KERATOS

Association Européenne sur les Pathologies de la Surface Oculaire
et les Dysfonctionnements Lacrymaux

Paris, 15/3/2009

Re: Withdrawal of preservative from ophthalmic preparations

Dear Dr, Isabelle Moulon,

Let me comment EMEA's answer regarding our query:

> Eye drops can be packaged in single or multi-dose containers. When multidose containers are used, preservatives may be necessary to prevent microbial contamination of the eye drop solution during use. Preservatives may also be used to increase the solubility or the penetration of the active substance.
>
> The preserved eye drops currently in use fulfil an important medical need, especially for the elderly and for patients with impaired vision, who may find small, single dose containers difficult to use because of problems with manual dexterity. In addition, preservatives are well tolerated in the majority of patients, even when used in the long term.

Although we've frequently heard such arguments notably by industry representatives, we cannot subscribe to this point of view and we have seldom heard them expressed by the patients themselves. After all, we do represent some elderly patients as well. Certainly, you are aware that specific multidose containers do not require preservatives by using specific micro-filtration tips or some other methods (this was precisely our point when mentioning the preservative-free ABAK and Comod containers). Therefore, it's possibly a matter of cost but certainly not a technical issue, nor a safety issue… nor even an ergonomic one. The containers are available, they are safe and have been accepted by various regulating agencies for the benefit of all patients and their respective ocular surfaces and sight. Elderly or poor sighted patient's commodity being resolved by these alternatives, there is no reason to undermine safety by adding henceforth unnecessary preservatives.

I have never seen a single independent study, demonstrating that indeed preservatives (such as benzalkonium chloride) are well tolerated over the long term. In fact most studies indicate otherwise.

Preserved drops do not fulfil at least one essential need, that is, patient corneal safety over the long term. Furthermore, due to the presence of preservatives and severe intolerances and limited corneal healing many patients are unable to treat themselves due to the very presence of these preservative. As such, preservatives do not fulfil another essential need: therapeutic options for all patients. Again, our point was that preservatives may be avoided altogether by either special containers or single use vials.

As for patient tolerance, the cytotoxic effect of benzalkonium was first discovered due to its overwhelming use in glaucomatous drops. These patients had originally healthy corneas

but with the long term use, many of them showed signs of surface disease (such as dry eye sufferers, etc). It is precisely because it was a frequent side effect that benzalkonium was identified has the culprit. This was later confirmed by other studies on other chronic eye diseases. I have never seen an independent ocular surface expert say that preservative-free formulations are not a giant leap for ocular surface safety and a clear benefit for patients.

As for the penetrating effect of benzalkonium, it's interesting that you should mention that, since it's precisely that corneal permeability induced by benzalkonium that frequently leads to superficial punctuate keratis or even worse corneal ulcers. While this may be an advantage in very specific cases (for some antibiotic use that requires penetration of other corneal tissues), this is seldom an advantage for most frequent uses. Moreover, it's clearly a risk for visual integrity of progressively fragile corneas. Surely anyone would want to keep most ocular surface diseases, dry eyes and ocular allergies (to mane a few) as much as possible a surface problem rather than a more in-depth issue…

We patients have a first-hand experience of that effect and we are clearly not exceptions. Considering all side effects of preservatives is a matter where patient "expertise" or experience may add some value when considering future policies. Benzalkonium has in fact many effects, as most preservatives, such as the detergent effect (lipid tear disruption notably), irritation, corneal permeability, inflammatory, allergenic effect, cytotoxic effect, diseccation, etc. We would like to draw your attention to most studies on this matter, some of them are cited on our site (additionally, Pr Baudouin and al, are very good references that may easily be found using Pubmed or more specific corneal publications):

You may further investigate this issue by reading the following links:
http://preservative.free.fr/English/consequences-of-preservatives.htm
http://preservative.free.fr/English/consequences-per-preservative.htm
http://preservative.free.fr/English/consequences-compare-preservatives.htm
All independent comparative studies to date have demonstrated the benefit for the patients and better compliance with the treatment.

All reported adverse reactions must also be described in the product information.

And this is clearly not the case, as we have never seen indicated anywhere in the package insert such deleterious effect as the lipid disruption or the abrasive effect of benzalkonium just to mention a few. Most leaflets only indicate allergy and tell patients to exercise caution when using contact lenses. So maybe the EMEA and the group lead by Keratos, Gêniris and AMALYSTE may cooperate on this matter as well…

> In addition, according to the official guidance (Excipients in the label and package leaflet of medicinal products for human use - Notice to Applicants, Volume 3B), when a warning or information statement, is required in the product information, it must be clearly linked to the presence of a particular excipient. Therefore, when a preservative is included in the eye drops, the relevant warnings - if necessary – will also be included in the product information.

Indeed, **further relevant warnings are necessary** particularly with regard to possible ocular surface disease.

> Furthermore, before applying for marketing authorisation, a pharmaceutical company is obliged to ensure that all excipients, including preservatives are used appropriately in the formulation of their medicinal products. The appropriateness of the pharmaceutical formulation is assessed by the regulatory authority in question, which needs to confirm that the formulation is suitable and complies with legislative requirements and the relevant scientific guidelines before a marketing authorisation can be granted.

Certainly you aware that benzalkonium was authorized many years ago. Scientific knowledge on this matter has evolved and so have the alternatives to address this problem such as the specific containers and singe use vials we mentioned earlier. Considering these satisfying alternatives, there is not reason that the EMEA policy on this matter should not evolve. We trust that you will consult ocular surface experts on this matter.

> Finally, we would like to inform you that the EMEA´s Committee for Medicinal Products for Human Use (CHMP) is considering further this issue in order to define clear criteria for the specific value and safe use of preservatives in eye drops.

Finally, we seem to agree on the fact that the EMEA should further investigate this issue and define clear criteria in order not only to regulate preservative use but also more importantly to ensure patient safety regardless of the limited additional cost of alternatives currently. This could easily be done by limiting the overwhelming (almost systematic) use of unnecessary benzalkonium preparations and replacing these by preservative-free preparations in either muti-dose specific containers such as ABAK and Comod (surely there are others) or single use vials. Thus, for us patients, the clear criterion would be that whenever there is a safer alternative it should be used in the patient's best interest.

Yours sincerely,

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