1.5. SPECIFIC REQUIREMENTS FOR DIFFERENT TYPES OF APPLICATIONS

1.5.2. Information for generic, "hybrid" or bio-similar applications

The present application of Travoprost-Timolol/Pharmathen (40 micrograms/mL + 5 mg/mL) preservative free eye drops, solution in multi dose container complies with the definition of a "hybrid" medicinal product as stated in Article 10(3) of Directive 2001/83/EC as amended, as it has:

- the same qualitative composition in active substances with essentially similar physicochemical properties as the reference medicinal product, with the exception of the preservative
- the same pharmaceutical form as the reference medicinal product (eye drops solution)
- the bioavailability studies cannot be used to demonstrate bioequivalence

The reference medicinal product is DuoTrav® 0.004% w/v & 0.5% w/v eye drops, solution preserved with polyquaternium-1 (Alcon Laboratories (UK) Ltd), which has been authorized in the European community for more than ten years (first approved on 24/04/2006) by means of a Centralized procedure.

The application is a "hybrid" application, since bioequivalence cannot be demonstrated through bioavailability studies. Thus, the application complies with Article 10(3) of Directive 2001/83/EC as amended.

Regulatory provisions

The present argumentation will be based on the provisions of Volume 2 Notice to Applicants Volume 2b Presentation and content of the dossier Common Technical Document, June 2004, which states that the summary should include details on medicinal product, its active substance and its safety/ efficacy profile in comparison to the active substance of the medicinal product to which such similarity is claimed, as well as details relating to the bio-availability and bioequivalence where necessary of the medicinal product concerned.

This application is made under 10.3 of DIR 2001/83/EC in cross-reference to the pharmaco-toxicological and clinical data supporting the existing product DuoTrav® 40 μg/ml / 5 mg/ml eye drops, solution (Alcon) and so it is necessary to demonstrate essential similarity with the originators formulation. Pharmaceutical equivalence testing has illustrated that they are essentially similar in terms of the active content and assay of related substances. Bioequivalence between the originator product 'DuoTrav® 4 0 μg/ml + 5 mg/ml eye drops, solution (Alcon)' and 'Travoprost-Timolol/Pharmathen (40 micrograms/mL + 5 mg/mL) preservative free Eye drops, solution' cannot be demonstrated through bioavailability studies for locally acting products subsequent to the CPMP/EWP/239/95 final '*Note for Guidance on clinical requirements for locally applied, locally acting products containing known constituents'*, and therefore abridged applications for such products should be regarded as hybrid applications.

Formulations of Travoprost/Timolol have been well established in Europe for more than a decade.
Pharmathen S.A. recognizes the fact that Travoprost & Timolol are effective and safe substances for their indicated use and has developed a generic formulation of this medication.
DuoTrav® 40 μg/ml + 5 mg/ml eye drops, solution (Alcon)' comparator products sourced from other European countries possess an identical appearance and other characteristics under the conditions selected within this application.

Pharmaceutical Equivalence
The applicant's product displays similar osmolality and pH results to Duotrav. The two formulations present stable and similar final pharmaceutical product characteristics.
As all pharmaceutical properties of the applicant's product are similar to those of reference product, the therapeutic equivalence of the products is assured.

Comparative testing
An important aspect of essential similarity is to provide documented evidence confirming that Travoprost-Timolol 0.04mg/ml – 5mg/ml preservative free eye drops, solution final product has a similar profile to the originator products. Each product was analysed according to the established analytical methods for assay and impurities described in 3.2.P.5.2 Analytical Procedures.

Table 1. Profile comparison of Travoprost Timolol 0.04mg/ml – 5mg/ml preservative free eye drops solution and Duotrav reference product.

Tests/ Specifications	**Travoprost Timolol 0.04mg/ml – 5mg/ml eye drops solution preservative free**			**DUOTRAV (GR)**	**DUOTRAV (DE)**
	LOT	**LOT**	**LOT**	**B/N:**	**B/N:**
Appearance	Clear, colorless aqueous solution in white plastic bottle with ophthalmic dispenser	Clear, colorless aqueous solution in white plastic bottle with ophthalmic dispenser	Clear, colorless aqueous solution in white plastic bottle with ophthalmic dispenser	Clear, colourless solution	Clear, colourless solution
Extractable volume					
pH					
Osmolality					

Tests/ Specifications	**Travoprost Timolol 0.04mg/ml – 5mg/ml eye drops solution preservative free**			**DUOTRAV (GR)**	**DUOTRAV (DE)**
	LOT	**LOT**	**LOT**	**B/N:**	**B/N:**
Surface Tension mN/m (for information only)					
Drop Volume (µL) (for information only)					
Assay					
Assay					
Related Substances of Travoprost					
5,6-trans-Travoprost NMT 1.5%					
Any Individual Unknown					
Total:					
Related Substances of Timolol					
Impurity B NMT					
Any Individual Unknown					
Total:					
Enantiomeric Purity of Timolol					
Impurity A NMT					

Profile comparison between Travoprost Timolol 0.04mg/ml – 5mg/ml eye drops solution preservative free and DUOTRAV reference products (ALCON) reveals similarity between the product of Pharmathen and the originator product.
The results for the physicochemical characteristics are almost the same. Impurities profiles are not similar regarding the total amount of impurities, but they are similar regarding which impurities are present in the product.

Efficacy / Safety Profile
Bearing in mind that:

a) all excipients of the proposed generic formulation are the same as those used in the originator preparation, except from the preservative Polyquaternium-1 and are well known and commonly used in pharmaceutical preparations
b) pharmaceutical equivalence testing has illustrated that they are essentially similar in terms of the active content and assay of related substances
c) the SmPC was drawn up considering the originator's SmPC centrally approved in EU

It is concluded that the toxicological data of the originator product apply for the proposed generic product and that no safety concerns should arise.

Conclusions
The applicant has demonstrated that the comparative composition of the test and reference products is qualitatively the same with essentially similar physicochemical properties with the exception of the preservative, and that the method and means of administration are also the same as the reference.