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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE (CHMP)

GUIDELINE ON CLINICAL TRIALS WITH HAEMATOPOIETIC GROWTH FACTORS FOR THE PROPHYLAXIS OF INFECTION FOLLOWING MYELOSUPPRESSIVE OR MYELOABLATIVE THERAPY

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This Guideline replaces NfG on Clinical Trials with Haematopoietic Growth Factors for the prophylaxis of infection following Myelosuppressive or Myeloablative Therapy (CPMP/EWP/555/95)

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1. INTRODUCTION (background)

Colony stimulating factors (CSFs) that act on the myeloid lineage have already been marketed in the EU. These notes are intended to provide guidance for the evaluation of products used to reduce the risk of infection, caused by neutropenia induced by cytotoxic chemotherapy or by myeloablative therapy preceding bone marrow transplantation.

This Guideline should be read in conjunction with other relevant guidelines listed below:

- Note for Guidance on Statistical Principles for Clinical Trials (ICH E9)
- Note for Guidance on Choice of Control Group in Clinical Trials (ICH E10)
- Note for Guidance on Good Clinical Practice (ICH E6)
- Note for Guidance on General Considerations for Clinical Trials (ICH E8)
- Guideline on the Choice of the Non-inferiority margin (CPMP/EWP/2158/99)
- Guideline on Comparability of Medicinal Products containing Biotechnology-derived Proteins as Drug Substance – Non clinical and Clinical Issues (CPMP/3097/02/REV)
- Guidance on biosimilar biological medicinal products containing recombinant human granulocyte-colony stimulating factor.

For a Marketing Authorisation (MA) application dossier of a CSF claimed to be biosimilar to a reference product already authorised, comparability of the test product to an authorised reference product in the EU, should be demonstrated.

One particularly important purpose of this note for guidance concerning clinical trials performed to support such applications is to give guidance on the major efficacy end points that should be investigated in confirmatory trials before the submission of a marketing authorization application. The guidance given herein specifically addresses trials of CSFs for the already authorised therapeutic indications, further guidelines may be required when new therapeutic indications for these agents are developed.

The following guidance is applicable to new biological products including bioengineered biologics involving either new or existing products and biosimilars. Developments in the modification of colony stimulating factor proteins through pegylation or other bioengineering methods can modify not only the CSF formulation properties but also both its pharmacokinetic (PK) and pharmacodynamic (PD) performance. This translates into the development of a long-acting CSF requiring less frequent dosing than its parent drug through a longer half-life and slower elimination rate. Accordingly, trial methodology as currently specified, may not be the most appropriate under such circumstances. For these reasons alternative designs of clinical studies are needed and these issues are covered in section 7 of this guideline.

2. DESIGN OF HUMAN PHARMACOLOGY TRIALS

The aim of human pharmacology trials is to acquire data on safety and dose response in the initial exposure of humans to the new CSF. The study population could be healthy volunteers or, preferably, cancer patients who are not concomitantly receiving myelosuppressive or myeloablative therapy. The choice of healthy subjects/patients should be justified by the applicant. Other factors to take into account are:

Design: single and/or repeated dose escalation in successive groups.

Assay Methodology: PK, PD and immunogenicity

Data Analysis: PK and/or PD parameters, PK/PD relationship

2.1 Studies in Volunteers

In general, trials on healthy volunteers are suitable for determining basic pharmacokinetic data after single administration and could be used with repeated administration. If, however, significant side effects with the new growth factor are of concern, studies will have to be conducted exclusively in patients.

In addition, repeated dosing with a CSF in healthy volunteers may lead to excessive hyper-leucocytosis (>70,000 x10^9/L) without reaching maximum tolerable dose for another AE other than hyper-leucocytosis, which itself may gives rise to the potential risk of splenic enlargement and spontaneous rupture. Accordingly, trials in patients may be required to investigate repeated dosing at higher dose levels.

2.2 Studies in Patients

If the side effects encountered during the preliminary testing of a new CSF give rise to ethical concerns about tests in healthy volunteers, human pharmacology trial(s) should be conducted in patients who may have a chance of benefiting from the new drug. In such a situation the design of the trial(s) may be as follows: patients who are eligible for (first-line) palliative cytotoxic chemotherapy will be recruited for human pharmacology trials with a new CSF before the cytotoxic chemotherapy starts. Human pharmacology investigations, including pharmacokinetics and the documentation of adverse events should be performed prior to chemotherapy.

In the exploratory trials a correlation between the blood concentration (e.g. C_{max}, AUC, trough levels) and the desired clinical effect should be investigated.

In addition to the determination of the basic pharmacokinetic data, the relationships between pharmacokinetics and pharmacodynamics should be investigated and an analysis of the relationships between pharmacokinetic measures (e.g. AUC) with both pharmacodynamic measures (e.g. neutrophil count) and adverse effects should be performed. Both PK and PD data should ideally be collected from the same study to minimise inter-study variability and better characterise PK/PD relationship. Immunogenicity data should also be collected from human pharmacology studies.

The trials should preferably be conducted with the final drug formulation. After completing human pharmacology trials, it should be possible to conclude that the new CSF can be safely used in a range of single doses and /or used for the duration of the specified period at a selected dose level. Side effects to be expected, as well as effects on the myeloid and non-myeloid cells including monocytes, lymphocytes, platelets and erythroid cells should be described.

The trials should allow for recommendation of some doses for repeated administration, or some single dose levels for a single administration in the case of a prolonged release form (e.g. pegylated) of a CSF, to be further investigated in exploratory trials, i.e. in patients after start of cytotoxic chemotherapy or myeloablative therapy.

The absolute neutrophil count is an acceptable surrogate marker in pharmacodynamic (PD) studies.

When trials in healthy volunteers are feasible, efforts should be directed at studying the effects of the new CSF on other cytokines.

2.3 Bioassay Methodology

Usually, a bioassay will be available for the concentration assays when a new CSF reaches human pharmacology trials. However, a more specific test system (e.g. RIA, EIA, ELISA) should be developed and employed for the pharmacokinetic investigations. (Refer to NfG on PK in therapeutic proteins CPMP/EWP/89249/04).

3. EXPLORATORY CLINICAL TRIAL

3.1 Objectives

The object of the exploratory studies is to evaluate dose dependent effects of the CSF in patient groups after receiving myelotoxic therapy.

Exploratory trials should be concluded with the recommendation of a dosage regimen for confirmatory trials. The confirmatory protocols should include justifications, based on the data from exploratory trials, as to the timing of the initiation of treatment and as to its duration. The dosage regimens used in the confirmatory trials should take account of any evidence of differences in dose-response relative to the intensity of the myelosuppressive regimen from the data acquired in the exploratory trials.

The trials should answer questions about how the incidence, degree and duration of the neutropenia can be modified by the dosage and or dose regimen.

If more than one route of administration has been investigated, recommendations as to the preferred route or routes should be justified. Data on the equivalence (or non-equivalence) of the pharmacodynamic effects on neutropenic end points for the different routes will be required.

3.2 Design of Exploratory Trials

The trial population should represent the patients to be treated as suggested by the indication wording. The design of the study should be double-blind, randomised, parallel group dose response. As regards dosage/administration, the variables that should usually be investigated are: magnitude of daily dose and cumulative dose during the chemotherapy cycle, route of administration and optimum time of first dose in relation to chemotherapy.

3.3 Endpoints to be Studied on a Regular Basis

The following measures of the differential white blood cell count should be determined in the exploratory trials:

- Neutropenia: Incidence of Grade 4 neutropenia, duration of neutropenia (number of days with < 500 and < 100 neutrophilic granulocytes per µl), incidence of febrile neutropenia (defined as a rise in axillary temperature to above 38.5 centigrade for a duration of more than 1 hour while having an absolute neutrophil count $< 0.5 \times 10^9$ /l)

  Further, median time to absolute neutrophil count recovery as defined, depth of the nadir of absolute neutrophil count, duration from the beginning of myelosuppressive or myeloablative therapy to the occurrence of the nadir and frequency of a nadir of < 500 and < 100 absolute neutrophil count per µl should also be determined.
- Adverse events including frequency of (culture-confirmed) infections and neutropenic fever
- Laboratory safety monitoring including haemoglobin, lymphocyte and platelet count
- The percentage of the actually delivered vs. scheduled cumulative chemotherapy dose
- Cumulative CSF dose
- Number of transfusions
- Mobilisation of CD34+ cells (AUC and maximum concentration) where possible
- PK data
- Immunogenicity data

Studies should be carried out in a well-defined group of patients (e.g. one type of cancer, same stage of disease) using only one chemotherapy regimen in each trial. Groups should be stratified with regard to chemotherapy regimen at randomisation provided that different chemotherapy regimens are to be studied. The myelosuppressive intensity of the chemotherapeutic regimen must always be specified (see 4.2 below).

4. CONFORMATORY TRIALS

4.1 Objectives

The efficacy of the CSF will be determined by the demonstration that its administration as recommended in the SPC:

a) Significantly reduces incidence, duration and/or severity of febrile neutropenia and is supported by improved outcomes such as reduction in the frequency of documented infections, days of hospitalisation, intravenous antibiotic usage, or improvement in quality of life or survival.

   And/or

b) Is equivalent to a validated standard therapeutic procedure such as antibiotics and supportive care with respect to frequency of outcomes as mentioned above in (a)

Furthermore, the confirmatory trial must provide sufficient data to assure that the administration of the CSF is safe in the above-mentioned therapeutic situation (the effect on other organs and receptors should also be identified).

4.2 Intensity of Chemotherapy Regimens

For all new products, superiority to a placebo add-on a (standard) chemotherapy regimen with established frequency of febrile neutropenia should be demonstrated whenever possible. However, a non-inferiority design could be an acceptable option:

If the duration and frequency of febrile neutropenia is well documented (there are more than 20% of patients with febrile neutropenia on a given chemotherapy regimen): placebo is considered unethical and a 2-arm trial versus active comparator is recommended.

If the incidence of febrile neutropenia by regimen is between 10-20% then the use of a placebo arm may be justified provided high-risk patients are excluded. Assessment of individual or study patient characteristics and risk factors (age > 65 years etc.) may increase the overall risk of febrile neutropenia to the level where placebo control is no longer ethical, and active comparator may be needed.

If the incidence of febrile neutropenia is less than 10%, then the use of a placebo arm only is acceptable.

Should a placebo arm be utilised in a trial of colony stimulating factors, secondary G-CSF prophylaxis for subsequent cycles of chemotherapy should be available by protocol to any patient in the placebo arm that experiences febrile neutropenia or a related event in a prior cycle.

If however, the duration of febrile neutropenia is not well documented for a given chemotherapy treatment regimen, a placebo arm and an active comparator arm should be used in a 3-arm study. A statistically significant superiority of the test product over placebo and non-inferiority with the reference product should be shown for the primary endpoint.

Cytotoxic regimens can be categorised according to their myelosuppressive intensities; i.e. the incidence of febrile neutropenia. It is possible that the dose of a CSF required to counteract the white cell effect of different cytotoxic regimens will differ according to the myelosuppressive intensity of the regimens. The applicant should justify the categories used to define the intensity of myelosuppression. The trial reports should state explicitly whether or not patients were stratified by intensity of myelosuppressive cytotoxicity before they were randomised into treatment groups.

In the case of haematological malignancies trial reports should document whether, for example, standard chemotherapy or high dose intensive chemotherapy regimens have been utilised. Additionally, the use of CSFs to sensitise patients to chemotherapy should be recorded. Full details of these chemotherapy regimens should be documented.

4.3 Design of Confirmatory Trials

As a rule, confirmatory trials should be double-blind, randomised and placebo-controlled when feasible and should demonstrate superiority of the test treatment. In so far as effective alternative treatments are already authorised it may be unethical to treat patients with a placebo. In such cases double-blind, non-inferiority trials, with the best available standard therapy as control, should be carried out.

The selection criteria should include information regarding prior therapy with CSFs, previous prophylactic treatment (antibacterial/ antifungal /other) co morbidity and histological type of tumour (where applicable). It is acceptable to include in the analysis afebrile patients receiving antibiotics, who cannot be assessed for febrile neutropenia. However, such patients should be analysed separately for duration and incidence of severe neutropenia. Both analyses should show similar results, for test and comparator otherwise the SPC should accurately reflect findings from observed data.

More than one regimen of the growth factor may need to be tested if exploratory data are not clear.

The intensity of the chemotherapy regimens investigated should be classified as outlined under 4.2 above and the choice of the comparator (placebo, active and/or both) should be justified, based on this.

Where multicentre studies are carried out all efforts should be directed at standardising concomitant therapies (e.g. antibiotic policies) between centres. The criteria for discharge from hospital should be specified and should be the same for all study centres. Similarly, the criteria for the initiation and discontinuation of treatment with intravenous antibiotics agents should be specified and should be the same for all centres.

It is recommended to use the same chemotherapeutic regimens in the same population of patients in pivotal studies.

4.4 Surrogate Endpoints for the Reduction of Infection

The primary endpoint for confirmatory clinical trials should adequately demonstrate efficacy of the CSF which should be clinically meaningful so that, for example, it significantly reduces the frequency of documented infections. However, this may not always be appropriate or possible since it is dependent, for example, on the disease population being studied (e.g. solid tumours or haematological malignancies), as well as the intensity of chemotherapy and or radiotherapy being utilised (myeloablative or non-myeloablative), which may affect important considerations such as sample size, thus making clinical trials impractical. Accordingly, appropriate surrogate endpoints need to be considered which would indirectly imply a reduction in infections. Incidence and duration of febrile and/or severe (Grade 4) neutropenia in relation to the first chemotherapy cycle would be acceptable surrogate endpoints.

4.5 Primary Endpoints

Incidence and duration of febrile and/or severe (Grade 4) neutropenia in relation to the first chemotherapy cycle.

Febrile neutropenia is defined as a rise in axillary temperature to above 38.5°C for a duration of more than 1 hour while having an absolute neutrophil count (ANC) $<0.5 \times 10^9$/l.

Definitions of infection and/or fever and definition of the leucocyte/neutrophil count should be provided.

It is strongly recommended that the effect of treatment with the new CSF on mortality due to infections and overall mortality should be investigated.

4.6 Secondary Endpoints

The following endpoints should usually be investigated and support the conclusions of confirmatory endpoints. Infection, however, is the most important secondary endpoint.

- Frequency and types of infections - The criteria for infections due to the neutropenic state should be clearly specified; two criteria are recommended as follows:
    - positive culture of pathogenic organisms during the neutropenic state or clinically diagnosed infections
    - fever (defined as a temperature above 38.5°C) during the neutropenic state
- Full haematology including haemoglobin and recovery of platelet and granulocyte count
- The numbers of transfusions used to treat thrombocytopenia and anaemia
- Time in hospital
- Time in Intensive Care Unit
- Use of iv antibiotics

Since a variety of infections occur in neutropenic patients, it is recommended that a distinction be made between bacterial and non-bacterial infections, between primary infection and superinfection and between cultures confirmed and unconfirmed infections.

Data should also be documented with respect to the site of infection, pathogen distribution (gram positive, gram negative and the most frequently identified pathogen), resistance patterns and response.

- Percentage of scheduled chemotherapy dose that was delivered
- Proportion with chemotherapy doses reduced, omitted, or delayed
- Number of days of delay of chemotherapy
- Occurrence and/or resolution of chemotherapy-induced mucositis
- Overall quality of life

4.7 Safety Evaluation

In addition to the collection and reporting of adverse events for safety evaluation, the following points should be analysed and reported for every confirmatory trial for safety considerations:

- Overall survival.
- Any adverse effect on efficacy of the chemotherapy regimen(s) in terms of time to progression and frequency of (complete) objective tumour remissions.
- if the CSF is a protein, anti-CSF antibodies should be monitored for at least 12 months .

If applicable and depending on the therapeutic situation (non-infectious), complications of myelosuppressive or myeloablative therapy such as frequency of acute and chronic GVHD, frequency of transplant failure, reactivation of latent viral infection and other opportunistic infections should be analysed and reported. However, the initial development of novel CSFs should not be undertaken in the more complex field of allogeneic transplantation. Additional safety considerations include biological agents which affect interactions between bone marrow stroma and haematopoietic stem cells that may have an adverse safety profile which should be further characterised.

Although actual numbers are not specified, there should be an adequate safety database, which should be justified. The safety database is dependent on the experience of the innovator and reference products as well as on the general considerations for recombinant growth factors.

Immunogenicity

Even if no clear immune-mediated adverse effects of the original product have been recorded, such reactions are by no means excluded for new/changed products. The CHMP guideline for comparability, non-clinical and clinical issues, gives detailed guidance for the investigation of immunogenicity (EMEA/CPMP/3097/02). While no absolute numbers are specified, the pre-authorisation immunogenicity safety database should include between 300-600 patients including healthy volunteers followed up for at least a year or the size of the database should be justified if this is not possible. (Refer to Immunogenicity Guideline CHMP/BMWP/246511/05)

5. POINTS TO CONSIDER FOR THE INDICATION

The indication should reflect the group of patients studied, the dose intensity of the myelosuppressive or myeloablative chemotherapy studied and the data generated in the clinical trials.

If a number of studies are to be performed, they should be planned to cover different diseases.

If in any phase of the clinical trial particular diseases (e.g. myeloid malignancies) were excluded from the protocol due to a particular concern of the investigators, these diseases and the reasons for their exclusion should be listed under the heading "Warning"; the reason for the warning should be given, namely: lack of evidence of safety and efficacy in these groups of patients.

6. COMBINATIONS OF CSFS

Two different situations can be considered:

6.1 A New CSF (A) has an Additive Effect to a Licensed Growth Factor (B) and is Effective as a Monotherapy

In this situation the new growth factor should be investigated in human pharmacology and exploratory trials as described above. In addition to monotherapeutic pharmacodynamics and safety, the combination of A and B should be studied as described under item 6.2. It should be demonstrated in trials with 3 arms consisting of A alone, B alone and the combination of A and B, to demonstrate that the combination of A and B provides a benefit greater than either A or B used alone.

6.2 A New CSF (A) has an Additive Effect to a Licensed CSF (B), but is Not Effective as Monotherapy

After the new drug has been tested in human pharmacology trials, the combination should be studied as if it were one drug.

In exploratory trials particular efforts should be made to determine the optimum dose ratio of drug A and B.

In confirmatory trials it should be confirmed that the optimum dose ratio of the combination is superior to B alone.

7. PEGYLATED AND OTHER BIOENGINEERED PRODUCTS

The guidance provided above is applicable to all products, however, the following exceptions with respect to pegylated and other bioengineered products are outlined below.

However, it is appreciated that these guidelines may need to be amended as appropriate when novel haematopoietic growth factors are being studied.

7.1 Human Pharmacology Studies

Design of human pharmacology trials

The study population could be healthy volunteers, or preferably cancer patients who are not concomitantly receiving myelosupressive or myeloablative therapy. The choice of healthy subjects/patients should be justified by the applicant. Other factors to take into account are:

- Design: single and/or repeated dose escalation in successive groups.
- Assay Methodology: PK, PD and immunogenicity
- Data Analysis: PK and/or PD parameters, PK/PD relationship
- The pharmacokinetic parameters including AUC, C_{max}, T_{max}, $T_{1/2}$ and CL, should be determined after a single dose.
- Studies in Patients

A randomised, open label, dose escalation study should be used to evaluate the pharmacokinetics, efficacy and safety using the PK parameters defined above (i.e. AUC, C_{max}, T_{max}, $T_{1/2}$ and CL). The PK linearity and dose dependence should be determined from such studies.

7.2 Design of exploratory trials

A dose finding study should be used to determine the optimum dose of the pegylated or other bioengineered products to provide both neutrophil support and tolerability profile. The design should include at least 3 dose levels of the pegylated or other bioengineered product and should be compared with the standard dose of the non-pegylated or non-bioengineered product. PK linearity and dose dependence should be determined and serum levels should be compared with neutrophil recovery.

A randomised exploratory study should be used to compare an optimal single dose of the pegylated product with the standard dose of the non-pegylated or non-bioengineered product.

7.3 Confirmatory trials

Pegylated or other bioengineered products should be evaluated using, double blind, randomised, controlled trials in the patient population and compare weight based and/or fixed doses of pegylated or other bioengineered versus non-pegylated or non-bioengineered products. These should demonstrate non-inferiority with the comparator. Trial design should also take into account the incidence of febrile neutropenia with the cytostatic regimen and choice of comparator as outlined in section 4.2. An appropriate primary endpoint for these trials would include duration of severe neutropenia. However, secondary endpoints as outlined in section 4.6 need not be defined in the case of pegylated or other bioengineered products.