Annex II

Scientific conclusions

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About the product

Gelisia and associated names is an eye gel containing timolol 1 mg/g.

Timolol is *a β*1 and *β*2 non-selective adrenergic receptor-blocking agent. Ocular hypertension most often occurs as the result of impaired drainage of aqueous humour from the anterior chamber. The consequential build-up of intraocular pressure (IOP) is considered the most important risk factor for the development and progression of glaucoma, a blinding optic neuropathy (Johnson et al., 2010).

Glaucoma can be classified as open-angle, closed-angle or congenital, with each type being subdivided into primary and secondary types when the underlying cause of glaucoma can be identified or not. The mechanism of action by which timolol lowers IOP has to do with the decrease of aqueous humour formation, but the precise mechanism is not clearly defined. However, it is believed that its action is mediated by the inhibition of the increased cAMP synthesis caused by endogenous β-adrenergic stimulation. Following topical ophthalmic administration, timolol causes systemic adrenergic β-blockage in the ciliary epithelium, inhibiting the synthesis of cAMP, which leads to the decrease in aqueous humour production and, consequently, to the reduction of IOP (Nieminen et al., 2007; Kiland et al., 2016; Sah et al., 2017).

The topical administration of ophthalmic timolol, especially for the aqueous formulation, may lead to systemic adrenergic β-blocking caused by the absorption of timolol from the eye through the conjunctival epithelium, lacrimal channels, nasal mucosa and gastrointestinal tract into the systemic circulation, which may lead to cardiovascular and respiratory adverse effects (Nieminen et al., 2007; Volotinen et al., 2011). Gel formulations of ophthalmic timolol have been developed as an alternative to aqueous ones with the objective of reducing their systemic absorption and the consequent adverse effects while maintaining the required therapeutic activity (Nieminen et al., 2007).

Proposed indications

Gelisia and associated names is proposed to be indicated for:

Reduction of elevated intraocular pressure in patients with:
- *ocular hypertension,*
- *chronic open-angle glaucoma.*

The indication is fully in accordance with the reference product Geltim.

Regulatory background

The *Draft Guideline on quality and equivalence of topical products* (CHMP/QWP/708282/2018), describes scenarios where equivalence testing of topical products may support a claim of therapeutic equivalence with comparator medicinal products *in lieu* of therapeutic equivalence clinical trials. Equivalence with respect to quality can, where appropriate, be established using comparative data with the comparator medicinal product regarding pharmaceutical form, qualitative and quantitative composition, microstructure/physical properties, and product performance (e.g., dissolution, *in vitro* release test, and method of administration). This is termed "extended pharmaceutical equivalence" for the purpose of this guideline.

The proposed product initially contained similar excipients to the reference medicinal product (initial formulation). During the DCP assessment phase, the applicant reformulated the finished product (commercial formulation). After this reformulation, the qualitative composition of Gelisia 1 mg/g eye gel is the same as that of the reference product Geltim LP 1 mg/g eye gel.

In order to support the hybrid application, the applicant presented data to support the extended pharmaceutical equivalence, consisting of comparative data for appearance, colour, opalescence, particle size, timolol identification, timolol assay, pH, osmolality, viscosity and related substances in three batches of the reference product and four batches of the test product, of which three made with the initial formulation and one with the final formulation as proposed for commercialisation.

The extended pharmaceutical equivalence acceptance criteria were considered met in line with the guideline. Therefore, no clinical equivalence study was provided.

The applicant claimed that no statistical analysis was possible for the parameters appearance, colour, opalescence, particle size and identification, as the results are not numerical but only stated as compliance with the acceptance criterion, which was accepted. Also, for related substances, the results are all so low that a statistical analysis is not possible; however, it is observed that the impurities profiles are comparable.

Comparability was demonstrated for osmolality, density and surface tension. However, as opposed to the RMS NL, this was not considered possible by CMS ES for the parameter viscosity because very heterogeneous data were provided without an adequate sampling strategy.

Overall, the CMS ES considered the comparability of the viscosity, the most critical quality attribute, insufficiently demonstrated, namely: *in vitro* equivalence for the parameter viscosity had not been shown with an adequate statistical methodology in line with the *Reflection paper on the statistical methodology for the comparative assessment of quality attributes in drug development*. There was no "quality attributes data comparison protocol" in which the sampling strategy was defined which raised concerns about the representativeness of the batches used; inadequate samples were analysed to assess viscosity during shelf-life. Additionally, justifications of the clinical irrelevance of viscosity could not be agreed.

Additionally, in support of this application, the applicant performed an *in-vitro* drug release test (IVRT). The test was performed according to the principles of the above-mentioned guideline; however, it was noticed that the information provided about the method was not sufficient in relation to the experimental conditions, amount of sample and achievement of sink condition. In addition, the validation of the IVRT was not discussed with respect to intermediate precision, robustness and discriminatory power.

The applicant justified not performing intermediate precision and robustness studies as this test is not intended for routine QC testing and has been performed only once. Since the discriminatory power was not demonstrated, the results of the IVRT study could be considered only as supportive. However, the results confirmed that no significant difference between the test and reference product could be observed in IVRT.

Overall summary of the scientific evaluation by the CHMP

Three main issues were raised in the CHMP referral procedure, which pertained to 1) *In vitro* equivalence between the applied product and the reference product for the parameter viscosity was not shown with an adequate statistical methodology referring to the *Reflection paper on the statistical methodology for the comparative assessment of quality attributes in drug development*; 2) concern about the representativeness of the batches used to evaluate the parameter viscosity; 3) unacceptability of *post-hoc* justifications of the clinical irrelevance of viscosity.

With regard to the first and second points, an additional statistical comparison on viscosity was conducted by combining the available stability data on the dynamic viscosity of the test product with the viscosity data of test and reference product submitted for the justification of the biowaiver, in order to increase the sample size and to obtain samples from batches with similar age.

Considering the data available and the additional calculations performed, the CHMP concluded that the similarity of viscosity of the test and reference products was established considering all number of batches available. Therefore, overall, extended pharmaceutical equivalence was considered demonstrated.

Concerning the third point, the CHMP also acknowledges that viscosity might not be the factor limiting the release of timolol, and it is known from the literature (Zhu et al., 2008) that the viscosity of the finished product has minimal impact on the absorption of timolol *in vivo*. Nonetheless, as viscosity is considered a relevant quality attribute, a demonstration of similarity would be expected.

In conclusion, the CHMP considers that the extended pharmaceutical equivalence has been demonstrated, including *vis-à-vis* viscosity, and in turn, the therapeutic equivalence of Gelisia and associated names to the reference medicinal product is established. Therefore, CHMP considers the benefit-risk balance of Gelisia and associated names favourable.

Grounds for the CHMP opinion

Whereas,

- The Committee considered the referral under Article 29(4) of Directive 2001/83/EC.
- The Committee considered the totality of the data available in relation to the objections raised as a potential serious risk to public health on demonstration of equivalence, specifically on the quality parameter viscosity.
- The Committee considered that the data available established the therapeutic equivalence of Gelisia and associated names to the reference medicinal product based on a demonstration of extended pharmaceutical equivalence.

The Committee, as a consequence, considers that the benefit-risk balance of Gelisia and associated names is favourable and therefore recommends granting the marketing authorisation(s) for the medicinal products referred to in Annex I of the CHMP opinion. The product information remains as per the final version achieved during the Coordination group procedure, as mentioned in Annex III of the CHMP opinion.