Decision by the Medicines Evaluation Board (hereinafter: the MEB) regarding the objection by Alcon Laboratories (UK) Ltd. in Hertfordshire (UK), represented by C. Schoonderbeek, solicitor in Amsterdam (hereinafter: Alcon) against the decision based on the Medicines Act (hereinafter: the Medicines Act) by the MEB on 24 February 2015 to grant a marketing authorisation to the company Teva Nederland B.V. in Haarlem (hereinafter: TEVA) for the medicinal product **Brinzolamide Teva 10 mg/mL, eye drops, suspension (RVG 112007),** hereinafter: Brinzolamide Teva.

I. Course of the procedure

On 26 April 2012, TEVA applied for a first admission for the medicinal product Brinzolamide Teva. The application was submitted simultaneously in various member states of the European Union according to a decentralised procedure. This is a so-called hybrid application, as defined in article 10(3) Directive 2001/83/EC. The Netherlands is the Reference Member State (RMS). The other concerned member states (CMS) are: Iceland, Finland, Estonia, Latvia, Lithuania, Poland, Romania, Italy. Brinzolamide Teva contains the active ingredient brinzolamide, a carbonic anhydrase inhibitor.

Brinzolamide Teva eye drops are used in the treatment of elevated intraocular pressure (glaucoma) to prevent loss of visual acuity.

Receipt of the application was confirmed on 1 May 2012.

The application was deemed incomplete and a decision of preliminary rejection for processing was announced on 17 May 2012.

Once TEVA dealt with this error, the application was accepted for processing on 18 July 2012.

In consultation with the concerned member states, the RMS drafts an assessment report (the Preliminary Assessment Report, abbreviated to D70 PrAR). This assessment reveals that an application was submitted based on essential similarity, comparative testing and a bio-waiver. However, referring to the *Note for Guidance on the clinical requirements for locally applied, locally acting products containing known constituents,* clinical data are required to demonstrate therapeutic equivalence. For that reason, the bio-waiver cannot be accepted. There is a lack of clinical data. TEVA is granted the opportunity to resolve this omission.

The application was postponed (Clock Stop) until 6 November 2014, to give TEVA the opportunity to perform a clinical study and submit the results of that study. TEVA submitted the results of the clinical study to the RMS on 31 July 2014, 3 August 2014 and 6 November 2014. The RMS announced to TEVA and the concerned member states that the processing period for the procedure has resumed, from 6 November 2014 (Re-start).

The RMS formulated a Draft Assessment Report (abbreviated to D120 DAR), which was submitted to the concerned member states and TEVA for comments on 24 November 2014.

Once the reactions from the concerned member states and TEVA had been received, the RMS formulated the Assessment Report (abbreviated to D180 AR). The RMS sent this report to all the concerned member states, asking them to indicate whether they can agree with the D180 AR.

Following receipt of the reactions, it was apparent that the concerned member states agree with the assessment. The RMS concluded the procedure on 18 February 2015.

TEVA was informed about the start of the national phase on 18 February 2015. TEVA still needed to submit a few documents: good Dutch translations of the final product information (SmPC, package leaflet and flat labelling texts), mock-ups and also a completed and signed Braille declaration and a completed and signed Technical declaration of legibility.

Following receipt and approval of these documents, the MEB sent the marketing authorisation and the approved summary of the product characteristics (SmPC) to TEVA on 2 March 2015.

Alcon – not the holder of the marketing authorisation – objected to the granting of the marketing authorisation for Brinzolamide Teva. Alcon is the holder of a marketing authorisation that was granted via the centralised procedure. This pertains to the medicinal product AZOPT, registration number EMEA/H/C/00267, for which the first marketing authorisation was granted by the European Commission on 9 March 2000. The active ingredient of this medicinal product is brinzolamide. The area of application corresponds to that of Brinzolamide Teva.

The public assessment report (PAR) for Brinzolamide Teva was published on the MEB website on 25 May 2015 and was also sent to the parties involved.

II. Admissibility

The marketing authorisation for Brinzolamide Teva (RVG 112007) was sent to TEVA on 15 March 2015. Registration in Government Gazette 2015, No. 11652 was announced on 1 May 2015. The MEB lists the date of awarding the marketing authorisation as 24 February 2015 on its website. Assuming that publication in the Government Gazette counts as the announcement of the decision to admit Brinzolamide Teva, parties had until Monday 8 June 2015 to submit an objection. Alcon submitted an objection on 31 March 2015. The objection was submitted within six weeks after the assumed announcement of the decision. The objection also meets the requirements set by the General administrative law act (Awb), making the objection admissible.

III. Legal framework

The marketing of medicinal products in the European Union has been completely harmonised. There are two “community legal codes” that apply to the marketing of medicinal products: Directive 2001/83/EC and Regulation (EC) 726/2004.

Directive 2001/83/EC assigns a number of tasks to the “competent authority” of a Member State. Primarily, this relates to the following tasks:

- the granting, suspension and revocation of marketing authorisations for medicinal products;
- the categorisation of medicinal products (legal status of supply):
- the pharmacovigilance.

The MEB is the “competent authority” in the Netherlands. Pursuant to article 9, paragraph one, of the Medicines Act, tasks assigned to the MEB include making decisions relating to applications for marketing authorisations for medicinal products for human use.

The provisions under and pursuant to the Medicines Act form the implementation of the stipulations in Directive 2001/83/EC (OJ EC. 2001, L 311) (hereinafter referred to as: the directive).

It is prohibited to market a medicinal product without a marketing authorisation from the European Commission or the MEB. This is stipulated in article 40, paragraph one, of the Medicines Act for national marketing authorisations and article 6 (1) of the directive for marketing authorisations that are valid in the European Union. The Regulation Medicines Act describes the application procedures of the MEB and the requirements that apply.

Based on article 26 (1) and (2) of the Directive (and article 45, paragraph one, of the Medicines Act), a marketing authorisation will not be granted if verification of the data and documents referred to in article 8 and articles 10 through 10.4 reveals that:

- the risk-benefit ratio is unfavourable;
- the therapeutic effect of the medicinal product has not been demonstrated sufficiently by the applicant;
- the medicinal product does not possess the qualitative and quantitative composition stated; and
- the documents or data submitted to support the application do not correspond to article 8 and articles 10 through 10.4.

There are four options for awarding a marketing authorisation:

- Following submission of an application to the European agency in London (EMA), a marketing authorisation that is valid for the European Union is granted via the *centralised procedure.* This procedure is compulsory for certain medicinal products based on biotechnology and for medicinal products that contain a new active ingredient intended for the treatment of AIDS, cancer, neurodegenerative conditions or diabetes. The procedure can also be followed on a voluntary basis for other innovative medicinal products. The marketing authorisation via the centralised procedure is granted by the European Commission based on Regulation (EC) No. 726/2004 (OJ EC 2004, L 136).
- The *mutual recognition procedure (MRP)* compels member states - at the request of the marketing authorisation holder, to adopt the marketing authorisation granted by another member state for a medicinal product (article 28 onwards of directive 2001/83 and article 44, paragraph three, of the Medicines Act read in conjunction with article 3.4 and article 3.5 of the Regulation Medicines Act). If the second member state has strong objections to this - due to a possible severe risk to public health - an arbitration procedure must be instituted with the *Committee for Human Medicinal Products* (CHMP).
- The *decentralised procedure (DCP)* is used to submit applications for a marketing authorisation in several member states for a medicinal product for which the Union has not yet granted a marketing authorisation. An application for a marketing authorisation in the Netherlands is submitted to the MEB. The assessment of these applications is performed by a member state appointed by the applicant, the Reference Member State (RMS), in close consultation with the other concerned member states (CMS) where an application has been submitted. Once the assessment report has been synchronised between the RMS and the CMS and the RMS has concluded that there is a consensus on the assessment report, the concerned member states will make a decision on the application separately, within thirty days, in accordance with the purport of the assessment report. This procedure

results in the granting of national marketing authorisations in the concerned member states (RMS and CMS) or the refusal to award a marketing authorisation. Refer to article 3.2 onwards of the Regulation Medicines Act and article 28 onwards of the directive.

- The *national procedure* is used to apply for and grant a marketing authorisation in a single Member State. A request for a marketing authorisation for the Netherlands is submitted to and processed by the MEB. The MEB assesses the application and decides whether to award the marketing authorisation or not.

A Notice to applicants (NTA) has been drafted by the European Commission[1] to act as a guidance for the processing of an application, the preparation of the application dossier and the explanation that must be given to the stipulations in the directive and regulation.
The applicant adds data and documents about the medicinal product to the application for the marketing authorisation therefor. The information that must be submitted is described in article 8, paragraph three, of the directive (c.f. article 3.7 of the Regulation Medicines Act), including the results of tests relating to physical chemical properties, pharmacology, toxicology, and clinical studies. Each application dossier has the same composition. The structure is always the same:

Module 1: administrative data, including the summary of product characteristics, the package leaflet and the labelling text.
Module 2: summaries of the chemical-pharmaceutical, pharmacological-toxicological and clinical-pharmacological dossiers.
Module 3: chemical-pharmaceutical data, i.e. all data about the composition and preparation as well as quality control of a medicinal product.
Module 4: pharmacological-toxicological data. This is all the information about a medicinal product's toxicity and mechanism of action obtained from its use in animals.
Module 5: clinical-pharmacological data. The data on the efficacy and safety of the product in humans appear in this part of the dossier.

If an application has been submitted, the competent authority will check according to article 19 of Directive 2001/83 whether the dossier corresponds to article 8 and article 10 through 10.4 of Directive 2001/83 and the authority will investigate whether the conditions for awarding of the marketing authorisation have been met.

In certain cases, the applicant of a marketing authorisation is not obliged to submit the results of pre-clinical and clinical trials. For example, article 10 of Directive 2001/83 stipulates that for applications for a marketing authorisation for generic medicinal products, notwithstanding article 8, paragraph three, under i), the applicant is not required to submit the results of pre-clinical and clinical trials if the applicant can demonstrate that the medicinal product is a generic of a reference medicinal product for which a license has been granted in accordance with article 6 for at least 8 years in a member state or the European Union (dossier protection). However, generic medicinal products of this kind may not be placed on the market within ten years following the granting of the original marketing authorisation to the reference medicinal product (market exclusivity).

Article 10(3) of Directive 2001/83 (and article 42, paragraph 6 of the Medicines Act) stipulates that notwithstanding article 8, section 3, under i), regarding pre-clinical and clinical data and documents, it is sufficient for the applicant to submit the pre-clinical or clinical trials used to cover the discrepancies with regard to the data submitted for the relevant reference medicinal product.

The applicant submits the required data and documents with the application. The applicant also asks the RMS to draft a report regarding the assessment of the medicinal product, the

[1] http://ec.europa.eu/health/documents/eudralex/vol-2/index_en.htm

design of the summary of product characteristics, the design of the labelling and the package leaflet, refer to article 3.3, first paragraph, of the Regulation Medicines Act and article 28, third paragraph, of the Directive. Together with the other concerned member states (CMS), the RMS assesses the submitted data and documents. The applicant is involved in this assessment to answer questions posed by the RMS and CMS. The RMS sends the preliminary assessment report (hereinafter: PrAR) and the abovementioned documents and particulars to all concerned member states (CMS). The CMS then test the PrAR. The RMS checks for general consensus. If consensus is achieved, the RMS will conclude the procedure and inform the applicant of this, see article 3.3, third paragraph, of the Regulation Medicines Act and article 28, fourth paragraph, of the directive. Within 30 days of this consensus, the concerned member states will award a marketing authorisation in accordance with the assessment report, see article 3.3, second paragraph of the Regulation Medicines Act and article 28, fifth paragraph of the directive.

Manual

A manual has been drafted for the assessment of locally administered and locally acting medicinal products that contain a known component, the “Note for guidance on the Clinical requirements for locally acting products containing known constituents”, EMA, CPMP/EWP/239/95 final, November 1995. This manual states which details are required (part iIC3, IV) for locally administered, locally acting medicinal products with a known active ingredient. The reason for this manual is that a change in the formulation of these medicinal products can influence the efficacy and safety of these medicinal products. The manual states that a complete dossier is not required. It is sufficient to refer to the reference medicinal product for which a marketing authorisation has already been granted based on a complete dossier. In order to demonstrate the clinical equivalence to the reference medicinal product, the applicant must submit the results of clinical studies:

Abridged applications
As is the case for systemically acting products, it is necessary to show for locally acting products that the product to be approved (either a generic or a reformulated product) is therapeutically equivalent to the product already approved i.e. that both products are “equivalent" with regard to efficacy and safety, so that data generated for the "innovator" product (i.e. a product for which the marketing authorisation has been obtained on the basis of a dossier with full documentation) apply also to the other product.

In order to demonstrate therapeutic equivalence clinical trials are in principle necessary, [….]

The granted marketing authorisation

Brinzolamide Teva and AZOPT are suspensions, locally acting medicinal products. As Brinzolamide contains a different surfactant to AZOPT, one cannot rule out that absorption and distribution into and out of the eye will differ. The bio-availability could differ.

TEVA claims that Brinzolamide Teva is therapeutically equivalent to AZOPT. The main point in this procedure is therapeutic equivalence. TEVA has submitted the results of a comparative study to prove this. This study compared the efficacy and safety of Brinzolamide Teva to AZOPT. The study was primarily set up to demonstrate that the efficacy of Brinzolamide Teva is no worse than that of AZOPT; in other words, the study into the effectiveness was set up in the form of a so-called “non-inferiority study”. The results of the study also demonstrate that the efficacy and safety of Brinzolamide Teva are comparable to those of AZOPT.

Because it has become apparent that there is a positive risk-benefit analysis, the medicinal product has the stated therapeutic effect, the medicinal product has the qualitative and quantitative composition as stated and also otherwise meets the chemical-pharmaceutical quality requirements and because the data or documents submitted to support the application are in accordance with the set requirements, the MEB, pursuant to article 45, paragraph one, of the Medicines Act, with due consideration of the assessment report (AR) adopted in consultation with the concerned member states, has granted the marketing authorisation.

IV. Hearing

A hearing took place on Friday 19 June 2015. Alcon and TEVA were able to clarify their standpoints before the (internal) Objections Committee of the MEB and answer the committee's questions. The report has been included with this decision.

V. Objection

Alcon believes that the marketing authorisation should not have been granted to TEVA. According to Alcon, the data submitted by TEVA are not in accordance with article 10(3) of Directive 2001/83 EC.
Alcon pointed out that the data and documents do not meet the scientific assessment guidelines used for the assessment of locally applied, locally acting medicinal products.

- With regard to the formulation, Alcon considers the particle size, viscosity and appearance (the uniformity of the suspension) as critical characteristics for the efficacy and safety of the medicinal product in question. Alcon is of the opinion that the use of a surfactant in the medicinal product by TEVA other than the one used in the reference medicinal product AZOPT can change the biological availability of the active ingredient brinzolamide, by affecting the three abovementioned characteristics. The medicinal product by TEVA contains the surfactant ingredient poloxamer 407, whilst AZOPT contains the surfactant ingredient tyloxapol.

- Alcon has concerns about the "data package" used by TEVA in the context of article 10(3). More specifically, Alcon is of the opinion that the bridging study that was submitted, which Alcon assumes is the study of Pharmathen with study number EudraCT 2013-001793-21), is not robust enough - in combination with the extrapolation of pre-clinical and clinical data from the dossier of the reference medicinal product AZOPT - to draw the necessary conclusions that the safety and efficacy of the medicinal product in question by TEVA is comparable to AZOPT.

  According to Alcon, this lack of robustness can be deduced from certain specific aspects of the protocol for the abovementioned Pharmathen study. According to Alcon this can be summarised as follows:

  - with regard to the chosen study design: Alcon is of the opinion that the chosen so-called "non-inferiority" study designdesign is not suitable for demonstrating therapeutic equivalence of either efficacy or safety in comparison to the reference medicinal product
  - with regard to the study: according to Alcon, the intra-ocular pressure ("IOP") was only measured by means of a single measurement during a single study visit. Furthermore, the peak efficacy and the trough efficacy were not determined as primary endpoints for the clinical test.

- with regard to the study: the sample size in relation to the so-called “non-inferiority margin” of 1.5 mmHg. Alcon is of the opinion that this margin is not suitable for demonstrating “non-inferiority”. Alcon also wishes to point to the scientific advice by the EMA for the medicinal product Simbrinza, in which more stringent criteria (i.e. smaller non-inferiority margin) were maintained.

As a supplement to the objection, Alcon also raised the point during the hearing that one can deduce from the public assessment report (PAR) that the medicinal product by TEVA is numerically more effective than AZOPT. Therefore, Alcon does not rule out the possibility that the medicinal product by TEVA has a better efficacy than AZOPT. The higher frequency of adverse events for the medicinal product by TEVA could be associated with this, according to Alcon.

Alcon emphasised once more that the efficacy of Brinzolamide Teva is no worse, i.e. non-inferiority has been demonstrated, but that this is not the same as therapeutic equivalence. According to Alcon, extrapolation of the data for the reference medicinal product can only be performed safely if therapeutic equivalence has been demonstrated.

VI. The standpoint of the marketing authorisation holder

TEVA does not share Alcon’s standpoint. According to TEVA, the correct application and the safety of poloxamer 470 have been substantiated by the data submitted with the application. There was also no difference in viscosity as a result of the substitution of tyloxapol by poloxamer 470. Furthermore, both formulations meet the same specification for particle size. The clinical study, which demonstrated non-inferiority, confirmed that the different surfactants do not alter the efficacy of brinzolamide, according to TEVA.

TEVA noted the following with regard to the study of Pharmathen that was used. The study is sufficiently robust to demonstrate therapeutic equivalence between the medicinal product by TEVA and AZOPT. For example, contrary to the single measurement stated by Alcon, three measurements were performed. The measurement point at 12:00 noon can also be used to assess the peak efficacy. TEVA cited a literature reference to support this. According to TEVA, the study duration of 12 weeks is standard for such studies, with TEVA citing four literature references to support this. According to TEVA, the non-inferiority study design is suitable for the assessment of therapeutic equivalence. TEVA wishes to point out that such a study design is recommended by the (French) medicines agency ANSM. TEVA also noted that the non-inferiority study design is also in line with the scientific advice as provided by the European Medicines Agency EMA to Alcon, for their medicinal product Simbrinza. Finally, the majority of individual measurement values for the medicinal product by TEVA were within the 1 mmHg margin based on 95 % confidence intervals, the blood concentrations of brinzolamide at the end of the study were comparable for the medicinal product by TEVA and AZOPT, both formulations exhibited comparable “responder rates” and safety profiles and the subjective scores assigned by the investigators were comparable for both formulations. TEVA is of the opinion that Alcon has not submitted any substantiated arguments to support their objection. Considering the abovementioned facts, TEVA is of the opinion that the objection by Alcon should be rejected.

VII. Discussion of the objections

The objections raised on the one hand against the bridging study (non-inferiority study) used and the formulation on the other hand will be dealt with separately below.

I With regard to the bridging study

I A Objection regarding the bridging study, namely that a "non-inferiority" study design as such is not suitable for demonstrating therapeutic equivalence of either efficacy or safety in comparison to the reference medicinal product

The MEB cannot follow Alcon's complaint that the chosen study design cannot serve to demonstrate therapeutic equivalence and that - contrary to article 10 (3) of Directive 2001/83/EC - therapeutic equivalence with the reference product has only been demonstrated by TEVA using the results of a non-inferiority study.

Firstly, there is no rule of law, (scientific) guideline or practice that stipulates that both a clinically relevant lesser efficacy and a clinically relevant improved efficacy must be ruled out for demonstrating therapeutic equivalence. The same applies to safety.

Alcon was unable to demonstrate such a rule of law, (scientific) guideline or relevance practice. The practical situation indicates that it must be stipulated for each disease which data are required to demonstrate the therapeutic equivalence. In the procedure in question, the Reference Member State (the Netherlands) and the other concerned member states agree that a non-inferiority study, in combination with medical-pharmaceutical considerations as applicable for the medicinal product in question (refer below), is acceptable.

It is important here to note the following with regard to therapeutic equivalence. If the difference in effect between two products falls within a certain upper and lower limit, then the two products are deemed to be therapeutically equivalent. These limits are called "therapeutic equivalence margins". If the effect falls within these margins, then this is a case of therapeutic equivalence. In other words, any difference in effect between two products within these margins is not clinically relevant. The selection of the cut-off values for the upper and lower limit is ideally based on clinical considerations. If no generally accepted clinical equivalence margin is available, statistical considerations can sometimes be used (for example, 50 % of the difference between the reference medicinal product and a placebo). The upper and lower limits for equivalence are not necessarily symmetrical. Acceptance of a "non-inferiority" study design indicates that the upper limit (or the upper limit of the 95% confidence interval) is deemed irrelevant, i.e.: it does not have any clinically relevant consequences in that case. The MEB is of the opinion that in the case in question, a cut-off point for the upper limit with regard to the study into the *efficacy* is indeed not important. The reason for this is that, provided the reduction in intraocular pressure falls within the normal range of values and does not result in problems, any reduction is relevant.
In the event - not applicable in this case - that a much stronger efficacy is revealed, such that this could be disadvantageous, the MEB notes the following: such a situation no longer relates to *efficacy,* but is instead a matter of *safety.* With regard to the safety in this case, the values as observed in the non-inferiority study do not pose a safety risk (also refer below).

As far as actually demonstrating the efficacy, the MEB refers to the discussion below under points I B and I C.

As far as the safety is concerned, the MEB rules as follows. The systemic biological availability of Brinzolamide Teva was no higher than that of AZOPT. Adverse events were experienced by 28.4% of the patients undergoing treatment with Brinzolamide Teva, compared to 14.8% of the patients treated with AZOPT. However, the incidence of treatment-

related adverse events was comparable, namely 11.4% for Brinzolamide Teva compared to 8.6% for AZOPT. No further action was required for 93.2% of the patients with adverse events caused by Brinzolamide Teva and in 76.5% of the patients with adverse events caused by AZOPT. At the end of the study, all patients also reported good to excellent tolerability with regard to the treatment received during the study.

The MEB deems that the abovementioned findings regarding the safety are adequate to draft a safety profile for Brinzolamide Teva. The study design that was used is suitable for this purpose. The safety profiles of Brinzolamide Teva on the one hand and AZOPT on the other hand are deemed comparable by the MEB. The point raised by Alcon about (more) adverse events with Brinzolamide Teva (whether related to a stronger efficacy or not) is hereby rejected.

The MEB has concluded that the "non-inferiority" study in the case in question is suitable for demonstrating therapeutic equivalence for both efficacy and safety, in comparison to the reference medicinal product.

This section of the objection is unfounded.

I B Objection regarding the bridging study, namely that the intra-ocular pressure ("IOP") was only measured by means of a single measurement during a single study visit. And that the peak efficacy and the trough efficacy were not determined as primary endpoints for the clinical test

The MEB is of the opinion that the postulation by Alcon, namely that the "IOP" was only measured by means of a single measurement during a single study visit, is incorrect. The "IOP" was measured twice in each eye and these measurements were performed at 8 o'clock in the morning, 12 noon and 4 o'clock in the afternoon. These measurements were performed at the start of the study ("baseline") and at 2, 6 and 12 weeks of treatment. If the difference between the two measurements performed on the same eye at a specific time point was greater than 4 mmHg, then the measurement was performed a third time. Please refer to the table below:

IOP target eye at different time points at baseline and mean IOP reductions during follow-up (full analysis set)

	Baseline		IOP reduction compared to baseline					
			2 weeks of treatment		6 weeks of treatment		12 weeks of treatment	
	Test (n=88)	Reference (n=81)	Test (n=86)	Reference (n=80)	Test (n=85)	Reference (n=75)	Test (n=83)	Reference (n=71)
8:00 a.m.	25.5 ± 2.2	25.7 ± 2.2	6.8 ± 3.3	6.4 ± 3.8	7.6 ± 3.6	7.3 ± 4.1	7.9 ± 3.6	7.4 ± 4
Test - reference			0.43 (-0.90, 1.75)		0.36 (-1.12, 1.83)		0.45 (-0.75, 1.60)	
12:00 p.m.	25.4 ± 2.0	25.5 ± 2.0	7.4 ± 3.1	7.2 ± 3.1	8.2 ± 3	8.0 ± 3.1	8.2 ± 3	7.9 ± 3.3
Test - reference			0.23 (-0.93, 1.40)		0.20 (-0.95, 1.36)		0.36 (-0.87, 1.60)	
4:00 p.m.	25.2 ± 1.9	25.4 ± 2.0	7.2 ± 3.1	7 ± 3.8	7.9 ± 3.3	8.1 ± 3.4	8.2 ± 3.3	8.0 ± 3.5
Test - reference			0.17 (-1.12, 1.47)		-0.17 (-1.44, 1.11)		0.13 (-1.19, 1.46)	

This section of the objection is unfounded.

I C Objection regarding the bridging study, namely that the sample size in relation to the "non-inferiority margin" of 1.5 mmHg is not suitable for demonstrating "non-inferiority".

The MEB wishes to point out that a "non-inferiority margin" of 1.5 mmHg was also used in the comparative efficacy studies that resulted in a "centralised" granting of a marketing authorisation (by the European Commission via the European Medicines Agency [EMA]) for brinzolamide/timolol eye drops (license number EU/1/08/482/001-002), for glaucoma and ocular hypertension.
Based on the results, the sample size turns out to be sufficient, because the outcomes fall within the non-inferiority margin.

Alcon also stated in the objection that the CHMP (previously CPMP) demanded a 95% confidence interval within 1.0 mmHg, with regard to Alcon's proposed non-inferiority study to compare the efficacy of brinzolamide/brimonide eye drops (combination product) to the combined administration of brinzolamide eye drops and brimonide eye drops (both as mono-preparations). However, a non-inferiority margin of 1.5 mmHg was applied in the non-inferiority study that was subsequently performed. Based partly on the results of the aforementioned study, Alcon was subsequently granted a marketing authorisation (again this was "centralised") for its medicinal product Simbrinza containing brinzolamide/brimonide (license number EU/1/14/933/001-002).

The two abovementioned examples demonstrate that a non-inferiority margin of 1.5 mmHg has been accepted for “centralised” application procedures for marketing authorisations of comparable medicinal products. The fact that these were “centralised” procedures is particularly important, because the medicines agencies of all member states of the European Union (supplemented by those of the European Economic Area) are involved in such procedures. The non-inferiority margin of 1.5 mmHg that was used can therefore be considered to be widely accepted within Europe. Therefore, the MEB concludes that a non-inferiority margin of 1.5 mmHg is acceptable for the Brinzolamide TEVA product in question, for the comparison of the treatment using the aforementioned medicinal product to the treatment with AZOPT.

This section of the objection is unfounded.

II With regard to the formulation of Brinzolamide Teva

Objection regarding the difference in particle size, viscosity and appearance, possibly due to the difference in surfactant and the biological availability or efficacy and safety of the TEVA medicinal product that could change as a result

The MEB is of the opinion that the particle size of the active ingredient in the medicinal product, the viscosity and the “uniformity of dose” during shelf-life are indeed important parameters. A difference in these parameters can affect the performance of the medicinal product in the patient (also described as “*in vivo*”). However, the MEB concluded during its assessment that the aforementioned parameters are comparable for both medicinal products [the MEB is unable to state further details about this, because this involves confidential information from Module III of the application dossier]. In addition, the following also applies: Now that we can conclude from the bridging study that Brinzolamide Teva and AZOPT are therapeutically equivalent, this means that even *if* there is any effect caused by potential differences in the abovementioned physical-chemical parameters, then this effect would not be clinically relevant in nature.

This section of the objection is unfounded.

In conclusion, the MEB has decided that the data submitted by TEVA, such as the results about the efficacy and adverse events in the “non-inferiority” study and the medical-pharmaceutical particulars, demonstrate therapeutic equivalence.

The suggested possible differences in physical-chemical parameters as a result of the use of a different surfactant have no clinically relevant therapeutic consequences.

The MEB has therefore decided that all the points of objection raised by Alcon are unfounded. Brinzolamide Teva can be considered therapeutically equivalent to AZOPT. The legal requirements as stipulated in article 10(3) of Directive 2001/83/EC have been met. There is no reason for revision of the marketing authorisation granted for Brinzolamide Teva 10 mg/mL, eye drops, suspension (RVG 112007).

The MEB deems the objections unfounded.

VIII. Decisions on objection

The MEB upholds the contested decision.

Yours sincerely,

Deputy. Chair	Second Secretary
Dr B.J. van Zwieten-Boot	F.W. Weijers