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Draft

**GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING
LOW-MOLECULAR-WEIGHT-HEPARINS**

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EXECUTIVE SUMMARY

This guideline lays down the non-clinical and clinical requirements for low molecular weight heparins (LMWHs) containing medicinal products claiming to be similar to another one already marketed. The non-clinical section addresses the pharmaco-toxicological requirements and the clinical section the requirements for pharmacokinetic, pharmacodynamic, efficacy and safety studies as well as pharmacovigilance aspects.

1. INTRODUCTION (background)

Heparin is a highly sulphated and heterogeneous member of the glycosaminoglycan family of carbohydrates consisting of various repeating disaccharide units. The most common disaccharide unit is composed of a 2-O-sulfated α -L-iduronic acid and 6-O-sulfated, N-sulfated α -D-glucosamine, IdoA(2S)-GlcNS(6S). Endogenous heparin is synthesised in the granules of mast cells and possesses the highest negative charge density of all known biological molecules.

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

Heparin catalyzes the inhibition of several serine proteases of the plasmatic coagulation system by antithrombin (AT). For the binding of heparin to AT a specific pentasaccharide sequence, which contains a 3-O-sulphated glucosamine residue, is important. Upon binding to the enzyme inhibitor antithrombin, heparin causes a conformational change in the antithrombin molecule which results in its active site being exposed for inhibition of activated coagulation factors. Furthermore, heparin acts as a catalytic template to which the inhibitor and activated serine proteases such as thrombin and factors IXa and XIa bind. This effect depends essentially on the number of monosaccharides in the heparin molecule. Heparin molecules containing fewer than 18 monosaccharides do not catalyze inhibition of thrombin but still inactivate factor Xa. Heparin enhances the rate of thrombin–antithrombin reaction at least a thousand-fold resulting in a stable 1:1 complex after the serine-protease attacks a specific Arg-Ser peptide bond in the reactive site of antithrombin.

In addition, heparin has numerous other plasmatic and cellular interactions, but overall, in comparison with the anticoagulatory effect, the clinical relevance of these interactions is uncertain and insufficiently investigated.

Heparin is administered parenterally, as it is degraded when taken orally. It can be injected intravenously or subcutaneously, whereas intramuscular injections should be avoided because of the risk of inducing hematomas.

Low molecular weight heparins (LMWHs) are prepared from unfractionated heparin by various chemical or enzymatic depolymerisation processes. Thus, the starting material of LMWHs is of biological origin and the manufacturing process defines the characteristics of the drug substance.

The complexity of LMWH results largely from the nature of the starting material (unfractionated Heparin extracted from porcine mucosa), the extraction, the fractionation and the production processes.

Several state of the art methods for physico-chemical characterisation of LMWH products are available. However, it is presently not known to which extent the multiple different subfractions contribute to the clinical efficacy of LMWH.

A specific LMWH differs from unfractionated heparin and from other LMWHs in its pharmacokinetic and pharmacodynamic properties. As a result of the depolymerisation process they normally contain mainly molecules with less than 18 monosaccharide units. This reduction of molecule size is associated with a loss of thrombin inhibition activity in comparison to standard heparin and a more selective inhibition of Xa.

Due to difficulties in the physical detection of LMWH, conventional pharmacokinetic studies cannot be performed. Instead, the absorption and elimination of LMWHs are studied by using pharmacodynamic tests, including anti-FXa and anti-FIIa activity.

There are several authorised 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.

The most common adverse reactions of heparins are bleedings, whilst the most serious one is the rarely observed Heparin-induced thrombocytopenia type II (HIT II). This antibody-mediated process is triggered by the induction of antibodies directed against neoantigens of platelet-factor 4 (PF4)-heparin complexes. Binding of those antibody-PF4-heparin complexes activates platelets and generates thrombogenic platelet microaggregates. Patients developing thrombocytopenia are in danger of arterial and venous thromboembolic complications. Although the risks for these adverse reactions seem to be reduced in comparison to unfractionated heparin, it is obligatory to monitor the platelet count regularly in all patients using LMWH and to test for PF4-heparin complex-antibodies in those who develop thrombocytopenia or thromboembolic complications during heparin treatment.

In conclusion, the heterogeneity of LMWH is very high, the mode of action is not completely understood and it is uncertain whether the PD markers are representative for the clinical outcome. Thus, the major burden of demonstrating two LMWHs being similar biological medicinal products is on a clinical trial.

2. SCOPE

The guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CPMP/42832/05/) lays down the general requirements for demonstration of the similar nature of two biological products in terms of safety and efficacy.

This product specific guidance complements the above guideline and presents the current view of the CHMP on the application of the guideline for demonstration of comparability of two LMWH-containing medicinal products.

3. LEGAL BASIS

Directive 2001/83/EC, as amended in particular in Directive 2001/83/EC Art 10(4) and Part II of the Annex I of Directive 2001/83/EC, as amended.

4. MAIN GUIDELINE TEXT

4.1 NON-CLINICAL STUDIES

Before initiating clinical development, non-clinical studies should be performed. Non-clinical studies should be comparative in nature and should be designed to detect differences in pharmacotoxicological response between the similar biological medicinal product and the reference LMWH and not just assess the response *per se*. The approach taken will need to be fully justified in the non-clinical overview.

Pharmacodynamic studies

In vitro studies:

In order to compare any alterations in activity between the similar biological medicinal product and the reference LMWH, data from a number of comparative bioassays (e.g. for anti-Xa and anti-IIa activity), many of which may already be available from bioassays submitted as part of the quality dossier, should be provided. Standardised assays (e.g. in accordance with the European Pharmacopoeia) should be used to measure activity.

In vivo studies:

The *in vivo* pharmacodynamic activity of the similar biological medicinal product and the reference LMWH should be quantitatively compared in

- an appropriate *in vivo* pharmacodynamic model (e.g. by evaluation of pharmacodynamic markers such as anti-Xa and anti-IIa activity and TFPI (in extenso). If feasible, these evaluations can be performed as part of the described repeat dose toxicity study.

and/or

- a suitable animal venous or arterial thrombosis model.

Toxicological studies

Data from at least one repeat dose toxicity study in a relevant species (e.g. the rat) should be provided. Study duration should be chosen in accordance with the intended duration of clinical application, however, should be at least 4 weeks. The study should be performed in accordance with the requirements of the "Note for guidance on repeated dose toxicity" (CPMP/SWP/1042/99). Special emphasis should be laid on the determination of effects on blood coagulation/hemostasis and on potential development of osteoporosis.

Data on local tolerance in at least one species should be provided in accordance with the "Note for guidance on non-clinical local tolerance testing of medicinal products" (CPMP/SWP/2145/00). If feasible, local tolerance testing can be performed as part of the described repeat dose toxicity study.

Safety pharmacology, reproduction toxicology, mutagenicity and carcinogenicity studies are not routine requirements for non-clinical testing of a similar biological medicinal product containing LMWH.

4.2 CLINICAL STUDIES

Pharmacokinetic/Pharmacodynamic studies

Due to the heterogeneity of LMWHs conventional pharmacokinetic studies cannot be performed. Instead, the absorption and elimination characteristics of LMWHs should be compared by using pharmacodynamic tests as surrogate markers for PK/PD assessment such as anti-FXa and anti-FIIa activity and Tissue Factor Pathway Inhibitor (TFPI) activity. In addition, the ratio of anti-FXa and anti-FIIa activity should be compared. Assessment of these PD parameters will provide a fingerprint of the different molecular species.

These pharmacodynamic properties of the similar biological medicinal product and the reference product should be compared in a randomized, single dose two way crossover study in healthy volunteers using subcutaneous administration.

Equivalence margins should be pre-specified and appropriately justified.

The selected dose should be in the sensitive part of the dose-response curve in view of the fact that dose-response curve is not linear and varies for the different indications.

Clinical efficacy

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

Surgical patients have the highest prevalence of venous thromboembolism (VTE). Furthermore, the vast majority of published trials have been performed in surgical patients with high VTE risk, especially in patients with hip and knee surgery, and thus the knowledge about influence of types of surgery, duration of trials and risks for bleeding is the most accurate for this patient population.

Therefore, it is recommended to demonstrate efficacy in the prevention of VTE in patients undergoing surgery with high VTE risk. Preferably, the trial should be conducted in major orthopaedic surgery such as hip surgery. In this clinical setting, patients with hip fracture should be well represented in the study as they have both high thrombotic risk and high perioperative bleeding risk. The posology and administration should follow European recommendations for prophylaxis with the reference product in patients requiring prolonged VTE prophylaxis.

In the VTE-prevention setting, the clinically most relevant endpoint consists of proximal deep vein thrombosis (DVT) pulmonary embolism (PE) and VTE-related death. However, the comparative efficacy and safety of the two products may also be assessed using the “surrogate” composite endpoint, consisting of total number of thromboembolic events (total DVTs, PE and VTE-related death). Adjudication of VTE events by a central independent and blinded committee of experts is strongly encouraged.

The study should follow a strict equivalence design where equivalence margins have to be defined a priori and appropriately justified, primarily on clinical grounds. The study should be powered to show therapeutic equivalence on one of the two recommended endpoints mentioned above.

State of art imaging technique should be used for the endpoint assessment. While proximal DVTs could be diagnosed with high specificity and sensitivity using ultrasonography, a clear assessment of distal DVT is only possible by using bilateral venography. Thus, this diagnostic procedure is mandatory in trials including total DVT in the endpoint.

The most relevant components of the primary endpoint (in particular in the number of proximal DVTs, PE and deaths) should favourably support the biosimilarity of the two products.

Assessment of the primary endpoint should be performed at the time of occurrence of symptoms suggestive of VTE or, in asymptomatic patients, at end of treatment. The overall follow-up should be at least 60 days to detect late thrombotic events.

The principles as laid down in the overarching CHMP guideline on Similar Biological Medicinal Products (CHMP/BMWP/42832/2005) should be followed.

Clinical safety

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

Usually, comparative safety data from the efficacy trial will be sufficient to provide an adequate pre-marketing safety database. Major bleeding events and clinically relevant non-major bleeding events should be carefully assessed and documented. A consistent and clinically relevant classification of bleedings should be used. Similar to the efficacy evaluation, the adjudication of bleeding events by a central independent and blinded committee of experts, using pre-specified limits is strongly encouraged.

For the detection of immune-mediated type of Heparin-induced Thrombocytopenia (HIT Type II) monitoring of platelet count and an adequate diagnostic procedure in patients developing thrombocytopenia during the trial has to be performed.

Liver function testing is recommended.

4.3 EXTRAPOLATION OF INDICATION

Demonstration of comparable efficacy and safety in surgical patients at high risk for VTE as recommended may allow extrapolation to other indications of the reference medicinal product if appropriately justified by the applicant.

4.4 PHARMACOVIGILANCE PLAN

Within the authorisation procedure the applicant should present a risk management programme/ pharmacovigilance plan in accordance with current EU legislation and pharmacovigilance guidelines. The risk management plan should particularly include rare serious adverse events of the similar biological medicinal product containing LMWH such as Heparin-induced Thrombocytopenia Type II (HIT Type II).

REFERENCES (scientific and / or legal)

Directive 2001/83/EC, as amended.

Guideline on similar biological medicinal products (CHMP/437/04/draft).

Guideline on clinical investigation of medicinal products for prophylaxis of high intra and post-operative venous thromboembolic risk (CPMP/EWP/707/98 Rev. 1 - draft)

Concept paper on similar biological medicinal products containing low molecular weight heparins – (non)clinical issues. (CHMP/BMWP/496286/2006).

Note for guidance on toxicokinetics: A Guidance for assessing systemic exposure in toxicological studies (CPMP/ICH/384/95).

Note for guidance on non-clinical local tolerance testing of medicinal products (CPMP/SWP/2145/00).

Guideline on risk management systems for medicinal products for human use (EMA/CHMP 96286/2005).

Note for Guidance on Good Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95).