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**COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE
(CHMP)**

REFLECTION PAPER

**NON-CLINICAL AND CLINICAL DEVELOPMENT OF SIMILAR MEDICINAL
PRODUCTS CONTAINING RECOMBINANT INTERFERON ALFA**

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EXECUTIVE SUMMARY

This reflection paper lays down considerations on the non-clinical and clinical development of recombinant Interferon alfa-containing medicinal products claiming to be similar to another such product already authorised.

CHMP is aware that treatment of viral hepatitis with non-pegylated recombinant Interferon-alfa is not current standard of care in the European Union. This reflection paper intends to highlight some principles which would be applicable for the development of a similar medicinal product containing recombinant Interferon alfa from now on referred to as Interferon alfa.

The non-clinical section addresses principles to be considered 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.

1. INTRODUCTION

Human interferon-alfa 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 Interferonalfa 2a 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. The sub-types Interferons alfa 2a and 2b have different clinical uses. IFN-alfa is used alone or in combination. Interferon alfa may have several pharmacodynamic effects. The relative importance of these effects in the different therapeutic indications is unknown. In general, interferon-alfa 2a or 2b use in oncology indications has reduced considerably and been superseded by other treatments.

The dose and treatment regimen required to achieve the desired response vary considerably between different therapeutic indications.

Interferon alfa is commonly used subcutaneously although it can also be used through intramuscular or intravenous route. Treatment with Interferon alfa 2a or 2b is associated with a variety of adverse reactions such as flu-like illness, fatigue, and myalgia. In addition Interferon alfa is associated with psychiatric, haematological and renal adverse effects.

Therapy with IFN-alfa 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 the therapeutic use of Interferon alfa.

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

2. SCOPE

This product specific reflection paper presents the current view of the CHMP on the non-clinical and clinical data for demonstration of comparability of two recombinant, non-pegylated, Interferon alfa containing medicinal products and should be read in conjunction with the requirements laid down in the EU Pharmaceutical legislation and other relevant CHMP guidelines (see References).

3. LEGAL BASIS

Directive 2001/83/EC, as amended and Part II of the Annex I of Directive 2001/83/EC, as amended.

4. NON-CLINICAL STUDIES

Before initiating clinical development, non-clinical studies should be performed. These studies would be comparative in nature and designed to detect differences in the pharmaco-toxicological response between the similar Interferon alfa and the reference Interferon alfa 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 differences in biological activity between the similar and the reference medicinal product, data from a number of comparative bioassays could be provided (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. Wherever possible, analytical methods should be standardised and validated according to relevant guidelines.

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. Wherever possible, standardised and validated 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 and the reference medicinal product could 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). If feasible, these measurements may be performed as part of the toxicological studies described below

or

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

or

-a suitable animal antiviral model.

Toxicological studies

Data from at least one repeat dose toxicity study in a relevant species should be considered (for example, human Interferon alfa may show activity in the Syrian golden hamster). The study duration should be at least 4 weeks.

The study should be performed in accordance with the requirements of the "Note for guidance on preclinical safety evaluation of biotechnology-derived pharmaceuticals" (CPMP/ICH/302/95) and the "Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues (CHMP/42832/05)".

Specific guidance on the design and conduct of this study can also be found in the "Note for guidance on repeated dose toxicity" (CPMP/SWP/1042/99). Appropriate toxicokinetic measurements should be performed ("Note for guidance on toxicokinetics: A guidance for assessing systemic exposure in toxicological studies", CPMP/ICH/384/95) as part of the repeat dose toxicity study and include a determination of antibody formation ("Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins", EMEA/CHMP/BMWP/14327/2006).

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 Interferon alfa as active substance.

5. CLINICAL STUDIES

Pharmacokinetic studies

The pharmacokinetic properties of the similar and the reference medicinal product could be compared in single dose crossover studies using subcutaneous and intravenous administration in healthy volunteers. The recommended primary pharmacokinetic parameter is AUC and the secondary parameters are C_{\max} and $T_{1/2}$ or CL/F .

Equivalence margins have to be defined *a priori* and appropriately justified.

Pharmacodynamic studies

There are a number of PD markers, such as $\beta 2$ microglobulin, neopterin and serum 2', 5'-oligoadenylate synthetase activity, which are relevant to the interaction between Interferon -alfa and the immune system. The selected doses 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. This could 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 is 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-alfa should be given in line with the current standard treatment for chronic HCV infection and in accordance with the SmPC of the reference product.

The study could be designed so that the primary efficacy analysis is performed at week 12 for all enrolled patients. Preferably, a homogeneous population is recommended (e.g. one single HCV genotype). However, if a mixed population is chosen, it should be stratified based on the HCV genotype.

Endpoints

Primary: Virologic response as measured by the proportion of patients with undetectable levels of HCV RNA by quantitative PCR at week 12. 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 week 4 and end-of-treatment; sustained virologic response (24 weeks after completion of treatment); change in liver biochemistry including transaminase levels and morbidity.

SAFETY

Safety data should be collected from patients after repeated dosing in a comparative clinical trial over the treatment period plus 24 weeks of follow-up. The number of patients should be sufficient for the comparative evaluation of the adverse effect profile. Laboratory abnormalities for immune mediated disorders should be included. The safety profile should be similar to the reference products for the common adverse events (such as flu-like illness, alopecia, myalgia, leucopenia, anaemia and thrombocytopenia).

Immunogenicity

Comparative immunogenicity data (antibody levels) should be presented during the treatment period plus 24 weeks of follow-up 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" (EMA/CPMP/42832/05/) and the "Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins" (EMA/CHMP/BMWP/14327/2006). Antibodies, if present, should be further evaluated e.g., for neutralising capacity and the resulting potential for impact on efficacy of r-IFN-alfa. In addition, any potential for neutralisation of the effect of endogenous interferon(s) (i.e., development of autoimmunity) should be addressed. Any impact of immunogenicity should be thoroughly evaluated in those individuals:

- not responding to treatment

- losing response during primary treatment
- exhibiting unexpected adverse reactions or known immune-mediated events.

6. EXTRAPOLATION OF EVIDENCE

In principle extrapolation from one therapeutic indication to another is appropriate where the mechanism of action and/or the receptor are 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 adequately justified.

7. 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

- 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: non-clinical and clinical issues (EMA/CHMP/BMWP/42832/2005).
- 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 local tolerance testing of medicinal products (CPMP/SWP/2145/00).
- Guideline on risk management systems for medicinal products for human use (EMA/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).
- Guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins” (EMA/CHMP/BMWP/14327/2006).