Module 1.5.2

Information for abridged applications under Article 10(3) of Directive 2001/83/EC

Introduction

The present application of Bimatoprost-Timolol/Pharmathen 0.3mg/mL + 5mg/mL, Preservative Free, Eye drops solution, multidose 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 and quantitative composition in active substances as the reference medicinal product,
- 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 GANFORT 0.3mg/mL – 5mg/mL preservative free eye drops solution in unit dose container (Allergan), authorised in the Community based on the basis of a complete dossier in accordance with the provisions set forth in Article 8 and 10 of Directive 2001/83/EC, as amended.

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 details on the medicinal product, its active substance, pharmaceutical form, strengths, therapeutic indications, route of administration as appropriate in comparison to the reference medicinal product, as well as details related to the bioavailability and bi-equivalence, where necessary, of the medicinal product concerned.

This application is made under 10.3 of DIR 2001/83/EC 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 'GANFORT 0.3mg/mL – 5mg/mL preservative free eye drops solution in unit dose container (Allergan)' and 'Bimatoprost-Timolol/Pharmathen 0.3mg/mL + 5mg/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 Bimatoprost-Timolol have been well established in Europe for more than a decade.

Pharmathen S.A. recognizes the fact that Bimatoprost and Timolol are effective and safe substances for their indicated use and has developed a generic formulation of this medication.

'GANFORT 0.3mg/mL – 5mg/mL preservative free eye drops solution in unit dose container (Allergan)'comparator products sourced from other European countries possess an identical appearance and physicochemical profile under the conditions selected within this application, and, although these are manufactured at different sites, as far as can be ascertained from the available information, are in fact identical in formulation.

The present marketing authorisation application for 'Bimatoprost-Timolol/Pharmathen 0.3mg/mL + 5mg/mL, Preservative Free, Eye drops solution,' is therefore submitted under 10.3 of DIR 2001/83/EC in cross-reference to the pharmaco-toxicological and clinical data supporting the existing product GANFORT 0.3mg/mL – 5mg/mL preservative free eye drops solution in unit dose container (Allergan).

Essential Similarity

1. **Formulation**

Bimatoprost-Timolol/Pharmathen 0.3mg/mL + 5mg/mL, Preservative Free eye drops solution is available in a multiple dose container. It contains the same active substances, bimatoprost and timolol, with the same excipient composition to Ganfort eye drops solution in single dose container authorised in the in the Community based on the basis of a complete dossier in accordance with the provisions set forth in Article 8 and 10 of Directive 2001/83/EC, as amended.

In the following table a brief qualitative comparison of the formulations between the originator GANFORT (Allergan) and Pharmathen's product is presented.

Bimatoprost-Timolol/Pharmathen 0.3mg/mL + 5mg/mL Preservative Free eye drops solution in multidose container	**GANFORT 0.3mg/mL – 5mg/mL preservative free eye drops solution in unit dose container (Allergan)**
Excipients	**Excipients**
Bimatoprost	Bimatoprost
Timolol maleate	Timolol maleate
Sodium Chloride	Sodium Chloride

Sodium phosphate dibasic heptahydrate	Sodium phosphate dibasic heptahydrate
Citric acid monohydrate	Citric acid monohydrate
Sodium hydroxide and/or hydrochloric acid	Sodium hydroxide or hydrochloric acid
Purified water	Purified water

Functionality of the excipients

All excipients that have been used in Bimatoprost-Timolol/Pharmathen 0.3mg/mL + 5mg/mL, Preservative Free eye drops solution were the same with those used in originator's product Ganfort eye drops solution in single dose container.

In particular, the inactive ingredients that have been used as well as their function are:

Name of Ingredient	**Function**
Sodium chloride	Tonicity agent
Sodium phosphate dibasic heptahydrate	Buffering agent / Tonicity agent
Citric acid monohydrate	Buffering agent / Tonicity agent
Hydrochloric acid or sodium hydroxide	pH adjuster
Water for injection	Solvent / vehicle

Pharmathen's target is the final solution to reveal substantially the same physicochemical properties (pH, Osmolality, Surface tension, Drop volume, viscosity, and specific gravity) compared to the originator.

As all pharmaceutical properties of the applicant's product are similar to those of reference product, the therapeutic equivalence of the products is assured (see table 1).

2. Comparative testing

The purpose of essential similarity study is to provide documented evidence confirming that Bimatoprost-Timolol/ Pharmathen 0.3mg/mL+5mg/mL eye drops solution preservative free 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.

BIMATOPROST-TIMOLOL/PHARMATHEN 0.3mg/ml +5mg/ml eye drops solution preservative free		
Country	**Name/Batch**	**Exp. Date**
Greece (Pharmathen)	BIMATOPROST TIMOLOL	N/A
Deutschland (DE) (ALLERGAN)	GANFORT 0.3mg/mL – 5mg/mL	10-2016

Nederland (NL) (ALLERGAN)	GANFORT 0.3mg/mL – 5mg/mL	02-2017
France (FR) (ALLERGAN)	GANFORT 0.3mg/mL – 5mg/mL	02-2018

Analytical results for BIMATOPROST- TIMOLOL 0.3mg/mL – 5mg/mL preservative free eye drops solution, multidose container and GANFORT 0.3mg/mL – 5mg/mL preservative free eye drops solution in unit dose container are provide in tables below:

Table 1. Profile comparison of Bimatoprost - Timolol 0.3mg/mL – 5mg/mL preservative free eye drops solution and Ganfort 0.3mg/mL – 5mg/mL reference product.

Tests/ Specifications	**BIMATOPROST- TIMOLOL 0.3mg/mL – 5mg/mL preservative free eye drops solution, multidose container**			**GANFORT 0.3mg/mL – 5mg/mL preservative free eye drops solution in unit dose container**		
				DE	**NL**	**FR**
Appearance	Clear, colorless aqueous solution in white opaque plastic ophthalmic dispenser	Clear, colorless aqueous solution in white opaque plastic ophthalmic dispenser	Clear, colorless aqueous solution in white opaque plastic ophthalmic dispenser	Clear, colourless solution	Clear, colourless solution	Clear, colourless solution
Surface Tension (for information only)						
Extractable volume NLT 3.0mL						
Drop Volume (µL) (for information only)						
pH 6.8-7.8						
Osmolality 261-319 mOsm/Kg						
Viscosity (cP) (for information only)						
Specific gravity (for information only)						
Assay *95.0-105.0% of the stated amount of Bimatoprost*						
Assay						

Tests/ Specifications	**BIMATOPROST- TIMOLOL 0.3mg/mL – 5mg/mL preservative free eye drops solution, multidose container**			**GANFORT 0.3mg/mL – 5mg/mL preservative free eye drops solution in unit dose container**		
				DE	**NL**	**FR**
95.0-105.0% of the stated amount of Timolol						
Related Substances of BIMATOPROST						
5,6-trans Bimatoprost NMT 1.0%						
15R-Bimatoprost NMT 1.0%						
Any unknown NMT 1.0%						
Total: NMT 5.0%						
Related Substances of Timolol						
Impurity B NMT 1.0%						
Any Individual Unknown NMT 1.0%						
Total: NMT 3.0%						
Enantiomeric Purity of Timolol						
Impurity A NMT 1.0%						

Profile comparison between Bimatoprost-Timolol 0.3mg/mL – 5mg/mL preservative free eye drops solution (Pharmathen) and Ganfort 0.3mg/mL – 5mg/mL eye drops solution in single dose container reference products (Allergan) reveals similarity between the product of Pharmathen and the reference product. The results for the physicochemical properties 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) contains the same active substances, bimatoprost and timolol, with the same excipient composition to Ganfort eye drops solution in single dose container well known and commonly used in pharmaceutical preparations. More importantly, all physicochemical properties are essentially similar between the two products; therefore assuring that both products will exhibit an essentially similar therapeutic profile.
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 the EU

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

Conclusions

The applicant has demonstrated that the proposed medicinal product exhibits pharmaceutical equivalence with regard to in vitro (comparative testing) performance to the medicinal product to which essential similarity is being sought. Moreover, the two products do not differ regarding their qualitative composition. In conjunction with the above results, this provides the assurance that not only same amounts of Bimatoprost and Timolol reach the systemic circulation, but that this amount will act in the same way as well, due to the same physicochemical properties which result from the similar composition of the eye drop solution. Since the above-mentioned parameters determine, although indirectly but yet satisfactorily, the product's efficacy, we can conclude that there are no differences between the two products that could be considered to be significant in terms of efficacy and that comparable systemic action is demonstrated.

In conclusion, the requirements of Volume 2 Notice to Applicants Volume 2b Presentation and content of the dossier Common Technical Document, May 2002 (final-revision 2) are adequately met. The grounds for claiming essential similarity have therefore been provided and a justification of submitting an application for a Marketing Authorization for Bimatoprost-Timolol/Pharmathen 0.3mg/mL – 5mg/mL preservative free eye drops solution, under Article 10.3 'hybrid application' of DIR 2001/83/EC in cross-reference to the pharmaco-toxicological and clinical data supporting the existing product 'Ganfort 0.3mg/mL – 5mg/mL eye drops solution in single dose container reference products (Allergan).