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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on similar biological product containing recombinant interferon beta

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1. INTRODUCTION

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS), which is particularly frequent in Europe and one of the most common causes of neurological disability in young and middle-age adults; the social and economical burden of the disease is thus considerable. Most patients (80-90%) develop the relapsing-remitting form of the disease (RRMS), which is characterised by episodes of neurological symptoms separated by periods of relative stability. About 50-70% of these patients eventually enter a phase of progressive neurological decline (secondary progressive MS) with or without superimposed relapses. The pathogenesis of the disease remains unsolved but it is believed to be predominantly an organ- or antigenic-specific autoimmune disease mediated by activated T-lymphocytes, which cross the blood brain barrier (BBB) and initiate a series of inflammatory events that result in demyelination and irreversible axonal loss.

Recombinant interferon beta (INF-β) is currently the mainstay of MS disease-modifying therapies. Endogenous human INF-β is a cytokine secreted by various cells in response to viral infection. A member of the INF type I family, it binds to its specific receptor IFNAR and regulates the transcription of hundreds of genes. The mechanism of action of INF-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 Th1 cells, promoting the production of anti-inflammatory cytokines by Th2 cells, activating suppressor T-cells and 2) inhibiting the destruction of the BBB and the infiltration of T-cells into the CNS.

Recombinant INF-β products are currently being developed as similar to products approved in the EU. A product-class specific guidance will lay down specific (non)clinical requirements for the demonstration of similarity of two recombinant INF-β containing products through a comparability exercise.

2. PROBLEM STATEMENT

Three products containing recombinant INF-β are currently centrally approved in the EU; they differ with respect to their molecular structure, injection route, recommended posology, and MS indications. Recombinant INF-β-1a is produced in CHO cells as a single glycosylated polypeptide chain containing 166 amino acids; of two products available, one is administered subcutaneously and the other intra-muscularly. Recombinant INF-β-1b is produced in E. coli 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; it has about 10% of the specific activity of the CHO-derived products and is administered subcutaneously.

Due to MS disease heterogeneity and INF-β multifaceted immunomodulatory mechanisms, a biosimilar development raises a number of non-clinical and clinical challenges. While its main focus is INF-β, the principles of this guideline may also be applicable to other complex products used in MS.

3. DISCUSSION (on the problem statement)

Non-clinical issues

While a complete set of routine non-clinical studies is not required for a recombinant INF-β developed as a biosimilar, recommendations will be given on the choice of appropriate species and models to be used for comparison of the pharmacodynamic effects of the test and reference products as well as for the requirements for toxicological studies.

Pharmacokinetic/Pharmacodynamic issues

Serum concentrations of INF-β are very low after the administration of therapeutic dosages and their measurement is technically difficult. Their quantification relies upon assays of antiviral biological activity, or more recently, enzyme-linked immunosorbent (ELISA) assays. Thus, markers of INF-β biological activity have been used as indirect measure of bioavailability. There is a long list of INF-β induced proteins but it is unclear which ones are involved in the therapeutic effects reported in MS; amongst others, it includes oligo-A-synthetases, neopterin, β2-microgloblin, interleukin 10, myxovirus resistance protein A (MxA), TNF-related apoptosis inducing ligand (TRAIL). Although there is no evidence for a functional role in MS, MxA eventually emerged as the most specific and sensitive marker of biological activity. MxA induction can be measured from peripheral blood leukocytes both at the protein and mRNA level. There is limited evidence of a dose-response relationship in the therapeutic dose range for some of these biomarkers.

Efficacy issues

All three INF-β products have been approved on the basis of demonstration of clinical benefit in patients with RRMS but their effect is modest with decreases in the frequency of disease attacks by approximately 30% as compared with placebo. While statistical differences have been reported in randomised trials comparing high frequency/high dose (HFHD) subcutaneous regimens with once weekly intramuscular dosing (i.e. different INF-β products), there has been little evidence of a clinical dose effect when the same product has been used.

Magnetic resonance imaging (MRI) is a sensitive tool for monitoring disease activity although correlation between MRI parameters and disability is weak to moderate. T2-weighted scans as well as gadolinium enhancement on T1-weighted MRI have been routinely used in clinical trials to quantify white matter lesions in MS. It is noteworthy that significant differences between treatment groups may be achieved earlier on MRI parameters than on clinical outcomes; furthermore, MRI parameters have been able to distinguish between two doses of the same INF-β product.

Safety issues

All INF-β products are associated with similar and well known adverse reactions, the most frequent being influenza-like symptoms during the first few months of therapy. Injection site reactions and asymptomatic liver abnormalities occur more frequently with the subcutaneous products.

The INF-β preparations differ with respect to their immunogenic potential. Both binding (BAbs) and neutralising antibodies (NAbs) have been described; in clinical trials, the incidence of NAbs has been shown to range widely, from 5% for intramuscular INF-β-1a given weekly to 45% for

subcutaneous INF-β-1b given every other day. Furthermore, it is important to consider the dynamic development as well as peak titres of NAbs. Most Nabs develop in the first year of therapy and their effect on MRI measures of disease burden is apparent by 12 months whereas their effect on clinical outcomes is not detected until 18-24 months of treatment. Following a request of the CPMP, a potential common assay methodology for the determination of neutralising antibodies was successfully developed and the MxA assay was eventually confirmed to be a suitable standardised test.

4. RECOMMENDATION

The Biosimilar Medicinal Products Working Party (BMWP) recommends drafting a guideline on the (non)clinical aspects of the development and assessment of similar biological medicinal products containing recombinant INF-β.

The main topics to be addressed include:

Non-clinical: pharmacodynamic activity in comparison with the reference product; repeat-dose toxicity study of sufficient duration with assessment of antibody development;

PK/PD: choice of appropriate design, dose(s) and biological markers of INF-β activity;

Efficacy: choice of design, target population, duration, primary and secondary endpoints, with particular emphasis on the need for assay sensitivity of the comparative trial;

Safety including immunogenicity: strategy for antibody testing (BAbs and NAbs) with assessment of their evolution over time and their impact on clinical efficacy and safety;

Risk Management Plan: requirements regarding long-term immunogenicity and loss of efficacy;

Extrapolation between MS indications.

5. PROPOSED TIMETABLE

Release for consultation in March 2010, deadline for comments 11 June 2010.

6. RESOURCE REQUIREMENTS FOR PREPARATION

A joint drafting group consisting of BMWP experts will develop the guideline. At least 2 formal meetings of the drafting group will be required in the margins of the working party meetings. Contribution of experts from EWP, BWP, SAWP, SWP and PhVWP will be required.

7. IMPACT ASSESSMENT (Anticipated)

Guidance on the investigation and assessment of biosimilar INFs-β will ensure a more rational and consistent development and assessment of these products by industry and regulators. Since biosimilar INFs-β are already under development, the guidance is expected to give more reassurance as regards regulatory expectations.

8. INTERESTED PARTIES

Competent authorities of the member states, pharmaceutical industry.

Working parties: EWP, BWP, SAWP, SWP and PhVWP.

9. REFERENCES TO LITERATURE, GUIDELINES ETC

- Guideline on Similar Biological Medicinal Products (CHMP/437/04).
- Note for Guidance on Preclinical Safety Evaluation of Biotechnology-derived Pharmaceuticals (CPMP/ICH/302/95).
- 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 Rev. 1).
- Guideline on Immunogenicity Assessment of Biotechnology-derived Therapeutic Proteins (EMEA/CHMP/BMWP/14327/2006).
- Beta-interferons and neutralising antibodies (in multiple sclerosis) (EMEA/CHMP/BWP/580136/2007).