoeia monograph for heparin sodium (01/2015:0333).

Stability studies have been performed with the drug substance. No significant changes in any parameters were observed. The proposed retest periods for each active substance supplier are justified.

II.3 DRUG PRODUCT
Pharmaceutical development
The finished formulation has been justified. Suitable product development data have been submitted with this application.

Manufacture of the product
A suitable batch formula has been provided for the manufacture of the finished product. A suitable description and flow chart of the manufacturing process has been provided, including a suitable account of any critical steps and intermediates.

Suitable process validation data have been provided from pilot-scale batches of the finished product.

Finished Product Specification
The finished product specification is appropriate.

Description and validation of the analytical methods have been provided and are satisfactory.

Batch analysis has been performed on batches of the finished product in the packaging proposed for marketing. The batch analysis results show that the finished product meets the specification. It has been confirmed that there is a validated test method available to the drug product to test for (i) oversulphated chondroitin sulphate and (ii) dermatan sulphate and chondroitin sulphate, if requested by a competent authority.
Stability
The conditions used in the stability studies are according to the ICH stability guideline. The tests and specifications for the drug product are adequately defined.

The shelf-life of 5 years for the drug product, with storage conditions “do not freeze” is considered acceptable. After reconstitution, it is stated that “chemical and physical in-use stability after reconstitution in glucose 5% and in 0.9% sodium chloride solution has been demonstrated for 48 hours at 18-22°C.”

II.4 Discussion on chemical, pharmaceutical and biological aspects
The grant of a marketing authorisation is recommended.

III NON-CLINICAL ASPECTS
III.1 Introduction
This is a decentralised application for heparin sodium made under Article 10(a) well-established use application of amended Directive 2001/83/EC.

No specific non-clinical studies were performed.

III.2 Pharmacology
The pharmacology of the product is well-established. The company has submitted a bibliography of published material to support its claims on the pharmacology of heparin in the stated indications.

III.3 Pharmacokinetics
The company describes parenteral administration, protein binding, distribution, metabolism, excretion and pharmacokinetic interactions for heparin.

III.4 Toxicology
The toxicology profile is considered to be well-established.

III.5 Environmental Risk Assessment
This product is intended for generic substitution and is, therefore, not considered to lead to an increased exposure to the environment. An environmental risk assessment is not deemed necessary.

III.6 Discussion on non-clinical aspects
There are no objections to the approval of this product from a non-clinical point of view.

IV CLINICAL ASPECTS
IV.1 Introduction
This is a decentralised application for heparin sodium made under Article 10(a) well-established use application of amended Directive 2001/83/EC.

IV.2 Clinical Pharmacology
As this application is based on well-established use, a review of clinical pharmacology based on a literature review has been submitted and is acceptable.

IV.3 Pharmacodynamics
As this application is based on well-established use, a review of pharmacodynamics based on
a literature review has been submitted and is acceptable.

**IV.4 Efficacy**
As this application is based on well-established use, a review of efficacy based on a literature review has been submitted and is acceptable.

**IV.5 Clinical Safety**
As this application is based on well-established use, a review of clinical safety based on a literature review has been submitted and is acceptable.

**IV.6 Risk Management Plan**
The marketing authorisation holder has submitted an 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 Heparin.

**IV.7 Discussion of the clinical aspects**
There are no objections to the approval of a product licence from a clinical point of view.

**V USER CONSULTATION**
A user consultation with target patient groups on the PIL has been performed.

**VI. OVERALL CONCLUSION AND BENEFIT-RISK ASSESSMENT**

**QUALITY**
The important quality characteristics of Heparin 5,000 I.U./ml, solution for injection, are well defined and controlled. The specifications and batch analytical results indicate consistency from batch to batch. There are no outstanding quality issues that would have a negative impact on the benefit/risk balance.

**NON-CLINICAL**
There are no non-clinical reasons why a marketing authorisation should not be granted.

There are no non-clinical points for clarification.

**EFFICACY**
The company refers to published reviews and meta-analyses of clinical experience of heparin.

**SAFETY**
The data do not raise any unexpected or serious issues over the likely safety of heparin in clinical use.

**PRODUCT LITERATURE**
The approved SmPC and PIL are satisfactory, and in-line with those for products of this type. The final labelling is satisfactory and in-line with current guidelines.
The current approved UK SmPC and PIL are available on the MHRA website. The current approved UK labelling is provided below.

**RISK-BENEFIT ASSESSMENT**

The UK considers that the risk-benefit relationship for the use of Heparin as detailed in the SmPC is favourable.
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
(Type II variations, PSURs, commitments)

<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>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
