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Concept paper on the need of a guideline for clinical investigation of medicinal products for the treatment of chronic constipation

Agreed by Gastroenterology Drafting Group	September 2012
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Comments should be provided using this template. The completed comments form should be sent to gastroenterologydg@ema.europa.eu

Keywords	Constipation, chronic constipation, functional gastrointestinal disease, laxatives, life-style modification, opioid induced constipation, bowel cleansing, study design, active comparator, special patient populations, withdrawal and rebound

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1. Introduction

Historically, constipation has been defined based on a reduced frequency of defecation. It is considered to be one of the most frequent gastrointestinal disorders, the prevalence of which is estimated to be around 11-18% in the general community, both in adults and children, with a huge variability, depending on the definition of the disease, gender, geographical area, race, and concomitant drug intake. Because of its high prevalence and chronicity, the disease is responsible for considerable health care utilisation and cost.

More recently, constipation is more specifically defined on the basis not only of infrequent stools, but additional symptoms, such as reduced stool consistency, straining at stool, and sense of incomplete bowel evacuation. The Rome III criteria for functional gastrointestinal disorders define functional constipation (in adults) as the presence of at least two of the following: Straining, lumpy or hard stools, sensation of incomplete evacuation, sensation of anorectal obstruction/blockage, manual manoeuvres to facilitate defecations (to be present of at least 25% of defecations), and fewer than three defecations per week. These criteria have to be fulfilled for the last 3 months with symptom onset at least 6 months prior to diagnosis. Additionally, the diagnostic criteria include that loose stools may only rarely be present without the use of laxatives, and that there are insufficient criteria for irritable bowel syndrome.

Functional constipation is usually used synonymously to chronic constipation, although the latter also includes "organic" disease, such as endocrine, neuorgenic and drug-induced constipation. Chronic constipation can be divided based on the underlying pathyphysiology (e.g. slow-transit and normal transit constipation), however, with unclear relevance as regards treatment. In contrast to the unclear relevance of the latter distinction, a clear need to distinguish constipation from evacuation disorders has been identified.

2. Problem statement

The development of medicinal products influencing gut transit and defecation is one of the oldest principles of pharmacological treatment. Numerous products have been introduced into the market even at times before drug regulation laws came into force within Europe. Nevertheless, the requirements for drug approval in this setting have never been laid down before, and the analysis of the data in support of many commonly used substances in the field have revealed that there is only insufficient evidence available to adequately support efficacy and safety of many of these substances.

Recent developments leading to approval of new medicines in this field have been relatively rare and have partly also suffered from clear regulatory guidance not being available. The uncertainties identified relate to the appropriateness of the definition of the patient populations suffering from chronic, functional constipation, to the adequate choice of endpoints, to the necessary duration of documentation of efficacy and safety, and to the necessary use of active comparators or placebo.

Traditionally, the problem of chronic constipation has been viewed as relating to lifestyle problems, and increased fluid intake and exercise were regarded to be appropriate "first-line" treatments to lead to improvement in symptoms. This has recently been questioned, and it might be necessary to define whether and to what extent life-style changes should be considered within development programmes for new medicinal products. Also traditionally, laxatives were suspected to lead to abuse, and – if given long-term – to a subsequent deterioration of the symptoms, which has recently been challenged. Whether and how this (and the general problems of withdrawal and rebound effects) will have to be addressed within clinical development programmes therefore needs regulatory definition.

Recently, the development of products aimed at treating a special subgroup of constipation –the constipation induced by opioids – has also generated the need to provide guidance in order to define such a population and the specific features of such a development programme. There also is an obvious need to define the regulatory details for appropriate therapeutic claims once the general constipation population and/or the opioid induced population have been studied with new medicinal products.

The requirement to address the needs of special populations in this indication is obvious. In clinical trials in chronic constipation, the overwhelming majority of patients are usually of female gender, and although there is a clear female preponderance in the disease, the male population included runs the risk of being too small to derive clear conclusions thereof. Moreover, there is a clear need for these medications in children, constipation being one of the most prevalent disease conditions in childhood. Also, the elderly – for which an increased incidence of constipation has been postulated – deserve to be specifically addressed within a regulatory framework for the indication due to their increased susceptibility to potential adverse effects on water, electrolyte, and acid base balance and their consequences.

Traditionally, laxatives have also been used as purgatives for the cleaning of the bowel before endoscopic examination, and surgery. Whether the latter can be the basis for a drug approval appears to be a matter of debate and needs regulatory guidance. Colon cleansing medications, however, have previously been licensed on a large variety of data without any validation of outcome measures. Therefore, it is conceived that the proposed guideline should also include an elaborate chapter on the development of medicinal products for bowel cleansing.

3. Discussion (on the problem statement)

The following items (among others) deserve clear recommendations and definitions in order to facilitate drug development in the field and have been identified to be dealt with in the future guideline:

- The patient population to be included in clinical trials under consideration of most recent evidence-based and consensus guidelines
- The necessary duration of clinical studies in the field as regards the adequate demonstration of efficacy and of safety
- Recommendations for the representation of European patients (and potentially of different European countries) within global clinical programmes.
- Adequate efficacy endpoints relating to the fact that – as with all functional disease – patient reported outcome measures (PROs) will form the basis of evaluation under consideration of the fact that there is still absence of a general guideline on the development of PROs in Europe.
- Adequate safety endpoints in medications potentially influencing water, electrolyte, and acid-base balance, including in special populations that are potentially more vulnerable to these effects (children and the elderly).
- Adequate comparators (placebo or active) to be used in clinical trials under consideration of the large number of products being available on the market.
- A statement whether life-style modification as factor influencing the condition should play a role in clinical trials and the need to document withdrawal and rebound effects.

- Adequate consideration of relevant special patient groups, such as males, the elderly, and children (including the need for separate trials).
- Special features of developments addressing opioid-induced constipation only (e.g. including documentation of exclusion of opioid withdrawal in the CNS).
- Relating to the distinction between "general" constipation and opioid induced constipation, regulatory guidance will be needed as to which development would support general or special claims (e.g. for the opioid-induced constipation subgroup) for new medicinal products.
- The appropriate development of laxatives for bowel cleansing, including endpoints and necessary safety documentation, and possible treatment claims.

4. Recommendation

It is proposed to prepare a CHMP Guideline addressing the clinical investigation of medicinal products for the treatment of chronic constipation in order to achieve a European common position on the above-mentioned issues.

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 this Guideline will primarily involve the Gastroenterology Drafting Group, including one Rapporteur and one Peer Reviewer. The chapter on opioid-induced constipation will potentially require the input of the CNS-WP.

7. Impact assessment (anticipated)

The elaboration of the Guideline on clinical investigation of medicinal products for the treatment of chronic constipation will be helpful to achieve consensus in the evaluation of such products by regulatory authorities. Furthermore, it is expected that such guidance document would eliminate uncertainties and improve quality and comparability of submitted development programmes within the pharmaceutical industry.

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

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