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COMMITTEE FOR MEDICINAL PRODUCTS FOR HUMAN USE

(CHMP)

CONCEPT PAPER ON THE NEED FOR A GUIDELINE ON THE EVALUATION OF DRUGS FOR THE TREATMENT OF GASTROESOPHAGEAL REFLUX DISEASE (GERD)

AGREED BY EFFICACY WORKING PARTY	January 2009
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KEYWORDS	*Gastroesophageal Reflux Disease (GERD), reflux oesophagitis, non-erosive reflux disease (NERD), CHMP, EMEA, guideline*

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1. INTRODUCTION

Gastroesophageal reflux disease (GERD) has been identified as the most common gastrointestinal diagnosis during visits in outpatient clinics. Estimations suggest that up to 20% of adults are affected (weekly complaints over on an observation period of 1 year).[1]

According to the current most cited (Montreal) consensus definition of GERD[2], the disease is defined as a condition which develops when the reflux of stomach contents causes troublesome symptoms and/or complications. Typical symptoms (such as heartburn and acid regurgitation) and their frequency in order to be "troublesome" have also been defined.

GERD has traditionally been divided into the erosive forms ("reflux oesophagitis") and the non-erosive disease form ("NERD"). The advent of highly efficacious medication, such as PPIs, however, has partly shifted the disease classification into "typical" and "atypical" forms, or to PPI responsive, partly-responsive and non-responsive (refractory) disease states.

The pathophysiological factors causing GERD can be split into those inducing greater exposure of the oesophagus to stomach contents, and those that provide increased mucosal damage or increased perception of reflux. Key elements representing these factors have been identified to be transient lower oesophageal sphincter relaxations, and oesophageal hypersensitivity as a result of visceral neural pathways dysfunction.

Recent years have also seen a clearer standardisation and further development of diagnostic tools for the disease. The (visual) classification of reflux oesophagitis has been widely standardised with the introduction of the so-called Los Angeles classification. Moreover, other diagnostic modalities have enabled more accurate diagnosis and further insight into the pathophysiology of the disease, such as 24-hour pH monitoring, impedance measurements, Bilitec monitoring, manometry and newer imaging tools (e.g. magnification endoscopy, chromoendoscopy, narrow band imaging, confocal laser endomicroscopy etc.).

Moreover, paediatric gastroesophageal reflux disease has also come into focus, as the evaluation of PPIs for the young and very young population has made progress. In older children and adolescents the prevalence of heartburn and regurgitation symptoms approach adult values. The definition of GERD in children is neither consistent nor homogeneous. Whereas the development of the upper gastrointestinal tract as such is considered as a process of continuous maturation, and GERD could therefore be considered as the same pathophysiological process in infants, children, and adults[3], there are on the other hand, important differences made between infancy GERD and GERD in children and adults.

2. PROBLEM STATEMENT

- No available regulatory guidance.
- New definition and an academic guidance already existing (consensus sponsored by industry) may not reflect the current regulatory position.
- Possible future MAAs.
- Paediatric need.
- Several requests for Scientific Advice have identified specific problems in drug development for GERD. The advices have concerned different products such as:
  - Proton pump inhibitors for children;
  - Proton pump inhibitors;

[1] Dent J et al: Epidemiology of gastro-oesophageal reflux disease: A systematic review. Gut 2005; 54: 710-717.

[2] Vakil N et al: The Montreal Definition and Classification of Gastroesophageal Reflux Disease: A global evidence-based consensus. The American Journal of Gastroenterology 2006; 101: 1900-1920.

[3] Vandenplas Y et al: A critical appraisal of current management practices for infant regurgitation – recommendations of a working party. European Journal of Pediatrics. 1997; 156: 343-357. Vandenplas Y and B Hegar: Diagnosis and treatment of gastro-oesophageal reflux disease in infants and children. Journal of Gastroenterology and Hepatology 2000. 15: 593-603.

- Fixed dose combination of a proton pump inhibitor and a H2-antagonist;
- GABA-B agonists;
- Potassium – competitive acid blocker (P-CAB).

3. DISCUSSION (ON THE PROBLEM STATEMENT)

No regulatory guidance for the evaluation of drugs for the treatment of GERD exists within the EU.

Several academic consensus conferences have been held (under the sponsorship of pharmaceutical companies) in order to determine definitions of the disease, and most recently, on the clinical trial design in adult reflux disease[4].

Traditionally, antisecretory agents (antacids, H2-blockers and PPIs) have been evaluated and licensed for GERD in the past.

In case of H2-blockers and PPIs, the evaluation went from the more severe disease states (reflux oesophagitis) to the less severe "symptomatic only" forms (NERD). Especially for NERD, standardized evaluations of efficacy were not available and a great variety of different endpoints was used (and have gained different acceptance by different regulatory agencies).

The proton pump inhibitors have become standard in the treatment of GERD, the only problem being their relatively slow onset of action. Some patients, however, are refractory to these highly efficacious drugs and especially night-time symptoms can be troublesome despite use of a PPI.

Currently several newer acid suppressive agents appear to be under development (modifications of existing PPIs, new PPIs, K^+-competitive acid blockers). There is also a focus on the evaluation of existing substances in atypical syndromes of GERD and, even more recently, on the development of new substances in PPI resistant or refractory populations, with a completely different mechanism of action, namely acting on the lower oesophageal sphincter [5].

Several Scientific Advices have already been provided for this type of substances.

Problems that have arisen from these procedures include the following:

Children: Age group definition; inclusion of newborns and/or premature children; inclusion of children with neurodevelopmental delays and their differences to "normal" juvenile GERD.

Adults: The need for endoscopic evaluation of patients despite the treatment having a clear focus on symptomatic treatment only; the need for the development of appropriate endpoints (PRO) and their validation; and the assessment of Quality of Life in this patient population.

4. RECOMMENDATION

The Working Party recommends the drafting of a new guideline on the evaluation of drugs for the treatment of gastroesophageal reflux disease. The guideline should include (among others) definitions of several disease states, the requirements for evaluation in early drug development (pharmacodynamics), recommendations for the conduct of the pivotal trials and their appropriate endpoints, and recommendations for the evaluation of such compounds in the pediatric population.

5. PROPOSED TIMETABLE

It is proposed that a first draft version of this new guideline can be drafted for 2nd / 3rd Quarter 2009, with subsequent release for consultation.

6. RESOURCE REQUIREMENTS FOR PREPARATION

The preparation of the guideline would only involve the EWP.

[4] Dent J et al: Clinical trial design in adult reflux disease: a methodological workshop. Alimentary Pharmacology and Therapeutics 2008; 28: 107-126.

[5] Farré R and D Sifrim: Regulation of basal tone, relaxation and contraction of the lower oesophageal sphincter. Relevance to drug discovery for oesophageal disorders. British Journal of Pharmacology 2008; 153: 858-869.

7. IMPACT ASSESSMENT (ANTICIPATED)

Introducing a new guideline in a field where no such guideline exists in EU will be of benefit for industry as the design of development programmes will be supported. Moreover, it may lead to a consistent approach between Member States in the assessment of applications related to this therapeutic indication.

8. INTERESTED PARTIES

United European Gastroenterology Federation (UEGF).
Association of National European and Mediterranean Societies of Gastroenterology (ASNEMGE).
European Society of Esophagology (ESE).
European Society for Paediatric Gastroenterology, Hepatology and Nutrition (ESPGHAN).

9. REFERENCES

Vakil N *et al:* The Montreal Definition and Classification of Gastroesophageal Reflux Disease: A global evidence-based consensus. The American Journal of Gastroenterology 2006; 101: 1900-1920.

Dent J *et al*: Clinical trial design in adult reflux disease: a methodological workshop. Alimentary Pharmacology and Therapeutics 2008; 28: 107-126.