European Medicines Agency

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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE

(CHMP)

CONCEPT PAPER ON THE REVISION OF THE CHMP POINTS TO CONSIDER ON CLINICAL INVESTIGATION OF MEDICINAL PRODUCTS FOR THE MANAGEMENT OF CROHN'S DISEASE

AGREED BY THE EFFICACY WORKING PARTY	11 January 2006
ADOPTION BY CHMP FOR RELEASE FOR CONSULTATION	26 January 2006
END OF CONSULTATION (DEADLINE FOR COMMENTS)	2 May 2006

The proposed guideline will replace the current Points to consider on clinical investigation of medicinal products in the management of Crohn's disease (CPMP/EWP/2284/99)

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1. INTRODUCTION

Crohn's disease (CD) is a chronic relapsing, remitting inflammatory disease of the gastrointestinal tract, the cause of which remains unknown. The disease affects the gastrointestinal tract discontinuously from mouth to anus, but most commonly the disease is located both in ileum and colon (40%), followed by a disease in the small bowel only (30%), and in the colon only (25%). It occurs in a relatively young population and there is no marked sex difference. The incidence of CD in European countries is estimated to be 6-7/100.000. Patients with CD have a normal life expectancy, however, most individuals experience an impact of the disease on their daily lives.

The current Points to consider (PtC) came into operation in June 2001, hence the need for a revision warrant discussion in 2006. The aim of this PtC document was to provide preliminary guidance in a field where experience was limited, but since then knowledge and experience has evolved and thus there is a need for a more complete and updated guideline. New treatment alternatives are available now, both for treating active inflammation as well as fistulas in CD.

The current PtC reflects to a great extent the clinical practice and trials available at that time in active inflammatory CD. A large number of trials in CD, have been conducted since then, for many different biologicals. A revised guideline should reflect these trials as well as the experience gained with approved products.

Furthermore, the Strategic Research Agenda has identified inflammatory diseases, (including inflammatory bowel disease), as an area of unmet medical need and the requirement for update on regulatory guidelines has been mentioned specifically.

2. PROBLEM STATEMENT

Several sections of the PtC are in need of revisions including:

- 2.1 Disease stages to be studied
- 2.2 Management of Crohn's disease and potential claims
- 2.2.1 Treatment of active disease/Induction of remission
- 3.1 Long-term safety
- Addition of a section with regard to the sub-population children/adolescents is needed

3. DISCUSSION (ON THE PROBLEM STATEMENT)

The section numbers as occurring in the current guideline are cited below:

2.1 Disease stages to be studied

Experience with trials in CD has shown that study population has not always been clearly defined and has not reflected the proposed indication, e.g. as regards steroid dependent/refractory CD. Steroid dependent and steroid (and immunosuppressive) refractory state may have to be defined in better detail, e.g. with regard to duration of treatment before determining whether a patient is dependent or refractory to steroids, and new treatment alternatives available now may have to be taken into consideration.

2.2 Management of Crohn's disease and potential claims:

The current PtC does not address fistulising CD apart from stating that "fistula healing" should not be mentioned in the indication. Since then infliximab has been approved for the indication "fistulising CD". Guidance with regard to endpoints in clinical trials in fistulising CD is needed.

2.2.1. Treatment of active disease/Induction of remission:

The choice of comparator can be discussed. With biologicals on the market, use of placebo only control only in CD trials may no longer be acceptable for a second/third line indication.

The endpoints can be discussed. The current PtC defines response as a decrease in CDAI score of at least >70 and recommends this as a secondary efficacy endpoint together with the primary endpoint, induction of remission. The problem of study failure due to high placebo response using the 70 as cut-off is reflected in several recent trial designs, where a decrease in CDAI score of >100 has been used to obtain better separation from placebo. The clinical relevance of >70 has also been questioned and reduction in CDAI was not recommended as primary endpoint by a consensus group (Gastroenterology 2002). Thus, a discussion is needed on whether 1 or 2 primary endpoints could be recommended as well as the cut-off for decrease in CDAI score. The value of the relative change in CDAI in addition to absolute reduction should also be discussed.

As regards maintenance treatment, there may be a need to re-classify the aims of treatment into preventive treatment after induction of remission (surgically or medically induced) versus long-term maintenance treatment of chronic, active inflammation.

3.1 Long-term safety:

With mainly new immunomodulating biotechnological products in the pipeline for the treatment of CD, pharmacovigilance measures (post-marketing) specifically related to this type of products could be addressed in more detail. Especially with regard to opportunistic infections and malignancy (lymphoma, other malignancies) there is a need for an update and Risk Management Plan (RMP) post-marketing should preferably be discussed in a guideline on CD.

Addition of a section on sub-populations:

As CD occurs in a relatively young population, often diagnosed during childhood and adolescence, separate studies in these patients may be needed.

4. RECOMMENDATION

The Working Party recommends revising the guideline on clinical investigation of medicinal products in the treatment of CD. Revision is recommended with respect to several sections of the current PtC; mainly with regard to the definition of disease stages/study population; fistulising CD; choice of comparator in CD trials; primary endpoints, aims of long-term treatment; and long-term safety.

5. PROPOSED TIMETABLE

It is expected that a draft revision of the guideline be released for consultation in 3/4Q2006.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The preparation of this Guideline will only involve the EWP.

7. IMPACT ASSESSMENT (ANTICIPATED)

The revised guideline will provide updated guidance to both industry and Regulatory Authorities regarding the clinical development and assessment of medicinal products for Crohn`s Disease. This is expected to contribute to a consistent approach in development and assessment of these products.

8. INTERESTED PARTIES

- United European Gastroenterology Federation (UEGF)
- International organisation of inflammatory bowel disease (IOIBD)
- European Crohn’s and colitis organisation (ECCO)
- Groupe d’Etude Therapeutique des Affectiones Inflammatoires Digestives
- European Society for Paediatric Gastroenterology Hepatology and Nutrition (ESPGHAN)
- Patient organisations

9. REFERENCES TO LITERATURE, GUIDELINES ETC

Points to Consider on clinical investigation of medicinal products for the management of Crohn's disease (CPMP/EWP/2284/99).

A review of activity indices and efficacy endpoints for clinical trials of medical therapy in adults with Crohn's disease (Gastroenterology 2002; 122: 512-513)