2.6 Nonclinical Summary

As Travoprost and Timolol are not new chemical entities, this application is related to a generic medicinal product claiming essential similarity to Duotrav® eye drops solution, with the exception of preservative (Alcon Laboratories (UK) Ltd). Furthermore, a comparative study concerning the physicochemical properties between the two products showed that they are essentially similar. The physicochemical parameters compared were appearance, pH, extractable volume and osmolality. Moreover the surface tension and the average drop volumes were found similar. The above demonstrate that Travoprost-Timolol/Pharmathen (40micrograms/ml + 5 mg/ml) preservative free Eye drops, solution will not lead to any different systemic absorption as compared to the reference product.
Additionally, guideline CPMP/EWP/239/95 final states: *'Generally safety and local tolerance may be guaranteed by knowledge of the active substance and the choice of known inactive ingredients'*. Therefore, tolerability study is not necessary and as no new additional studies have been provided within the documentation, Non-Clinical Summaries are not mandatory. For a bibliographical research report on all studies carried out on Travoprost please refer to *Module 4* of this application.

To ensure the sterility and microbiological safety of the non-preserved product, the 3K-System is equipped with a patented double protection mechanism. The outlet opening of the 3K-System is constructed with germ-reducing components containing oligodynamically active silver as an additional safe-guard.

Sterility of the final Travoprost-Timolol product is established by filling of containers under aseptic conditions. The container's ability to maintain sterility has been ascertained in a series of microbial challenge and in use tests by both the container's and finished product manufacturers. All challenge tests were carried out under extreme and exaggerated microbial conditions. These challenge tests include critical parameters such as a high viable microbial count (e.g.10^6 cfu/mL), a bacterial test organism well known as a successful contaminant (*Pseudomonas aeruginosa*) and frequent sequential contaminations that cover the proposed in-use period. Developed challenge tests include dynamic challenge tests, in-use challenge tests simulating patient use and oligodynamic effect tests for the active tip silver. All above tests follow general pharmacopeial antimicrobial test principles and recommendations, while appropriate number of positive and negative controls were also included in all of the above testing scenarios. Results from all of the above challenge tests with all tested Travoprost-Timolol containers with the 3K system, have shown absence of microbial growth.

Overall, despite the extreme test challenge parameters, which exceed actual in-use patient conditions, sterility of finished Travoprost-Timolol preservative free product with the 3K nozzle system remains unaffected.