European Medicines Agency

London, 18 October 2007
Doc. Ref. EMEA/CHMP/BMWP/102046/2006

COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

DRAFT

GUIDELINE ON SIMILAR MEDICINAL PRODUCTS CONTAINING RECOMBINANT INTERFERON ALPHA

AGREED BY BIOSIMILAR MEDICINAL PRODUCTS WOKRING PARTY (BMWP)	October 2007
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	October 2007
END OF CONSULTATION (DEADLINE FOR COMMENTS)	April 2008

Comments should be provided electronically in word format using this template to BMWP.secretariat@emea.europa.eu

KEYWORDS	Interferon alpha, recombinant, similar biological medicinal products, comparability, non-clinical, clinical, pharmacovigilance, immunogenicity

7 Westferry Circus, Canary Wharf, London, E14 4HB, UK
Tel. (44-20) 74 18 84 00 Fax (44-20) 74 18 86 13
E-mail: mail@emea.europa.eu http://www.emea.europa.eu

GUIDELINE ON SIMILAR MEDICINAL PRODUCTS CONTAINING RECOMBINANT INTERFERON ALPHA

EXECUTIVE SUMMARY

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 non-clinical and clinical requirements for the development of similar biological medicinal products.

The present guideline gives further guidance on the development of interferon alpha-containing medicinal products claiming to be similar to another one already marketed.

The non-clinical section addresses the data required for comparative pharmaco-toxicological assessment. The clinical section addresses the requirements for comparative pharmacokinetic, pharmacodynamic, efficacy and safety studies as well as the risk management plan. Extrapolation of clinical data to other indications approved for the reference medicinal product is addressed.

1. INTRODUCTION (background)

The Marketing Authorisation (MA) application dossier of a new recombinant interferon-alpha 2a or 2b claimed to be similar to a reference product already authorised, shall provide the demonstration of comparability of the product applied for to a reference product authorised in the EU.

Human interferon-α 2a or 2b are well-known and characterized proteins consisting of 165 amino acids. The non-glycosylated protein has a molecular weight of approx. 19,240 D. It contains two disulfide bonds, one between the cysteine residues 1 and 98, and the other between the cysteine residues 29 and 138. The sequence contains potential O-glycosylation sites. Physico-chemical and biological methods are available for characterisation of the proteins.

Recombinant IFN-α2a or 2b is approved in a wide variety of conditions such as viral hepatitis B and C, leukaemia, lymphoma, renal cell carcinoma and multiple myeloma. It is used alone or in combination in oncology indications. Interferon-alpha may have several pharmacodynamic effects. The relative importance of these effects in the different therapeutic indications is unknown.

The dose and treatment regimen required to achieve the desired response vary considerably.

It is commonly used subcutaneously although it can also be used through intramuscular or intravenous route. The sub-types Interferons alpha 2a and 2b have different clinical use.

In general, interferon-α 2a or 2b use in oncology indications has reduced considerably and been superseded by other more effective treatments.

Treatment with recombinant interferon alpha 2a or 2b is associated with a variety of adverse reactions such as flu-like illness, fatigue, and myalgia. In addition r-IFN-α are associated with psychiatric, haematological and renal adverse effects.

Therapy with IFN-α 2a or 2b may induce development of auto-antibodies. A variety of immune-mediated disorders such as thyroid disease, rheumatoid arthritis, systemic lupus erythematosus, neuropathies and vasculitis have been observed with r-IFN-α.

Both non-neutralising and neutralising antibodies against the administered interferon have been observed.

Throughout the development program the same approved reference product – according to the treatment as per the current standard of care - should be used. Posology should be as for the reference product.

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 recombinant interferon alpha-containing medicinal products.

3. LEGAL BASIS

Directive 2001/83/EC, as amended 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. These studies should be comparative in nature and should be designed to detect differences in the pharmaco-toxicological response between the similar r-IFN-α and the reference r-IFN-α and not just assess the response *per se*. The approach taken will need to be fully justified in the non-clinical overview.

Pharmacodynamics studies

In vitro studies:

In order to compare any alterations in reactivity between the similar and the reference medicinal products, data from a number of comparative bioassays (e.g. receptor-binding studies, antiviral effects in cell culture, antiproliferative effects on human tumour cell lines), many of which may already be available from bioassays submitted as part of the quality dossier, should be provided.

The limitations of studying anti-viral effects in cell culture systems expressing HCV, however, should be recognised, as the results do not correlate well with clinical response. Standardised assays should be used to measure activity and potency.

In vivo studies:

To support the comparability exercise for the sought clinical indications, the pharmacodynamic activity of the similar biological medicinal and the reference medicinal product. should be quantitatively compared in:

- an appropriate pharmacodynamic animal model (e.g. evaluating effects on pharmacodynamic markers as for example serum 2′,5′-oligoadenylate synthetase activity). Pharmacodynamic measurements may be performed as part of repeat-dose toxicity studies.

and/or

- a suitable animal tumour model (e.g. nude mice bearing human tumour xenografts)

and/or

- a suitable animal antiviral model.

Toxicological studies

Data from at least one repeat dose toxicity study in a relevant species should be provided (for example, human IFN alphas may show activity in the Syrian golden hamster). Study duration should be at least 4 weeks. The study should be performed in accordance with the requirements of the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues "and the "Note for guidance on repeated dose toxicity" (CPMP/SWP/1042/99) and include appropriate toxicokinetic measurements in accordance with the "Note for guidance on toxicokinetics: A guidance for assessing systemic exposure in toxicological studies" (CPMP/ICH/384/95).

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 similar biological medicinal products containing recombinant human IFN-α as active substance.

4.2. CLINICAL STUDIES

Pharmacokinetic studies

The pharmacokinetic properties of the similar biological medicinal product and the reference medicinal product should be compared in single dose crossover studies using subcutaneous and intravenous administration in healthy volunteers. The recommended pharmacokinetic parameters are AUC, C_{max} and $T_{1/2}$. Equivalence margins have to be defined *a priori* and appropriately justified.

Pharmacodynamic studies

There are a number of PD markers, such as β2 microglobulin, neopterin and serum 2′,5′-oligoadenylate synthetase activity, which are relevant to the interaction between IFN-α and the immune system. The selected dose should be in the linear ascending part of the dose-response curve. Whereas the relative importance of these effects in the different therapeutic indications is unknown. a comprehensive comparative evaluation of such markers following administration of test and reference products could provide useful supporting data.

EFFICACY

Patient population

The mechanism of action of interferon comprises of several different unrelated effects.

Demonstration of similar efficacy between test and reference products is required and it is recommended that this should be performed in treatment-naïve patients with chronic hepatitis C (HCV) as delineated by the indication for the reference product. Other patient population(s) might be studied depending on the indications desired (see under Extrapolation of evidence).

Study design and duration:

A randomised, parallel group comparison against the reference product over at least 48 weeks is recommended. If possible, the study should be double-blind at least until data to complete the primary analysis have been generated. If this not feasible, justification should be provided and efforts to reduce/ eliminate bias should be clearly identified in the protocol.

The posology (i.e., dose, route and method of administration) should be the same as for the reference product. IFN-α should be given in line with the current standard treatment for chronic HCV infection in the EU and in accordance with the SPC of the reference product.

The study could be designed so that the primary efficacy analysis is performed at week 24 for all enrolled patients followed by a secondary analysis at 48 weeks. Preferably, a homogenous and sensitive (e.g. genotype selection) patient population is recommended to best detect differences. The choice of the patient population should be justified. If a mixed population is chosen, they should be pre-stratified based on the HCV genotype.

The 48-week time point would constitute end-of-treatment for those patients with genotype 1.

For patients with genotypes 2 and 3, week 48 would usually constitute 24 weeks post-therapy, during which time the status of antibodies to INF-α and the relapse rates could be assessed.

Endpoint(s)

Primary: Virologic response as measured by the proportion of patients with undetectable levels of HCV RNA by quantitative PCR at week 24. The assay used to measure HCV RNA and the cut-off applied should be justified. A 2-log decrease in viral load may be a co-primary endpoint.

Secondary: virologic response at weeks 4, 12, 48; change in liver biochemistry including transaminase levels and morbidity.

SAFETY

Safety data should be collected from a cohort of patients after repeated dosing in a comparative clinical trial over a period of 48 weeks and should be presented with marketing authorisation application. The number of patients should be sufficient for the comparative evaluation of the adverse effect profile, including laboratory abnormalities for immune mediated disorders. The safety profile should be similar between test and reference products for the common adverse events (such as flu-like illness, alopecia, myalgia, leucopenia, anaemia and thrombocytopenia).

Immunogenicity

Antibody data should be presented for a minimum of 48 weeks according to the principles described in the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues" EMEA/CPMP/42832/05/. Antibodies, if present, should be further evaluated e.g., for neutralising capacity and the resulting potential for impact on efficacy of r-IFN-α. In addition, any potential for neutralisation of the effect of endogenous interferon(s) should be addressed.

Any impact of immunogenicity should be thoroughly evaluated in those:

- not responding to treatment
- losing response during primary treatment
- exhibiting unexpected adverse reactions or known immune-mediated events.

EXTRAPOLATION OF EVIDENCE

In principle extrapolation from one therapeutic indication to another is appropriate where the mechanism of action is known to be the same as the condition(s) for which similarity in efficacy has been established.

If indication(s) are sought, where the mechanism of action is not known to be the same, such extrapolation should be justified by relevant data.

4.3 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.

Attention should be paid to immunogenicity and potentially rare and/or delayed serious adverse events, especially in patients undergoing chronic administration. Safety should be collected from patients representing all approved indications.

REFERENCES (scientific and/or legal)

- 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/draft).
- Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (EMEA/CPMP/42832/05/draft).
- Note for guidance on repeated dose toxicity (CPMP/SWP/1042/99).
- Note for guidance on toxicokinetics: A Guidance for assessing systemic exposure in toxicological studies (CPMP/ICH/384/95).
- Note for guidance on non-clinical locale tolerance testing of medicinal products (CPMP/SWP/2145/00).
- Guideline on risk management systems for medicinal products for human use (EMEA/CHMP 96286/2005).
- Note for Guidance on Good Clinical Safety Data Management: Definitions and Standards for Expedited Reporting (CPMP/ICH/377/95).
- ICH Note for Guidance on Planning Pharmacovigilance Activities (CPMP/ICH/5716/03 - Final approval by CHMP on PHV).