European Medicines Agency
Evaluation of Medicines for Human Use

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

CONCEPT PAPER ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING RECOMBINANT ALPHA-INTERFERON

ANNEX TO THE GUIDELINE ON SIMILAR BIOLOGICAL MEDICINAL PRODUCTS CONTAINING BIOTECHNOLOGY DERIVED PROTIENS AS ACTIVE SUBSTANCE – (NON) CLINICAL ISSUES

AGREED BY BIOSIMILAR MEDICINAL PRODUCTS WORKING PARTY	April 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	26 April 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	1 August 2006

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KEYWORDS	Alpha-interferon, recombinant similar biological medicinal products, comparability, non-clinical studies, clinical studies

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1. INTRODUCTION

Human alpha interferons (α-IFN) are a family of naturally occurring signalling proteins. At least 23 of these predominantly non-glycosylated recombinant α interferons (r-α-IFN) comprising of 165 amino acids and weighing between 19,000 and 20,000 Daltons are recognised. They are used therapeutically for their properties of inducing anti-viral effect, immunomodulation and inhibition of cellular proliferation.

An applicant may choose to develop a new recombinant α interferon (r-α IFN) containing medicinal product claimed to be "similar to an original, r-α-IFN -containing medicinal product (reference medicinal product), which has been granted a marketing authorisation in the Community.

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 with respect to safety and efficacy. A product class-specific guidance as Annex to the above guideline will lay down specific requirements for the demonstration of comparability of two r-α-IFN containing medicinal products with respect to safety and efficacy.

This guideline should be read in conjunction with the requirements laid down in the EU Pharmaceutical legislation and other relevant CHMP guidelines.

2. PROBLEM STATEMENT

Currently several recombinant human alpha interferons including interferon alpha 2a and interferon alpha 2b are authorised in the community. For a bio-similar r-α-IFN particular attention should be given to its ability to influence the various cellular functions.

Recombinant r-α-IFN are used in a wide variety of clinical indications such as viral hepatitis B & C, leukaemias, lymphomas, renal cell carcinoma and myeloma.

r-α-IFN are also associated with a variety of adverse reactions such as flu-like illness, fatigue, and myalgia. In addition r-alpha interferons are associated with psychiatric, haematological and renal adverse effects.

3. DISCUSSION

The guideline will address the requirements for pre-clinical and clinical data necessary to ensure that a new similar r-α-IFN product has a comparable safety and efficacy as compared to the reference medicinal product within the remits of current best practice.

The main topics addressed in the guideline are the following:

Pre-clinical requirements

While a complete set of routine toxicological studies is not required for a recombinant α-IFN developed as a similar biological product, recommendations will be given to the choice of appropriate species and models to be used to compare the various pharmacodynamic effects of the test and the reference product as well as for the requirements for toxicological studies.

Clinical requirements

Guidance will be given on the following critical points:

Pharmacokinetics

- Design of pharmacokinetic studies

Pharmacodynamics

- Pharmacodynamic requirements, including choice and relevance of pharmacodynamic markers

Efficacy

The effect of the new product should be compared to the reference product in randomised clinical trials that are sensitive to potential differences between the two medicinal products.

The efficacy guidance will address methodological considerations, including:

- Selection of the most relevant patient population(s)/therapeutic indication(s)
- Design and recommended primary and secondary clinical endpoints in efficacy studies
- Duration of the studies
- Pharmacodynamic markers as possible surrogates for efficacy

Safety

Guidance will be provided on the following items:

- Extent of the safety database
- Requirements for pre-approval safety evaluation
- Requirements for a pharmacovigilance risk management plan at the time of MAA

Extrapolation of clinical data

Recommendation will be provided on extrapolation of efficacy and safety data obtained in one therapeutic indication to other indications approved for the reference product.

4. RECOMMENDATION

It is proposed to draft an Annex to the guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues with respect to recombinant recombinant α-IFN-containing products.

5. PROPOSED TIMETABLE

Release for consultation on 26/04/06, deadline for comments 31/07/06, discussion in BMWP 3Q/06 to 4Q/06, discussion with BWP, EWP, SWP 1Q/07, proposed date for release of draft guideline 1Q/07, deadline for comments 3Q/07, re-discussion in BMWP 3Q/06 to 4Q0/07, expected dated for adoption by Committee 4Q/07.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The BMWP 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.

7. IMPACT ASSESSMENT (Anticipated)

N / A

8. INTERESTED PARTIES

Competent authorities of the member states, and pharmaceutical industry.
CHMP and its working parties EWP, BWP, BPWP, SWP and PhVWP.

9. REFERENCES TO LITERATURE, GUIDELINES ETC.

- 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)
- Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Quality Issues (EMEA/CHMP/BWP/49348/2005)
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CHMP/BMWP/42832/2005)
- ICH topic S6 - Note for guidance on Pre-clinical Safety Evaluation of Biotechnology-Derived Pharmaceuticals (CPMP/ICH/302/95)
- ICH topic E9 statistical principles for clinical trials – Note for guidance on statistical principles for clinical trials (CPMP/ICH/363/96)

- ICH topic E10 - Note for guidance on choice of control group in clinical trials (CPMP/ICH/364/96)
- Points to consider on switching between superiority and non-inferiority (CPMP/EWP/482/99)