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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the need for a guideline on the clinical development of thrombopoetin receptor agonists for the treatment of chronic immune (idiopathic) thrombocytopenic purpura

Agreed by Efficacy Working Party	April 2010
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1. Introduction

Thrombopoetin agonists constitute an innovative approach for the management of patients with chronic immune (idiopathic) thrombocytopenic purpura (ITP). Over the recent past, a number of requests for Scientific Advice and Marketing Authorisation Applications have been assessed by the CHMP, thus giving sufficient basis issuing recommendations on the clinical development of this type of drugs in ITP patients.

2. Problem statement

A number of Marketing Authorisation Applications of medicinal products for the treatment of ITP have been evaluated in the recent past by the CHMP. These drugs, being of substantially different origin and structure, share the same mechanism of action, namely the stimulation of thrombopoetin receptors. This is a completely innovative approach in the treatment of ITP, which is deemed a relevant added tool for the management of these patients. A number of important aspects dealing with the evaluation of both the safety and efficacy of this new type of drugs have triggered the need for specific CHMP guidance relating to the clinical investigation of these products in ITP.

3. Discussion (on the problem statement)

Considering the new therapeutic alternatives to deal with the thrombocytopenia based on the stimulation of production of platelets by megakaryocytes in the marrow, different molecules have been developed (a recombinant polypeptide and a low molecular weight, synthetic, non-peptide molecule are available which act as agonists of thrombopoetin receptor). Up to now, no formal EU guidelines on the clinical development of products for ITP were available, and the regulatory experience was limited to classical immunoglobulin therapy for which, considering the wide clinical experience, only limited clinical data had been requested. Thrombopoetin receptor agonists constitute an innovative therapeutic approach which certainly is felt to fill an unmet medical need in chronic refractory ITP patient population. This approach has lead however to carefully reconsider which type of clinical data, in terms of both safety and efficacy, should be requested to allow a proper benefit/risk evaluation. Key relevant aspects would be the dose selection, the definition of the therapeutic goal, identification of relevant target populations and discussion particular safety aspects linked to the mechanism of action of these drugs and /or their molecular structure. Importantly, children deserve specific reflections, since disease features may be different with respect to adults.

4. Recommendation

The CHMP recommends drafting a guideline on the clinical investigation of specific thrombopoetin agonists for the treatment of ITP.

A full guideline is recommended, dealing with the whole clinical development. Specific aspects that will deserve particular attention would be:

- Validity of PD/PK models in the prediction of platelet count response and dose selection.
- Identification of relevant target populations (platelet count, previous therapies, prior splenectomy).
- Reasonable therapeutic targets in initial and main clinical studies.
- Design of main therapeutic studies:
  - Duration of clinical studies.
  - Choice of the comparator.
  - Acceptable primary efficacy endpoints.
- Considering the differential features of the disease in children, specific recommendations will be considered regarding:
  - Definition of the disease and selection criteria.
  - Definition of treatment response.
  - Specific considerations for dose selection.
- Safety evaluation:
  - Effect on bone marrow.
  - Carcinogenicity.
  - Thromboembolic risk.

- Comorbidities associated with increased risk of toxicity.
- Immunogenicity (if applicable).
- Minimum amount of clinical data pre-authorisation.
- Key aspects to be addressed in the post-authorisation setting.
- Paediatric safety.

5. Proposed timetable

The draft guideline is expected to be discussed during 12 months. It is anticipated that a draft CHMP document will be released for external consultation during 2Q 2011. The period for external comments on the draft text of the guideline will be 6 months.

6. Resource requirements for preparation

The Efficacy Working Party (EWP) of the CHMP will be involved in the preparation of the guideline. In principle, no expert meeting is deemed necessary at this stage, since key elements to be discussed in the guidelines have been discussed already with experts in the area. In addition, since ITP may affect children, a section on paediatric development will be needed. Therefore, experts from the PDCO will be involved.

7. Impact assessment (anticipated)

A harmonised regulatory approach will encourage a more consistent assessment of products by regulators, and set clear standards and expectations for industry. In addition, this will provide physicians and patients with reassurance about the safe and effective use of these products. The resource implications for preparation of the guideline are considered justified by the fact that application of guidance will make assessment easier and will result in less resources being needed during assessment.

8. Interested parties

European Haematology Association.