



EUROPEAN MEDICINES AGENCY
SCIENCE MEDICINES HEALTH

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Committee for Medicinal Products for Human Use (CHMP)

Questions and answers on the use of phosphates in eye drops

The European Medicines Agency has completed an assessment of the use of phosphate buffers in medicinal products given as eye drops and whether these can cause corneal calcification (build-up of calcium deposits in the cornea, the clear layer at the front of the eye). The Agency's Committee for Medicinal Products for Human Use (CHMP) considered that the benefits of phosphate-containing eye drops outweigh their risks but that in very rare cases patients with significant damage to the cornea may develop corneal calcification during treatment with eye drops that contain phosphate, and that this should be mentioned in the product information.

What are phosphate-containing eye drops?

Phosphates are substances that are widely used in eye medicines: about a third of all medicinal products given as eye drops in the European Union (EU) contain phosphate, usually as part of a buffer system (a means of keeping the eye drop solution from being too acid or too alkaline, which can cause irritation). Very occasionally phosphates may be part of the active substance or included in the solution for other reasons.

Why was the use of phosphates in eye drops assessed?

Reports were identified of patients who developed corneal calcification while using eye drops containing phosphate, and there was concern that the phosphate in the eye drops might be causing the problem in these patients. Phosphate is known to bind to dissolved calcium and it was thought that the calcium deposits in the eye might be caused by the phosphate in the eye drop binding to calcium in eye fluids, forming deposits of calcium phosphate. The problem was first reviewed by the German medicines regulatory agency, but since phosphates were used in eye drops in many countries, the CHMP carried out an assessment looking at data coming from across Europe.

Which data has the CHMP looked at?

The CHMP examined information from the manufacturers on 655 different eye drop products, of which 236 contained phosphate. It also looked at reports of corneal calcification in patients using phosphate-containing eye drops, at published studies, and at estimates of how widely phosphate-containing eye drops are used.



What are the conclusions of the CHMP?

The CHMP examined 117 possible or confirmed case reports of corneal calcification. There was some evidence to suggest that patients who already had severe damage to the cornea might develop calcification during treatment with phosphate-containing eye drops. This could contribute to additional visual loss, which in some cases requires further treatment including surgery. However, phosphate-associated calcification was extremely rare, given the fact that many millions of bottles of eye drops containing phosphate had been distributed in the same time period. In addition, some patients with severe damage to the cornea developed calcification despite not using phosphate-containing eye medicines.

Based on the evaluation of the currently available data and the scientific discussion within the Committee, the CHMP considered that the benefits of the phosphate-containing eye drop medicines authorised in the EU continue to outweigh their risks, and therefore recommended that they can continue to be used. The evidence did not warrant a restriction on the use of phosphate buffers in eye drops, which might lead to patients being unable to obtain suitable treatments. However, in order to make prescribers and patients aware of the issue, it was recommended that the product information for these medicines should be updated. The Summary of Product Characteristics should have the following wording added to Section 4.8 (Undesirable effects):

Cases of corneal calcification have been reported very rarely in association with the use of phosphate containing eye drops in some patients with significantly damaged corneas.

Similarly, the patient leaflet for such medicines should be updated to include in Section 4 (Possible side effects) the wording:

In very rare cases, some patients with severe damage to the clear layer at the front of the eye (the cornea) have developed cloudy patches on the cornea due to calcium build-up during treatment.

This should be supported by an update of the EU guideline on excipients¹ (ingredients of medicines other than the active substances) to cover the problem of corneal calcification with phosphates in medicinal products given as eye drops.

Further information for patients

- Any risk of corneal calcification is very low (less than 1 reported case per 10,000 bottles distributed).
- Patients without pre-existing damage to their cornea do not seem to be at significant risk.
- Patients with pre-existing severe damage to their cornea, which is a sight-threatening condition, should not stop treatment without consulting their treating doctor.
- Patients who have any questions should speak to their doctor or pharmacist.

Further information for prescribers

- Of 655 unique eye drop products assessed, 236 contained phosphate. Another third used non-phosphate buffers, and the remainder were unbuffered. Phosphate, where present, occurred in varying amounts, but in all cases at higher concentrations than the physiological concentration in tear fluid. Calcium and phosphate have a high affinity for one another, and form a variety of insoluble crystalline compounds.

¹ Excipients in the label and package leaflet of medicinal products for human use. CPMP/463/00

- Toxicology studies in rabbit corneas, both *ex vivo* and *in vivo*, indicated that severe trauma combined with local treatment with phosphate-containing formulations was associated with the development of corneal calcification.^{1,2} However, during development, routine toxicity studies in rabbits, dogs, and Cynomolgus monkeys with undamaged corneas have not shown corneal calcification with phosphate-containing drug formulations or vehicles.
- The clinical data reviewed comprised 117 possible or confirmed case reports from company safety databases or literature reports (some of which were duplicates), and a cohort study on chemical eye burns.³ No clear association could be shown between the development of corneal calcification and the dose or concentration of phosphate, the type of phosphate or buffering system, or the frequency, indication or duration of use. Cases were most often associated with severe damage to the corneal surface, with exposure of Bowman's layer or the corneal stroma. However, calcification can also develop in such patients in the absence of treatment with phosphate-containing formulations.
- Taken together, the data support the plausibility of an association between use of phosphate-containing eye drops in some patients with severe corneal damage and the development of corneal calcification and opacity. However, although reporting of estimated usage is incomplete, many millions of units have been distributed, suggesting that any risk associated with the products is very low (less than 1 per 10,000 bottles), and even in patients with severe corneal damage the evidence does not support a universal recommendation to avoid treatment. In addition, calcification is a multifactorial condition that may occur in patients who have not used these products. Patients with severe existing corneal damage may have an urgent need for treatment, so the benefits of treatment with a phosphate-containing eye drop need to be weighed against the low risk of corneal calcification, taking into account the individual circumstances of each case.

Selected references.

1. Schrage NF, Schlossmacher B, Aschenbrenner W, Langefeld S. Phosphate buffer in alkali eye burns as an inducer of experimental corneal calcification. *Burns* 2001;27: 459-64.
2. Schrage NF, Frentz M, Reim M. Changing the composition of buffered eye-drops prevents undesirable side effects. *Br J Ophthalmol* 2010;94: 1519-22.
3. Kompa S, Redbrake C, Dunkel B, Weber A, Schrage N. Corneal calcification after chemical eye burns caused by eye drops containing phosphate buffer. *Burns* 2006;32: 744-7.