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4 Guideline on similar biological medicinal products
5 containing interferon beta
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7 Draft

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Guideline on similar biological medicinal products
containing interferon beta

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Executive summary

This guideline lays down the non-clinical and clinical requirements for interferon beta (IFN- β) containing medicinal products claiming to be similar to another interferon beta 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)

Three different medicinal products containing recombinant IFN- β are currently approved in the EU for the first-line treatment of multiple sclerosis (MS); they differ with respect to their molecular structure, injection route, recommended posology, and MS indications.

Recombinant IFN- β -1a is a single glycosylated polypeptide chain containing 166 amino acids. Two products are available, one is administered subcutaneously and the other intra-muscularly.

Recombinant IFN- β -1b is produced as a single non-glycosylated polypeptide chain of 165 amino acids with no methionine at the N-terminus and an amino acid substitution at position 17 and is administered subcutaneously.

Medicinal products containing recombinant IFN- β are currently indicated for patients with relapsing MS or at high risk of developing MS after a single demyelinating event. The mechanism of action of IFN- β in MS is not well established but it has been hypothesized that it acts as an immunomodulator by 1) interfering with T-cell activation in several ways, including downregulating the expression of Type II MHC molecules, inhibiting the production of pro-inflammatory cytokines by T_H1 cells, promoting the production of anti-inflammatory cytokines by T_H2 cells, activating suppressor T-cells and 2) inhibiting permeability changes of the blood brain barrier and the infiltration of T-cells into the CNS.

The clinical effects of recombinant IFN- β in relapsing MS (RMS) are modest with decreases in the frequency of exacerbations by approximately 30% as compared with placebo and inconsistent results on the progression of disability.

All products are associated with similar adverse reactions, which may affect patient adherence to therapy; the most frequent are influenza-like symptoms. Injection site reactions and asymptomatic liver and white blood cell abnormalities occur more frequently with the subcutaneous products. Less common adverse reactions include depression and autoimmune disorders manifested as thyroid or liver dysfunction. All products induce the development of antibodies, and in particular neutralising antibodies (NAb); in clinical trials, the incidence of NAb has been shown to range widely, from 5% for intramuscular IFN- β -1a given weekly to 45% for subcutaneous IFN- β -1b given every other day. Most NAb develop in the first year of therapy and they have the potential to impact clinical outcomes after 18-24 months of treatment.

2. Scope

The Marketing Authorisation application dossier of a new IFN- β claiming to be similar to a reference product already authorised is required to provide the demonstration of comparable quality, efficacy, and safety of the product applied for to a reference product authorised in the EU.

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

IFN- β and should be read in conjunction with the requirements laid down in the EU Pharmaceutical legislation and with other relevant CHMP guidelines (see references).

3. Legal basis

This guideline has to be read in conjunction with the introduction and general principles and part I and II of the Annex I to Directive 2001/83/EC as amended as well as all other pertinent EU and ICH guidelines and regulations, especially the following:

- Guideline on Similar Biological Medicinal Products - CHMP/437/04;
- Note for Guidance on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals - EMA/CHMP/ICH/731268/1998 (ICH S6);
- 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 Clinical Investigation of Medicinal Products for the Treatment of Multiple Sclerosis - CPMP/EWP/561/98;
- Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins - EMEA/CHMP/BMWP/14327/2006;
- Biologics Working Party Report to the CHMP Beta-interferons and neutralising antibodies (in multiple sclerosis) - EMEA/CHMP/BWP/580136/2007.

4. Non-clinical studies

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

***In vitro* studies**

In order to compare differences in biological activity between the similar and the reference medicinal product, data from a number of comparative bioassays should be provided (e.g. receptor-binding studies, antiviral effects in cell culture), many of which may already be available from bioassays submitted as part of the quality dossier. Wherever possible, analytical methods should be standardised and validated according to relevant guidelines (e.g. evaluation of antiviral effects in cell culture in accordance with the provisions of the European Pharmacopoeia).

***In vivo* studies**

Generally, *in vivo* studies in animals are not required.

If the outcome of the quality evaluation and/or the *in vitro* bioassays/pharmacological studies raises concerns, the need for additional studies should be considered.

These could include an *in vivo* pharmacological study and/or a general repeated dose toxicity study.

If it can be justified that further studies in a pharmacologically responsive animal species are not expected to provide relevant additional information, then such studies may be omitted.

5. Clinical studies

The clinical comparability exercise should follow a stepwise approach starting with pharmacokinetic and pharmacodynamic studies (PK & PD) and continuing with efficacy and safety studies.

Pharmacokinetics

The pharmacokinetic properties of the biosimilar and reference products should be compared in a crossover study for the route of administration applied for. Healthy volunteers are considered an appropriate study population. The selected dose should be in the sensitive part of the dose-concentration curve. The choice of a single or repeated dose (e.g. 3 doses over a week) regimen should be justified.

The design of the study should take into account the recommendations as outlined in the Guideline on the clinical investigation of the pharmacokinetics of therapeutic proteins (CHMP/EWP/89249/2004). In particular, the pharmacokinetic parameters of interest include AUC, C_{max} and also T_{1/2} or CL/F. The equivalence margin has to be defined *a priori* and appropriately justified, especially given the high variability of the relevant PK parameters. A two-stage design may be planned in the protocol provided adjusted significance levels are used for each of the analyses in accordance with the Guideline on the investigation of bioequivalence (CPMP/EWP/QWP/1401/98 Rev. 1/ Corr **).

Serum concentrations of IFN- β are very low after the administration of therapeutic dosages and their measurement is technically difficult. However, in healthy volunteers shortly after administration the serum levels of IFN- β may be high enough that determination is possible with the cytopathic effect (CPE) bioassay. Recently, more sensitive ELISA assays have been developed that allow determination of concentration as low as the pg level per mL.

Pharmacodynamics

Pharmacodynamics should preferably be evaluated as part of the comparative pharmacokinetic studies. There is currently no identified biological marker related to the mechanism by which IFN- β influences the clinical evolution of MS. However, a number of markers of the biological activity of IFN- β are well known and a comprehensive comparative evaluation of some of these markers could be used to support the similarity of the biosimilar and reference products ("fingerprint approach"). Amongst others, these markers include serum (2'-5')oligo-adenylate-synthetase activity, neopterin, β 2-microglobulin, interleukin 10, TNF-related apoptosis inducing ligand (TRAIL), and myxovirus resistance protein A (MxA). MxA induction can be measured from peripheral blood leukocytes both at the protein and mRNA level; it is currently considered as one of the most sensitive markers of the biological activity of interferons type I and should be one of the selected markers.

Clinical efficacy

Similar clinical efficacy between the biosimilar and reference product should be demonstrated in an adequately powered, randomised, parallel group equivalence clinical trial, preferably double-blind. The route of administration used in the clinical trial should be the route recommended for the reference product.

According to the Guideline on clinical investigation of medicinal products for the treatment of MS (CPMP/EWP/561/98 Rev 1), an acceptable primary efficacy variable for a disease modifying agent in RMS is the relapse rate, which has been used in the pivotal trials on medicinal products containing recombinant IFN- β . While in principle this would be the preferred option, such a trial is not necessary in a biosimilar framework, since the focus of the biosimilarity exercise is to demonstrate similar efficacy and safety compared to the reference product, not patient benefit *per se*, which has already been established by the reference product. For demonstrating clinical similarity of a biosimilar and

reference product, magnetic resonance imaging (MRI) of disease lesions in RMS may be sufficient. In addition, clinical outcomes such as relapse rate or percentage of relapse-free patients should be used as secondary endpoints in support of the MRI outcomes.

The design of the equivalence trial should ensure assay sensitivity, i.e. the choice of study design, population, duration, and MRI endpoints should make it possible to detect a difference between the biosimilar and reference products, if such difference actually exists. Regarding the study design, assay sensitivity could be shown by a three-arm trial including a placebo arm for a short period of time (e.g. 4 months) sufficient to demonstrate superiority of both the biosimilar and reference products over placebo using an MRI endpoint. Patients in the placebo arm could be subsequently crossed over to the biosimilar product and the trial continued with the two active arms. An alternative design could be a three-arm trial with the reference product and two doses of the biosimilar product, for which it can be reasonably assumed that they will exhibit differences in MRI and clinical outcomes over time.

Whatever the design, the duration of the trial should be sufficient to show comparable efficacy on MRI endpoints and provide relevant information on clinical outcomes, i.e. not less than 12 months.

The most sensitive patient population, which would enable to detect differences between the biosimilar and reference products, should be selected. This would be a homogeneous sample of patients with a confirmed diagnosis of relapsing-remitting MS (RRMS) and sufficient disease activity based on relapse frequency and/or MRI criteria to anticipate rapid changes in MRI.

MRI-based variables are acceptable primary endpoints in the context of a biosimilar comparison if backed up by clinical outcomes; no formal equivalence test is required for clinical outcomes, which would be expected to show the same trend as the MRI-based variables. Repeated MRI scans should be performed during the trial. The reading of the images should be central and blinded. The most sensitive documented MRI variable is the combined unique active lesions (CUA, defined as new gadolinium-enhancing T1-weighted lesions and new/enlarging T2-weighted lesions without double counting); a cumulative estimate over several scans may be used. Other MRI variables may also be used in future if adequately justified.

The equivalence margin for the primary MRI endpoint should be pre-specified and adequately justified based on available MRI data for the reference product. The trial should be adequately powered with particular attention paid in the protocol to the potentially high drop-out rate and the way of handling missing data.

Clinical safety

Comparative safety data from the efficacy trial are usually sufficient to provide an adequate pre-marketing safety database, and therefore should allow for reassurance of safety prior to marketing authorisation. Adverse events of specific interest include influenza-like symptoms, injection reactions and laboratory test abnormalities.

As IFN- β products are immunogenic, an assessment of immunogenicity by testing of sera from IFN- β -treated patients should be performed according to the principles defined in the Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins (EMA/CHMP/BMWP/14327/2006). Its main objective is the comparison of the immunogenicity profile of the biosimilar and reference products over time since the antibody characteristics and effects change as a result of affinity maturation of the antibody response and/or epitope spreading. A minimum of 12-month comparative immunogenicity data should be submitted pre-authorisation with further assessment to be continued post-approval for at least 6 months for the biosimilar product. A strategy that includes serum sampling at baseline and at regular intervals is necessary for assessing the comparability of the dynamics of antibody development during therapy, e.g., every month in the beginning of the treatment followed by every 3 months.

The use of a validated, highly sensitive antibody assay, capable of detecting all antibodies (i.e. of different affinities, class and sub-class) is mandatory. Approaches that avoid specific masking of particular epitope(s) should be considered to avoid false negative results, e.g., ELISAs using a monoclonal antibody to capture IFN- β . Following confirmation of antibody positive samples, further characterization including determination of the ability to neutralise the biological activity of IFN- β and cross-reactivity is required. It is recommended that the standardised MxA protein NAb assay or a NAb assay that has been validated against the MxA protein NAb assay is used (EMA/CHMP/BWP/580136/2007). The approach used to determine assay sensitivity (e.g., by using different cut-off points) should be described but the distribution of titres should also be presented at each time point for each treatment arm. Finally, patients should be categorised according to the evolution of their immune response over time using predefined criteria. For example, the patient's NAb status may be defined as antibody negative (-ve for all post-treatment samples according to predefined low/high dilutions or titres) or antibody positive, which can be categorised as 'transiently positive' (1 or more post-treatment samples +ve, followed by -ve samples at all subsequent and at least 2 sampling time points) or 'persistently positive' (2 or more consecutive post-treatment samples consistently +ve).

Although the clinical impact of binding, non-neutralising antibodies is not clear, an increased frequency of such antibodies for the test product relative to the reference product would contradict the concept of biosimilarity. The impact of NAb on clinical outcomes is unlikely to be ascertainable before 12 months of therapy and thus will need to be evaluated post-authorisation as part of the risk management plan.

6. Pharmacovigilance plan

Within the authorisation procedure a risk management plan should be presented in accordance with current EU legislation and pharmacovigilance guidelines. It should be based on the known identified and potential risks of the reference product as described in its product information. The risk management plan should particularly focus on rare events such as autoimmune disorders and on the potential effects of unwanted immunogenicity. This could be managed through the extension of the pre-authorisation trial or a dedicated observational study or the participation in an existing registry.

7. Extrapolation of indication

Although not precisely understood, the mechanism of action of IFN- β can reasonably be assumed to be the same whatever the stage of MS. Therefore, demonstration of efficacy and safety in confirmed RRMS will allow extrapolation to the other indications of the reference medicinal product in MS.