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Guideline on non-clinical and clinical development of similar biological medicinal products containing low-molecular-weight-heparins

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Comments should be provided using this template. The completed comments form should be sent to BMWP.secretariat@ema.europa.eu

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Guideline on non-clinical and clinical development of 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, low molecular mass heparins, LMMH) 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

Heparin is a highly sulphated and heterogeneous member of the glycosaminoglycan family of carbohydrates consisting of various 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 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 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 (F) 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 (FXa). 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, intra-arterially 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 or other animal tissues), the extraction, the fractionation and the production processes. Several state of the art methods for physico-chemical characterisation of LMWH products are available. However, although the inhibition of activated FXa activity and the inhibition of thrombin activation reflect the main anticoagulant activities of LMWH, it is presently not clear to which extent the multiple different polysaccharides contribute to the clinical effects relevant for efficacy and safety of LMWH.

A specific LMWH differs from unfractionated heparin and may differ from other LMWHs in its pharmacokinetic and pharmacodynamic properties. As a result of the depolymerisation process, LMWHs are mainly enriched in 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 an increased inhibition of FXa.

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 the measurement of anti-FXa and anti-FIIa activity.

There are several authorised LMWHs that differ in their source material, manufacturing process, pharmacokinetic/pharmacodynamic properties and therapeutic indications, which include treatment and prophylaxis of deep venous thrombosis and prevention of complications of acute coronary syndromes (unstable angina, non-ST elevation myocardial infarction (non-STEMI) and myocardial infarction with ST elevation (STEMI)).

The most common adverse reactions induced by 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 may activate platelets and generate thrombogenic platelet microaggregates. Patients developing thrombocytopenia are in danger of arterial and venous thromboembolic complications (heparin-induced thrombocytopenia and thrombosis, HITT). Although the risk of these adverse reactions appears 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 high, the structure-effect relationship is presently not fully elucidated and the PD markers anti-FXa and anti-FIIa activity may not fully reflect/predict efficacy. Thus, clinical trials will usually be necessary to address remaining uncertainties resulting from the physicochemical and biological comparison.

2. Scope

The 'Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005)' lays down the general requirements for demonstration of the similar nature of two biological products in terms of safety and efficacy.

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

This Guideline should be read in conjunction with the requirements laid down in the EU Pharmaceutical legislation and with relevant CHMP guidelines (see 2. Legal Basis and relevant guidelines).

3. Legal basis and relevant guidelines

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

- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005).
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: Quality issues (EMEA/CHMP/BWP/49348/2005 and EMA/CHMP/BWP/247713/2012)
- ICH guideline S 6 (R1) Preclinical safety evaluation of biotechnology-derived pharmaceuticals (EMA/CHMP/ICH/731268/1998)
- Guideline on clinical investigation of medicinal products for prophylaxis of high intra and post-operative venous thromboembolic risk (CPMP/EWP/707/98)
- Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins (EMEA/CHMP/BMWP/14327/2006)
- Guideline on good pharmacovigilance practices (EMA/500020/2012)
- Guideline on good pharmacovigilance practices, Module V – Risk management systems (EMA/838713/2011)

4. Non-clinical studies

Non-clinical studies should be performed before initiating clinical trials. The studies should be comparative in nature and should be designed to detect differences in the response between the biosimilar 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 pharmacodynamic activity of the biosimilar and the reference LMWH, data from a number of comparative bioassays (based on state of the art knowledge about clinically relevant pharmacodynamic effects of LMWH and including, at least, evaluations of anti-FXa and anti-FIIa activity) should be provided. If available, standardised assays (e.g. in accordance with the European Pharmacopoeia) should be used to measure activity. Such data may already be available from bioassays submitted as part of the quality dossier.

In vivo studies:
If physicochemical and biological characterisation of the biosimilar and the reference LMWH has been performed with a high level of resolution and convincingly demonstrated close similarity, *in vivo* studies are not required as part of the comparability exercise.

Otherwise, the *in vivo* pharmacodynamic activity of the biosimilar and the reference LMWH should be quantitatively compared in:

- An appropriate *in vivo* pharmacodynamic model, which takes into account state of the art knowledge about clinically relevant pharmacodynamic effects of LMWH and includes, at least, an evaluation of anti-FXa, and anti-FIIa activity and of release of tissue factor pathway inhibitor.

and/or

- In accordance with the intended clinical indication(s), either a suitable animal venous or an arterial thrombosis model.

Toxicological studies

Generally, separate repeated dose toxicity studies are not required.

In specific cases, e.g. when novel or less well studied excipients are introduced, the need for additional toxicology studies should be considered.

The conduct of toxicity studies to assess unspecific toxicity only, based on impurities is not recommended. A priori biosimilar and reference product are expected to be highly similar, which should be demonstrated with physicochemical methods. Impurities, such as proteins should be kept at a minimum in accordance with pharmacopoeial monographs, which is the best strategy to minimise any associated risk.

Studies regarding safety pharmacology, and reproduction toxicology, are not required for non-clinical testing of a biosimilar containing LMWH. Studies on local tolerance are not required unless excipients are introduced for which there is no or little experience with the intended route of administration. If other *in vivo* studies are performed, local tolerance may be evaluated as part of these studies.

5. 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 determining pharmacodynamic activities (including anti FXa and anti-FIIa), as surrogate markers for their circulating concentrations. In addition other pharmacodynamic tests such as Tissue Factor Pathway Inhibitor (TFPI) activity, as well as the ratio of anti-FXa and anti-FIIa activity should be compared. Assessment of these PD parameters will provide an important fingerprint of the polysaccharidic profile.

These pharmacokinetic/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. In case the originator product is also licensed for the intravenous or intra-arterial route, an additional comparative study should be performed via the intravenous route.

The selected doses should be in the sensitive part of the dose-response curve and within the recommended dose ranges for the different indications.

Equivalence margins should be pre-specified and appropriately justified.

Clinical efficacy

A comparative clinical efficacy trial will usually be required as part of the comparability exercise. Only if similar efficacy of the biosimilar and the reference product can be convincingly deduced from the comparison of their physicochemical characteristics, biological activity/potency and PD fingerprint profiles, based on the use of highly sensitive and specific methods, then a dedicated efficacy trial may be waived. It is expected that this is an exceptional scenario since the required amount of reassurance from analytical data and bioassays would be considerable.

Therapeutic equivalence should be demonstrated in an 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 biosimilar 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. The Guideline on clinical investigation of medicinal products for prophylaxis of high intra and post-operative venous thromboembolic risk (CPMP/EWP/707/98), although intended for novel medicinal products, may contain useful information for the conduct of such a trial. However, for the purpose of investigating potential product-related differences in efficacy between the biosimilar and the reference product, the patient population should ideally be as homogenous as possible.

In the VTE-prevention setting, the clinically most relevant composite endpoint consists of proximal deep vein thrombosis (DVT), pulmonary embolism (PE) and VTE-related death to demonstrate patient benefit. However, for the purpose of biosimilarity testing, a composite endpoint consisting of total number of thromboembolic events (total DVTs, including asymptomatic distal DVT, PE and VTE-related death) may be used. Adjudication of VTE events should be performed by a central independent and blinded committee of experts.

Equivalence margins have to be defined a priori and appropriately justified, both on statistical and clinical grounds. The study should be powered to show therapeutic equivalence on one of the two composite endpoints mentioned above.

State of the 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 invasive diagnostic procedure would be mandatory in trials including total DVT in the endpoint.

The most relevant components of the primary endpoint (in particular proximal DVTs, PE and VTE-related 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.

Clinical safety

Human safety data on the biosimilar will usually be needed pre-authorisation, even if similar efficacy can be concluded from the comparative data on physicochemical characteristics, biological activity/potency and PD fingerprint.

Comparative safety data from the efficacy trial will be sufficient to provide an adequate pre-marketing safety database. Care should be taken to compare the type, frequency and severity of the adverse reactions between the similar biological medicinal product and the reference product. 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 should be performed. Liver function testing is recommended.

Sufficient reassurance will be needed that the biosimilar LMWH is not associated with excessive immunogenicity compared to the reference product. For the detection of the immune-mediated type of Heparin-induced Thrombocytopenia (HIT Type II) monitoring of platelet count and an adequate diagnostic procedure (including determination of PF4-Heparin complex antibodies) in patients developing thrombocytopenia and/or thromboembolism (HITT) during the trial has to be performed. Monitoring of antibodies in all patients participating in the trials is not necessary. Since the frequency of immune-mediated HIT II is usually very low (< 0.1%) such events are not usually expected to occur in pre-authorisation clinical trials.

6. Pharmacovigilance plan

Within the authorisation procedure the applicant should present a risk management plan in accordance with current EU legislation and pharmacovigilance guidelines. The RMP of the biosimilar should take into account identified and potential risks associated with the use of the reference product and, if applicable, safety in indications authorised for the reference product that are claimed based on extrapolation. Rare serious adverse events known to be associated with LMWHs such as Heparin-induced Thrombocytopenia Type II (HIT II, HITT) as well as anaphylactoid and anaphylactic reactions should specifically be discussed in the risk management plan.

7. Extrapolation of indication

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