The European Agency for the Evaluation of Medicinal Products
Evaluation of Medicines for Human Use

London, 23 September1999
CPMP/EWP/863/98

COMMITTEE FOR PROPRIETARY MEDICINAL PRODUCTS (CPMP)

POINTS TO CONSIDER ON WORDING OF HELICOBACTER PYLORI ERADICATION THERAPY IN SELECTED SPC SECTIONS

DISCUSSION IN THE EFFICACY WORKING PARTY (EWP)	February 1998 - January 1999
TRANSMISSION TO THE CPMP	February 1999
RELEASE FOR CONSULTATION	February 1999
DEADLINE FOR COMMENTS	May 1999
RE-SUBMISSION TO THE EWP	September 1999
TRANSMISSION TO THE CPMP	September 1999
ADOPTION BY THE CPMP	September 1999

Points to Consider have been developed to provide advice on selected areas relevant to the development of medicinal products in specific therapeutic fields.

This document will be revised in accordance with the scientific advances made in this area.

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WORDING OF HELICOBACTER PYLORI ERADICATION THERAPY IN SELECTED SPC SECTIONS

INTRODUCTION

Recently, it has been established that Helicobacter *(H.) pylori* infection is the key factor in the pathogenesis of non-NSAID induced gastro-duodenal ulcers. The most optimal eradication of *H. pylori* with combination antibiotic therapy has become the mainstay in the management of *H. pylori* associated peptic ulcer disease. New antibiotic regimens in dual, triple, and quadruple combinations with (usually single) ulcer healing agents such as H2-receptor antagonists, bismuth salt, or proton pump inhibitors (PPI) are continuously being evaluated to achieve optimal high rates of *H. pylori* eradication so as to give lasting cure together with quick relief of symptoms and healing of such ulcers.

The following points to consider will be applicable for medicinal products intended for use in *H. pylori* eradication therapy.

GENERAL REMARKS

It goes without saying that all claims should be scientifically justified with the appropriate state of the art clinical trials and argumentation.

The rationale for the presence and contribution of each component to the efficacy of a new combination regimen for *H. pylori* eradication should be substantiated with appropriate data. Relevant advice may be found in the CPMP guideline for fixed combination products. This implies that the clinical development programme, where appropriate, will have to include clinical studies with factorial design. In case this is not performed e.g. depending on the extent of knowledge of efficacy of some components of the regimen, this should be justified.

The ***confirmatory*** trials should be double-blind controlled trials. The positive control should be the best available approved eradication regimen, with eradication rate > 80% (approaching 90%) and non-inferiority of the new regimen should be demonstrated. The lower limit of the 95% CI for the difference between eradication rates should be greater than the non-inferiority margin which should be clinically justified and specified in the protocol. It is considered necessary to demonstrate consistency of effect in several trials. Adherence to the CPMP interaction and ICH statistical guidelines must be observed.

When addition of a new eradication regimen is sought besides earlier approved eradication regimen(s) critical assessment of the latter regimen(s) in the light of new data and state of the art should be given. Questioned regimens should be discouraged. This implies that the benefit-risk ratio of some earlier approved but now questioned regimens need to be reviewed when safer or more efficacious regimens become available.

Clinical trials should take into account the epidemiology of resistance of *H. pylori* to antibacterials. The rate of primary resistance and development of secondary resistance and clinical implications should be adequately documented and analysed. In other words, the trials should reflect the appropriateness of claimed eradication therapy regimens for use at different sites in the EU where the product is to be marketed. Local clinical testing will be performed whenever indicated.

The clinical studies should also aim at finding the shortest duration of antibiotic treatment to achieve required (adequate) eradication rate in order to decrease the risk of undesirable effects associated with the use of antibiotics, hence, resulting in optimal benefit-risk ratio.

For fixed galenical formulations of combination products developed for the *H. pylori* eradication therapy, the CPMP guideline for fixed combination products will be applicable. The requirements for specific information on individual components of the combination and the claimed dose regimen should be addressed appropriately, depending on the extent of knowledge of efficacy and safety of some components of the regimen. Although, this category of products is not within the scope of this Points to consider document the points and criteria mentioned here for the *SPC* will be applicable also for such products. The information on antibacterial activity (in the Pharmacodynamic section) should focus on susceptibility of *H. pylori* to the involved agents.

In principle, the appropriate dose to be used in an indication for combination therapy should be mentioned in the individual product information of each component of the combination therapy.

For *H. pylori* associated conditions such as gastritis with serious abnormalities, post early gastric cancer resection, mucosa-associated lymphoid tissue (MALT) lymphoma (= MALToma)[1] adequate evidence of efficacy and safety in such clinical conditions and for each proposed combination regimen must be evaluated in appropriate state of the art and regulatory settings. These are not within the scope of this document. However, similar SPC formatting as for management of *H. pylori* associated ulcer disease may be used. In that case instead of ulcer disease the specific clinical condition is mentioned and the appropriate (and adequately evaluated) combination dosing regimens and corresponding success rates are mentioned.

For single-entity medicinal products the format for each category of the involved medicinal products is as follows.

1. Ulcer healing Agents *(UHA)*

Therapeutic indications (section 4.1)

"In combination with appropriate antibacterial therapeutic regimens for the eradication of *H. pylori* and prevention of relapse of peptic ulcers in patients with *H. pylori* associated ulcers. See section 4.2"

The documentation should contain sufficiently representative clinical trials controlled with the best available approved eradication regimen exploring the merits of the different combination regimens.

Posology and method of administration (section 4.2)

"Patients with gastro-duodenal ulcers due to *H. pylori* infection should be treated with eradication therapy with appropriate combinations of antibiotics with adequate dosing regimens. Selection of the appropriate regimen should be based on patient tolerability and therapeutic guidelines/ availability of the antibiotics. (Agent **X**) can be used in a dose of **Y** mg (twice or whatever appropriate) daily during the eradication therapy of ... week(s) duration, e.g.: Clarithromycin 200 mg BID + metronidazole 400 mg BID + UHA ... mg BID for 1 week.

For further information on the other components of the eradication therapy see the individual product data sheet".

Interaction with other medicaments and other forms of interaction (section 4.5)

[1] The European H. pylori Study Group, Maastricht Consensus (GUT 1997; 41: 8-13)

Absence of or presence of interaction with relevant antibiotics which are used in eradication therapy should be mentioned here on the basis of gathered literature and prospectively studied combinations.

Pharmacodynamic properties (section 5.1)

Information on the trial setting used for testing the sought and approved *H. pylori* eradication regimens should be briefly mentioned. The results in subgroups with primary resistance to any of the involved antibacterial agents and development of secondary resistance should be highlighted. See following example:

Most available clinical experience from controlled randomised clinical trials indicate that ...(agent PPI)...mg twice daily in combination with two antibiotics e.g. amoxicillin and clarithromycin or metronidazole and amoxicillin or clarithromycin and metronidazole (given at approved dose levels) for 1 week achieve >80% *H. pylori* eradication rate in patients with gastro-duodenal ulcers. As expected, significantly lower eradication rates were observed in patients with baseline metronidazole-resistant *H. pylori* isolates. Hence, local information on the prevalence of resistance ***and local therapeutic guidelines*** should be taken into account in the choice of an appropriate combination regimen for *H. pylori* eradication therapy. ***Furthermore, in patients with persistent infection, potential development of secondary resistance (in patients with primary susceptible strains) to an antibacterial agent should be taken into account in the considerations for a new retreatment regimen.***

2. Antibacterial medicinal products

Therapeutic indications (section 4.1)

As for category (1) with the following adjustment:

"In appropriate combination ... (and an appropriate ulcer healing agent)...".

Posology and method of administration (section 4.2)

As for category (1).

Interaction with other medicaments and other forms of interaction (section 4.5)

As for category (1).

Pharmacodynamic properties (section 5.1)

As for category (1). In addition, data on the prevalence of resistance of *H. pylori* to the antibacterials mentioned in the claimed eradication therapy regimens should be listed as outlined in the CPMP Note for Guidance on the Pharmacodynamic Section of the SPC for Antibacterial Medicinal Products.

Note: For combination products presentation of the information should be focused on the claimed sole indication "*H. pylori* eradication therapy", other antibacterial activities should not be mentioned here but reference should be made to approved individual SPCs. For combi-pack presentations the data on resistance prevalence can be summarised ***e.g.*** as follows: "The prevalence of metronidazole-resistant *H. pylori* strains has been described to be 30-50% in Western Europe. The prevalence of resistant strains to amoxicillin and clarithromycin is significantly below that, ***with rates ...%."***.