EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Concept paper on the revision of the guideline on the development of medicinal products for the treatment of ulcerative colitis (CHMP/EWP/18463/2006)

Agreed by Gastroenterology Drafting Group	September 2012
Adopted by CHMP for release for consultation	18 October 2012
Start of public consultation	14 November 2012
End of consultation (deadline for comments)	15 February 2013

The proposed guideline will replace the guideline on the development of medicinal products for the treatment of ulcerative colitis (CHMP/EWP/18463/2006).

Comments should be provided using this template. The completed comments form should be sent to gastroenterologydg@ema.europa.eu

Keywords	Ulcerative colitis, PUCAI, Mayo, mucosal healing, patient reported outcome (PRO), Health related Quality of Life (HrQoL)

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1. Introduction

Ulcerative colitis is an inflammatory gastrointestinal disorder in which abdominal pain, defecation urgency, diarrhoea, blood in stools are hallmarks of the disease. Approximately 20% of patients with UC are detected before the age of 20 years. The incidence of UC is gradually increasing from early childhood into a peak in early adulthood. While UC disease is quite similar in adult and paediatric patients in terms of overall disease pathology and progression, paediatric-onset UC is typically distinguished from adult-onset UC by a generally greater prevalence of moderate to severe disease, by a higher fraction of patients having extensive disease, by a higher rate of severe exacerbations and higher rates of steroid unresponsiveness. A multitude of genetic susceptibility loci have been identified to be implicated in the aetiology of CD and UC in children and adults, and probably the more severe gene defects are predisposing for manifestation at a younger age.

At this point in time the therapeutic consequences of the differences between children and adults are unclear, but might warrant consideration in paediatric drug development.

2. Problem statement

The "Guideline on the development of medicinal products for the treatment of Ulcerative Colitis (CHMP/EWP/18463/2006) currently includes only more general comments for the conduct of clinical studies in children. Moreover, in 2010, an expert meeting of European experts in paediatric gastroenterology and rheumatology published a statement, which is partly more decisive as regards the needs of and the mode of conduct of paediatric studies in ulcerative colitis than the guideline document, leading to obvious discrepancies, with a subsequent need of reconciliation.

The aim of the planned revision is therefore restricted to the chapter 4.4. "Special populations" and its paragraph on studies in children and adolescents. Besides the a.m. reconsideration of the obvious discrepancies of two public statements, it should also deal with a necessary update according to scientific progress and ongoing discussions in the scientific and regulatory community, and with the evaluation of the experiences with the data that have been generated during the last 5 years with a few products.

Moreover, the FDA and EMA have started with other international authorities to harmonise guidance for conduct of studies in children with IBD. This initiative followed the observation of some disharmony in regulatory requirements for studies in the field with consequently the apparent difficulties for global development programmes. An evaluation on opportunities to harmonise requirements appears to be warranted.

3. Discussion (on the problem statement)

Extrapolation:

Currently, the Guideline only generally states that "studies in children are encouraged". The main problem behind, namely the question whether and to what extent extrapolation from adults is possible, remains largely unexplored. Contrary to this, the above mentioned Expert Statement clearly states that "extrapolation from adult studies is limited" and that in most cases separate studies in children are needed. The intention is therefore to evaluate whether more clear statements should be included into the guideline, as to what extent extrapolation of adult data is possible, and whether criteria for extrapolation can be defined. Emerging scientific data on similarities and discrepancies between adult and paediatric disease have to be evaluated.

The need of pharmacokinetics in paediatric trials:

Evaluation of previous dossiers demonstrated a need for re-assessment of PK/PD models due to unexplained discrepancies in outcome between children and adults. The number of patients included was insufficient to support any firm conclusions regarding doses and dosing intervals in children, although available data did suggest a need for higher doses and shorter dosing interval.. A separate paragraph on the need to explore PK and PK-PD relationship according to age and different pathophysiology might be necessary.

Design of studies in children:

- Choice of endpoints:

The most obvious discrepancy between the before-mentioned Expert Statement and the current guideline refers to the recommendation of the guideline to use paediatric activity indices as primary endpoint in clinical trials, whereas the Expert Statement recommends the use of endoscopy, referring to the importance of mucosal healing as a predictor for the further overall course of the disease. A thorough evaluation of the available data on validity and feasibility of these divergent proposals has therefore to be made. The need for the inclusion of additional secondary endpoints, such as PROs and Quality of Life scales, or biomarkers, also has to be evaluated.

- Choice of comparator:

Currently, the UC guideline does not include a separate statement on the need or preference for placebo- or actively controlled studies in children. Contrary to this, the a.m. Expert Statement clearly prefers the conduct of actively controlled studies whenever feasible. It has therefore to be evaluated whether this question needs to be dealt with in a different way in children, as compared to adults.

4. Recommendation

The Gastroenterology Drafting group recommends the revision of the Guideline on the development of medicinal products for the treatment of Ulcerative Colitis as regards the chapter on the paediatric population:

Points to be addressed and evaluated concern the following fields:

1.) The need for more clear guidance as regards the possibility for extrapolation from adults, or the need to generate separate data in children.

2.) The need for inclusion of recommendations regarding exploration of adult PK/PD relationship in paediatric drug development, including the need for adaptation of the PK/PD model concerning dose finding both in terms of induction and maintenance therapy.

3.) The potential revision for the recommendations for the primary and secondary endpoints to be used in paediatric trials and as regards the design of paediatric trials with regards to the comparator treatment.

5. Proposed timetable

It is anticipated that a new draft CHMP Guideline may be available 9 months after adoption of the concept paper. The draft CHMP guideline will then be released for 6 months for external consultation and following receipt of comments it will be finalised in approximately 3 months. Finalisation will therefore be awaited for the first half of 2014.

6. Resource requirements for preparation

The preparation of the revision of the guideline will primarily involve the Gastroenterology Drafting Group.

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 the treatment Ulcerative Colitis in children. This is expected to contribute to higher consistency in the development of new products in the field.

8. Interested parties

European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN)

European Crohn and Colitis Organisation (ECCO)

United European Gastroenterology Federation (UEGF)

FDA

PRINTO

9. References to literature, guidelines, etc.

EMA paediatric gastroenterology and rheumatology expert meeting London, 28-06 2010 EMA/416878/2010

Guideline on the development of new medicinal products for the treatment of ulcerative colitis (CHMP/EWP/18463/2008)