European Medicines Agency

London, 24 January 2007
Doc. Ref. EMEA/CHMP/BMWP/496286/2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING LOW MOLECULAR WEIGHT HEPARINS[1] - (NON) CLINICAL ISSUES

DRAFT

AGREED BY BMWP	December 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	25 January 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	30 April 2007

Comments should be provided electronically in word format using this template to: BMWP.secretariat@emea.europa.eu

KEYWORDS	*LMW Heparin, similar biological medicinal products, comparability, non-clinical studies, clinical studies*

[1] Extracted heparin – synthetic heparins excluded from the scope of this guidelines

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

1. INTRODUCTION

Heparin is a sulphatated glycosaminoglycan.. Heparin is synthesised in granular cells, such as mast cells. Binding of heparin to anti-thrombin III (ATIII) will enhance the anticoagulant activity of ATIII that inactivates serine proteases, notably FX and FII.

In addition, heparin has numerous other plasmatic and cellular interactions of unknown clinical significance.

Heparin that is used for therapeutic purposes is sourced from domestic animals, mainly from porcine intestinal walls.

Low molecular weight heparins (LMWH) are prepared from un-fractionated heparin by various depolymerisation processes. Thus, the starting material of LMWHs is of biological origin. There is a manufacturing process that defines the characteristics of the drug substance. The drug substance is a very complex mixture of glycosaminoglycans of different sizes that can be characterised with difficulties by using state of the art analytical methods. In addition the quantitative composition of the polysaccharide chains vary from preparation to preparation.

Due to this heterogeneity, conventional pharmacokinetic studies cannot be performed. Instead, the absorption and elimination of LMWHs can be studied by using pharmacodynamic tests, including anti-FXa and anti-FIIa activity.

There are several licensed LMWHs that differ in their source material, manufacturing process, pharmacodynamic properties and therapeutic indications, which include treatment and prophylaxis of deep venous thrombosis and prevention of complications of unstable angina and non-Q wave cardiac infarction.

LMWHs offer certain advantages as compared to un-fractionated heparin, including longer dose intervals and more predictable pharmacokinetics and -dynamics.

This Guideline should be read in conjunction with the requirements laid down in the EU Pharmaceutical legislation and other relevant CHMP guidelines (see section 8).

2. PROBLEM STATEMENT

Marketing authorisation applications for LMWH have been submitted in several EU Member States. Assessment of these applications is difficult for several reasons: the physico-chemical characterisation of the LMWHs is limited due to the high complexity of the molecules and the limited knowledge about qualitative and quantitative contribution to safety and efficacy of each fraction.

The kinetics of LMWH is based on pharmacodynamic measurements. However, the quantitative correlation between the pharmacodynamics and clinical efficacy has not been demonstrated. Furthermore, the relative contribution of various interactions with proteins and cells of LMWHs to the efficacy in different therapeutic indications is controversial.

DISCUSSION (on the problem statement)

Classical bioequivalence studies are not sufficient to establish therapeutic equivalence between LMWHs. The design of an appropriate comparability program is complicated by the unknown pharmacodynamic and clinical significance of the numerous interactions with plasma components and cells and bythe rather complex mixture of the drug substances. Regulatory guidelines are regarded as a useful tool to harmonise the requirements across the EU.

3. RECOMMENDATION

The Working Party on similar biological medicinal products (BMWP) recommend drafting a guideline on the (non)clinical aspects of the development and assessment of similar biological medicinal products containing low molecular weight heparins. The guideline should address:

- Role of non-clinical studies in demonstration of comparability of two LMWHs

- Demonstration of comparable pharmacokinetics and pharmacodynamics
- Possibility of using pharmacodynamic markers only in demonstration of equivalent efficacy
- Need for and design of clinical studies to demonstrate comparable efficacy and safety.
- Extrapolation of clinical data from one therapeutic indication to others
- Risk Managements Plans

4. PROPOSED TIMETABLE

After adoption of the concept paper, it is anticipated that the draft guideline will be adopted and released for consultation during QX/200X.

5. RESOURCE REQUIREMENTS FOR PREPARATION

A joint drafting group consisting of BPWP experts will develop the guideline. At least 3 formal meetings of the drafting group will be required in the margins of the working party meetings. Contributions from experts from EWP, BWP, QWP, BPWP, SWP and PhVWP will be required.

6. IMPACT ASSESSMENT (Anticipated)

Guidance on the investigation and assessment of immunogenicity may contribute to a predictable and consistent assessment of the national marketing authorisation applications and facilitate the mutual recognition or de-centralised procedures involving LMWHs.

7. INTERESTED PARTIES

Competent authorities of the member states, and pharmaceutical industry.

8. REFERENCES TO LITERATURE, GUIDELINES

- Directive 2001/83/EC, as amended.
- Part II of the Annex I of Directive 2001/83/EC, as amended.
- Guideline on similar biological medicinal products (CHMP/437/04/draft)
- Note for guidance on repeated dose toxicity (CPMP/SWP/1042/99)
- Note for guidance on non-clinical local tolerance testing of medicinal products (CPMP/SWP/2145/00)