Author’s response to reviews

Title: EFFECTIVE AND SAFE PROTON PUMP INHIBITOR THERAPY IN ACID-RELATED DISEASES A Position Paper Addressing Benefits and Potential Harms of Acid Suppression

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Answers to the Referees

Reply to Professor Hungin’s Comments

This is a timely position paper as the use of PPIs is proliferating and in many instances there is little justification for their use.

This Position Paper is well researched, follows an acceptable methodological approach and is representative of various medical specialties, including primary care, from Italy. It has had advisory input from a number of highly respected international experts on the subject. This Position Paper will have international applicability and is likely to be quoted frequently.

We would like to thank the Referee for his kind words of appreciation of our paper. It was an extremely hard work and being reworded by leading scientists and clinicians does compensate for our efforts.
There are a few areas where clarification is needed: p9, Intro, "functional investigation" needs to be explained - this is not a commonly understood term; and, there is a small number of grammatical/syntax errors which can be corrected through the editing process.

In gastroenterology as well as other medical specialties, “functional investigation” refers to methodologies able to investigate the function of a given organ or system, e.g. functional respiratory evaluation means the quantification of all the lung respiratory function. In our case, dealing with GERD, functional evaluation refers to intra-esophageal pH and/or impedance recording, a technique able to detect and quantify different kinds of gastro-esophageal reflux (acid or non acidic, liquid or gaseous). As requested, this was specified in bracket the first time “functional investigation” was used (page 11, first paragraph).

The manuscript was read over with a British native colleague and the few spelling errors corrected. Also, some fine tuning of the English style was performed.

My main concern (although this is not a terminal issue here) is the way the functional upper GI problems are dealt with. Although there is mention of them within the paper under the different sections they constitute an important category in their own right. Indeed, they are probably the chief reason for patients using PPIs outside the more formally recognised indications. The Rome IV categorisations of the functional GI disorders create at least two distinct upper GI categories (functional oesophageal disorders, functional dyspepsia, and, additionally, globus disorder if this also counted). In each of these, the role of PPIs is covered within the Rome IV guidelines, including the limitations of PPI treatment. My suggestion is that the authors consider an additional section on the upper GI functional disorders - that would make the Position Paper more complete. However, I do not feel that this is absolutely necessary and I am happy to leave this as a discretionary requirement.

We fully understand Professor Hungin’s concerns. The Rome (now Rome IV) criteria, to which he largely contributed, have increased our understanding of pathophysiology and treatment of functional GI disorders. They are indeed quoted in both the GERD (page 11, third paragraph) and in Dyspepsia (page 26, second and third paragraphs) sections, while discussing reflux hypersensitivity and functional heartburn as well as functional dyspepsia, respectively. Along the same lines, the use and misuse of PPIs are discussed in the same section.

We feel, however, that adding to this position paper a section, devoted to functional GI disorders, could be misleading for the “general reader”. Indeed, several studies [1-9] have shown that these criteria are not routinely used in everyday clinical practice, where the diagnosis of functional disorders is still a “diagnosis of exclusion”. This is even more true for non gastroenterologists, that is primary care physicians and doctors, belonging to different specialties, to all of whom – as the Referee himself states – this position paper is addressed. A recent Italian survey [9]
concluded “the Rome III criteria do not influence diagnostic strategies and only slightly influence therapeutic strategies of GPs”.

We are indebted to Professor Hungin for leaving us the discretion of the final decision.

Finally, although the authors acknowledge that PPIs can be purchased by the public directly in many countries, this fact seems to have been given a very subsidiary role. We do not know what proportion of PPI use internationally is from such direct purchasing, but it may well represent the majority of PPI use globally. Whilst doctors may be influenced by guidelines, members of the public will remain free to buy these drugs directly, at will. This applies especially in Eastern Europe, Asia and South America. Perhaps, there needs to be a discussion in the Position Paper about whether PPIs need to be restricted in those countries, where regulations might permit it. In most countries, patients can approach the pharmacist directly for medications - how can we help to improve their appreciation of what should be sold and what not? Guidelines and position statements are not just for specialists and GPs!

We cannot agree more on this point with Professor Hungin and thank him very much for having raised this important issue, to which 2 paragraphs are now devoted in the Discussion of revised version (page 52, third and fourth paragraphs).

Reply to Professor Sachs’ Comments

An excellent review of the use and contraindications for PPIs.

We would like to thank the Referee for his great appreciation of our work.

The role of pH control and Hp eradication should be expanded.

Although not the focus of the Position Paper, the effects of PPIs on the Helicobacter microorganism and their interaction on intragastric pH were expanded with 2 new paragraphs (page 19, second and third paragraphs).

Also the controversy over CKI and Alzheimer’s should be mentioned and the issue of a relevant odds ratio brought up.

As already stated in the Introduction, the primary aim of the Position Paper was provide clinical practitioners with patient-oriented guidelines on appropriate PPI use. Since PPI therapy is often used long-term, the safety concerns dealing with such a therapy were also addressed to put
appropriateness in a benefit-to-risk perspective. As a consequence, the Safety section was intended as a summary of the many safety concerns, detailed in specifically written comprehensive reviews, which the reader is referred to.

Anyway, following Professor Sachs’ suggestion, the risks for development of both CKI and Alzheimer’s disease are now mentioned in Table 2. In addition, taking into account that the main emphasis of the Position Paper is on efficacy and appropriate use, to make its aims more clear to the reader, we decided to change the title into:

Effective and Safe (instead of Safe and Effective) Proton Pump Therapy in Acid-related Diseases