1. **NAME OF THE MEDICINAL PRODUCT**

Vitamin A-POS 250 I.U./g, eye ointment,

2. **QUALITATIVE AND QUANTITATIVE COMPOSITION**

1 g of ointment contains:

Retinol palmitate  250 I.U.

For a full list of excipients, see section 6.1

3. **PHARMACEUTICAL FORM**

Eye ointment

Yellow/white, lightly transparent, homogeneous eye ointment.

4. **CLINICAL PARTICULARS**

4.1 Therapeutic Indications

Supportive therapy for atrophic changes of the cornea and conjunctiva caused by vitamin A deficiency (e.g Keratomalacia, Xerophthalmia) and for trophic disturbances of cornea and conjunctiva caused by mucin deficiency by a well preserved protecting serous film.

4.2 Posology and Method of Administration

Instil one strip of eye ointment 3 times daily (especially at night time) into the conjunctival sac.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special warnings and precautions for use

Contact lenses should not be worn during treatment with Vitamin A-POS®.
4.5 Interactions with other medicinal products and other forms of interaction

No interaction studies have been performed.

4.6 Pregnancy and Lactation

In experiments on animals, overdoses and deficiency of vitamin A had teratogenic effects. Mutagenic effects were not documented.

In women, where the possibility of pregnancy cannot be excluded, a maximal daily dose of 8,000 up to a 10,000 I.U. of vitamin A, is determined.

Due to the fact that high doses of retinol palmitate have proved to have teratogenic effects, women in fertile age, and particularly during pregnancy, must stick to the restricted dose; the optimal intake of retinol during pregnancy (i.e. the recommended daily dose) is 2,600 I.U. daily, and during the lactation period 4,000 I.U. daily. Therefore, it is not dangerous to use an eye ointment with 1,250 I.U. in the whole tube. In ophthalmologic use the applied amounts are so small that no damage for the child has to be expected.

During pregnancy and the lactation period, women are allowed to use the Vitamin A-POS® preparation.

4.7 Effects on ability to drive and use machines

Vitamin A-POS has moderate influence on the ability to drive and use machines. Working persons and drivers should use Vitamin A-POS only at night because vision will be impaired after the application of the eye ointment. It is possible to consider Vitamin A-POS as reliable, but due to the possibility of a short deterioration of visual clearness, after the administration of the ointment into the eye, it is not recommended to drive or use a machine for 15 minutes.

4.8 Undesirable effects

Not known.

4.9 Overdose

No case of overdose has been reported.
5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic Properties

Pharmacotherapeutic group: ophthalmologicum, vitamin for reepithelialisation

ATC code: S01XA02

Vitamin A is essential for humans. Its alcohol, retinol, is of importance for growth and differentiation of epithelial and mesenchymal cell structures, for prevention of the mucous membranes against keratinisation, for growth and development of the long bones and for the functioning of the gonadals.

Its aldehyde (retinal) is involved in visualisation; other sensory perception (smelling, hearing, tasting) are dependent on a sufficient supply with vitamin A.

As known today, cellular growth and differentiation are regulated by vitamin A’s influence on the growing factors which are necessary for development and regeneration of cells.

Tears, conjunctival capillaries and aqueous humour supply these molecules which are necessary for the metabolism of the cornea. If more of these molecules are needed, which influence the regeneration of the epithelium, they cannot be supplied by the circulation alone (after oral or parenteral application). This applies especially to vitamin A which is bound to a protein complex in plasma. In the tears, vitamin A is bound to a different protein and regulates differentiation and regeneration of the corneal epithelium.

In course of a disease (e.g. due to mechanical lesions) the need of regenerating substances is elevated. This lack is balanced slowly by circulation but can be enhanced by topical application of vitamin A.

A continuous and sufficient supply of retinol to the cornea is required for controlled proliferation and differentiation of vitamin A dependent cells. Consequently, a systemic or local lack of vitamin A causes typical structural changes of the cells and distinct decrease of regeneration.

5.2 Pharmacokinetic Properties

Vitamin A is received by food as retinylesters or β-carotène. Before being absorbed by the mucosal cells of the gastrointestinal tract the esters are cleaved by esterases. Retinol is metabolised to chylomicrones which are deposited in the liver. Vitamin A is mobilised and transported in the blood as a protein complex which is bound to transthyretin. Reaching the receptors of the target cells retinol is decarboxylised and bound to a cellular protein. Within the cells retinol is metabolised to retin acid and deposited as retinylester.

Usually, vitamin A is transported by circulation. The non-vascular cornea depends on the supply of vitamin A by the tears. In the lacrimal gland retinol is stored in form of an
ester. After hydrolysis the alcohol is released into the tears and reaches the target cells in the cornea. The retinal esters in the lacrimal gland are formed by esterification of the plasma-bound retinol. Increased release of retinol into the tears can be achieved by quick hydrolysis of the retinol esters only. An increased absorption of retinol into the lacrimal gland for a short time is not possible because of the homeostatic regulation of the retinol plasma concentration.

Physiologic tears contain 16 ng/ml (0.5 x 10^{-7} M) all-trans-retinol which corresponds to about 20-30 % of the average concentration in serum. Specific receptors for retinol were detected in the cytosol of the cells in the corneal epithelium, the stroma and the endothel, which are different from the retinol binding protein in serum.

Additionally, there is cellular retinoic acid binding protein (CRABP) in the cystol of the cells in the human cornea. The absorption of topically applied retinol into the cornea of rabbits follows a coefficient of permeability of 0.61 x 10^{-5} cm/s. The permeability of the cornea is reduced in keratinised cornea which is symptomatic of xerophthalmia. Retinol is absorbed by the corneal epithelium, stroma and endothelium.

5.3 Preclinical safety data

Effects in non-clinical studies were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

Systemic effects are not to be expected after topical application of retinol.

Acute toxic symptoms occur in children after systemic application of 75,000 to 300,000 I.U. retinol, in adults after 2 to 5 millions I.U. retinol.

Symptoms of a chronic intoxication depend on duration of therapy and the applied doses. The lowest dose described in literature causing a hypervitaminosis was 41,000 I.U. daily for 9 years.

Vitamin A-overdosage is indicated by headache, giddiness, lack of appetite, dried and peeling skin and mucous membranes, hemorrhages.

In pharmacological experiments vitamin A overdosage is as teratogenic as lack of vitamin A. Therefore, for reasons of security, women who cannot exclude pregnancy should not exceed a daily intake of 8,000 to 10,000 I.U.

Vitamin A is neither mutagen nor cancerogen.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients

White vaseline; light liquid paraffin; liquid paraffin; wool fat
6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The duration of stability is 3 years. Vitamin A-POS should not be used beyond the expiration date (imprinted on the packaging carton).

With proper care Vitamin A-POS can be used up to 3 months after the first opening.

6.4 Special precautions for storage

Vitamin A-POS should not be stored above 25 °C.

6.5 Nature and contents of container

Tube with 5 g of eye ointment

6.6 Special precautions for disposal

No special requirements.

7. MARKETING AUTHORISATION HOLDER

Biem İlaç Ltd. Pti.
Denizciler Caddesi No. 7
6240 Ulus/Ankara, Turkey

8. MARKETING AUTHORISATION NUMBER

N.N.

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

N.N.

10. DATE OF REVISION OF THE TEXT

August 2008