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3 Committee for Medicinal Products for Human Use (CHMP)

4 Concept paper on the revision of the CHMP points to 5 consider on the evaluation of medicinal products for the 6 treatment of irritable bowel syndrome 7 (CPMP/EWP/785/97)

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End of consultation (deadline for comments)	31 August 2012

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9 The proposed guideline will replace "Points to consider on the evaluation of medicinal Products for the
10 treatment of irritable bowel syndrome CPMP/EWP/ 785/97".

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

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Keywords	*Irritable Bowel Syndrome, Rome criteria, patient reported outcome (PRO), Health related Quality of Life (HrQoL)*

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1. Introduction

Irritable Bowel Syndrome (IBS) is a functional gastrointestinal disorder in which abdominal discomfort or pain is associated with changes in bowel habits, stool consistency and other features of disordered defecation. The pathophysiological basis of the symptoms is still incompletely understood, but it features disturbances of motor and sensory function, subclinical inflammatory changes, and associated psychosocial disorders. The description and characterisation of IBS has been formalised in the Rome criteria (currently published in its third version), which are widely accepted as the state-of-the-art criteria for research purposes.

IBS is considered to be one of the most frequent clinical problems in gastroenterology with an estimated prevalence in the Western world of up to 20%. Contrary to the frequency of the syndrome, there is still a lack of adequately studied and more so of licensed medications in Europe, and a certain unmet medical need for IBS has still to be realised. Moreover, there is a wide history of unsuccessful drug development programmes in the field, and the number of Marketing Authorisation Applications for the indication has been very low. The current Points to consider (PtC) came into operation in September 2003.

2. Problem statement

The time-span evolved since the IBS PtC came into operation, with almost 10 years could warrant discussion and re-examination for this reason alone. Although the number of successful development programmes – resulting in an evaluation of the data by regulatory authorities –have been rare, a considerable amount of data have been generated during the last 10 years with a variety of products. The evaluation of the experience with the conduct of theses trials during the last 10 years and their relation to the fulfilment of the requirements of the PtC as of 2003 may generate the opportunity for improvement and completion of the PtC.

The update from a PtC document to a “guideline” according to the “Procedure for European Union Guidelines and related documents within the pharmaceutical legislative framework (EMEA/P/24143/2004/Rev 1 corr.”), will go along with the revisions of the content.

Moreover, the constant update of the scientific basis for the definition of IBS (expressed in the update of the Rome criteria and other guidance documents in the clinical field) do also potentially lead to a broader and deepened understanding of the requirements for the conduct of clinical trials for drug development.

In functional disease, such as IBS, patient reported outcomes (PROs) are the inevitable primary outcome measures and Quality of Life (QoL) evaluations are among the most important secondary outcome measures recommended by the current PtC. An evaluation of recent developments in this rapidly evolving field appears to be necessary.

In 2010, the FDA has published a “Draft Guidance” (“Guidance for Industry Irritable Bowel Syndrome – Clinical Evaluation of Products for Treatment” March 2010) which led to an obvious disharmonisation of the regulatory requirements for studies in the field with the apparent difficulties for global development programmes. An evaluation on opportunities to harmonise requirements appears to be warranted.

3. Discussion (on the problem statement)

1. The current PtC clearly recommend the inclusion of patients defined according to the Rome II criteria. In light of the fact that the Rome criteria have been updated to Rome III already in 2006, and a subsequent version may be published within a relatively short period, the recommendation for inclusion of patients should be updated. A more open wording may generally be needed in order to allow applicants to use the most up to date version for the definition of the syndrome. Moreover, although the Rome criteria have established IBS as a "positive" diagnosis from the symptoms alone, the PtC currently recommend the exclusion of certain other "organic" disease before inclusion of patients into clinical trials. Other clinical guidelines have also discussed the necessary amount of diagnostic workup (e.g. "red flags", imaging) divergently and some of them, even more extensively. The adequacy of the current recommendations should therefore be reconsidered.

2. The current PtC divide potential development programmes into the two categories "short-term treatment" with repeated treatment cycles and "long-term treatment" with continuous treatment. However, it currently only gives vague recommendations as regards the consequent characterisation of patient populations to be studied for these different types of products or development programmes. It is stated that only about 5% of the patient population have constant severe symptoms, and most patients would have mild to moderate symptoms with waxing and waning characteristic. More clear statements as to which patient populations are recommended to be included in which type of development programme may be needed. As regards the trials in "repeated short-term treatment", the current recommendations for the documentation of short-term treatment cycles recommend the documentation of at least one re-treatment cycle, and give two different ways to conduct such trials. Although the development programmes with repeated treatment cycles have been rare (e.g. tegaserod), both possibilities have inherent disadvantages, which may need to generally revise the recommendations in the direction of a more "naturalistic" trial design. Also, the current PtC do request the documentation of withdrawal effects, but do not give recommendations how such a documentation should be done. An inclusion of such recommendations may be warranted.

3. The current version of the PtC recommend the two co-primary endpoints "global assessment of symptoms" and "assessment of symptoms of abdominal discomfort/pain". Contrary to this, the Draft FDA guidance recommends the evaluation of abdominal pain intensity and stool frequency or stool consistency (depending on subtype of IBS). Due to this discrepancy, an evaluation and comparison of the validity of global assessments (and the way in which this was done) and of the methods to measure and assess certain symptoms appears to be warranted. The advantages and disadvantages of a "subtype-focused" primary endpoint should be discussed and it should be evaluated whether a more accurate characterisation of treatment effects with the "subtype-focused" evaluation could be possible. The potential danger of the exclusion of developments of substances for the treatment of IBS in a global sense (including all subtypes) with a subtype focused endpoint should also be taken into consideration. The inherent problems of having different statistical analyses within global development programmes may also be addressed from a statistical point of view. Also, the value of "abdominal discomfort" and the potential ways to evaluate this term may need further clarification. An evaluation whether more clear recommendations as regards the use of certain scales or newly developed PROs can be made is also desirable. The current statement regarding the choice of secondary endpoints, especially with regard to the statement that "Health related Quality of Life must (…) be considered as the most important secondary endpoint" may be not fully appropriate for the documentation of repeated short-term treatment cycles, when e.g. only up to 4-weeks

treatment durations are documented. The statement may also be regarded to stand in contrast to the current guidance document “Reflection paper on the regulatory guidance for the use of health-related Quality of Life (HRQL) measures in the evaluation of medicinal product EMEA/CHMP/EWP/139391/2004)”.

4. Currently, the PtC do not address needs for the documentation of safety and efficacy of a new compound in special patient populations. There is an obvious need to include chapters on the paediatric age group and the elderly patient populations into the guidance. Also – because many trials conducted failed to include an appropriate number of male patients – gender differences and the need to adequately document safety and efficacy in both, male and female patients should be addressed.

5. Global development programmes for new compounds in the field have mostly conducted their trials in North America. Although it is of course desirable that new compounds would be tested in the region/countries where they will potentially enter the market, a general evaluation and recommendations as regards the potential to accept foreign clinical data in the condition IBS may be needed. However, even if the transfer of foreign data may be acceptable, the guideline should clearly not discourage the development and testing of new compounds in the EU, a region which is characterised by high cultural and language heterogeneity and which may therefore appear to be more complex for development programmes, especially when it comes to cross-cultural and translation validation of PROs and Quality of Life measures, which are the inevitable instruments for evaluation in the setting.

4. Recommendation

The Gastroenterology Drafting group recommends the revision of the Points to Consider on the evaluation of medicinal products for the treatment of Irritable Bowel Syndrome.

Points to be addressed and evaluated concern the following fields:

- The revision of the recommended inclusion/exclusion criteria according to the scientific literature and academic guidance documents (e.g. Rome III).
- The need and possibilities for harmonisation of regulatory requirements in the field as regards the primary endpoints along with the examination and potential revision of the recommendations for the primary and secondary endpoints, and for the principal design of the trials for the repeated treatment cycle documentation.
- The amendment of the guideline with regard to needs for special patient populations (different gender, paediatric and elderly population).
- The potential amendment of the guideline with regard to acceptance of foreign clinical data

5. Proposed timetable

It is expected that this Concept Paper will be released for consultation within the 2nd quarter of 2012. Allowing for a 3-4 months public consultation time, a draft revision of the guideline should be made available by 4th quarter of 2012.

Revision of the guideline may come into force by the end of 2013.

6. Resource requirements for preparation

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

Consultation of the Statistics Working Party may become necessary when the revision of the guideline is drafted.

7. Impact assessment (anticipated)

The revised PtC/guideline will provide updated guidance to both industry and Regulatory Authorities regarding the clinical development and assessment of medicinal products for the treatment of IBS. This is expected to contribute to higher consistency in the development of new products in the field.

8. Interested parties

United European Gastroenterology Federation (UEGF)

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

European Society of Neurogastroenterology and Motility

Rome-Foundation

International Foundation for Functional Gastrointestinal Disorders

European Crohn's and Colitis Organisation

9. References to literature, guidelines, etc.

Points to Consider on the evaluation of medicinal products for the treatment of Irritable Bowel Syndrome CPMP/EWP/785/97

Guidance for Industry Irritable Bowel Syndrome – Clinical Evaluation of Products for Treatment. Draft Guidance. U.S. Department of Health and Human Services. Food and Drug Administration. Center for Drug Evaluation and Research (CDER). March 2010.

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