

Annex II

Scientific conclusions and grounds for positive opinion

Scientific conclusions

Overall summary of the scientific evaluation of Tobramycin VVB and associated names (see Annex I)

Introduction

UAB "VVB" submitted on 2 May 2014 a marketing authorisation application for Tobramycin VVB 300 mg/5 ml nebuliser solution (hereinafter "Tobramycin VVB") as an abridged application in accordance with Article 10(3) of Directive 2001/83/EC, referring to Nebcin solution for injection (PL 13621/0059) for the purpose of the data exclusivity, and to TOBI 300 mg/5 ml nebuliser solution (hereinafter "TOBI"; PL 00101/0935) for the purpose of the SmPC/clinical comparator.

The application was submitted to the reference Member State (RMS): Lithuania, and the concerned Member States (CMS): Bulgaria, Estonia, Hungary, Latvia, Poland and Romania.

The Decentralised procedure LT/H/0112/001/DC started on 24 September 2014.

On day 210, major issues on safety and efficacy were raised which remained unsolved; hence the procedure was referred to the CMDh, under Article 29, paragraph 1 of Directive 2001/83/EC by Lithuania on 24 July 2015. The CMDh 60 day procedure was initiated on 03 August 2015.

Day 60 of the CMDh procedure was on 01 October 2015 and since the Member States failed to reach an agreement, the procedure was referred to the CHMP in accordance with Article 29(4) of Directive 2001/83/EC.

Notification of a referral for arbitration, under Article 29(4) of Directive 2001/83/EC, to the CHMP was made by the Reference Member State Lithuania on 14 October 2015 based on concerns raised by the Concerned Member State Poland. Poland considered that the clinical superiority of Tobramycin VVB vs. the orphan-designated medicinal product TOBI Podhaler 28 mg inhalation powder (hereinafter "TOBI Podhaler") was not demonstrated, therefore derogation as per Article 8(3) of Regulation (EC) No 141/2000 was not fulfilled and a marketing authorisation as proposed by the RMS could not be granted.

The proposed medicinal product contains the same qualitative and quantitative composition and the same pharmaceutical form as TOBI 300mg/5 ml nebuliser solution, therefore clinical studies for demonstrating therapeutic equivalence can be waived in accordance with the scientific guidelines (EMA/CHMP/QWP/49313/2005 Corr. and CPMP/EWP/4151/00 Rev.1). RMS and CMSs agreed that Tobramycin VVB is comparable to TOBI 300 mg/5 ml nebuliser solution and therefore available efficacy and safety data for TOBI can be extrapolated to Tobramycin VVB.

Tobramycin is an aminoglycoside antibiotic. The proposed therapeutic indication for Tobramycin VVB 300 mg/5 ml nebuliser solution is the same as for TOBI Podhaler (EU/1/10/652, Tobramycin, inhalation powder) and identical to that of TOBI 300 mg/5ml nebuliser solution: *"suppressive therapy of chronic pulmonary infection due to Pseudomonas aeruginosa in adults and children aged 6 years and older with cystic fibrosis."*

The medicinal product TOBI Podhaler 28 mg inhalation powder is covered by an orphan designation in the condition *treatment of P. aeruginosa lung infection in cystic fibrosis* (orphan designation EU/3/03/140).

During the assessment of the marketing authorisation application for Tobramycin VVB and in the context of the abovementioned Article, a similarity assessment was performed concluding that Tobramycin VVB was similar to Tobi Podhaler. A Marketing Authorisation for Tobramycin VVB can therefore only be granted with the currently proposed indication if at least one of the derogation grounds set out in Article 8(3) of Regulation (EC) No 141/2000 is fulfilled.

The applicant of Tobramycin VVB has applied for a derogation from the market exclusivity of TOBI Podhaler 28 mg inhalation powder claiming that Tobramycin VVB 300 mg/5 ml nebuliser solution is clinically superior to the authorised orphan medicinal product (TOBI Podhaler 28 mg inhalation powder) in terms of providing greater safety in a substantial portion of the target population.

The EAGER study

The Applicant's claim for clinical superiority based on greater safety (tolerability) of tobramycin nebulizer solution (**TIS**) over tobramycin inhalation powder (**TIP**) in a substantial portion of the target population relies on clinical data generated by the open-label EAGER study¹ and its post hoc analyses².

This study evaluated the safety, efficacy and convenience of TIP vs TIS in CF patients aged 6 years and above with chronic P. aeruginosa infection. Safety was the primary endpoint of this study, nevertheless it was powered for efficacy (secondary endpoint) and therefore demonstrated non-inferiority in terms of efficacy only.

In the EAGER trial, the overall discontinuation rate was higher with TIP (26.9%) than TIS (18.2%). The most common reasons for discontinuation were adverse events (AEs) – 40 (13.0%) of TIP as compared to 17 (8.1%) TIS-treated patients.

With regards to the claim of clinical superiority on the ground of greater safety in a substantial portion of the target population, the applicant was requested by CHMP during the procedure:

- To substantiate the relevance of difference in the incidence of adverse events (e.g. cough, discontinuation, etc.) between Tobramycin VVB and the orphan-designated medicinal product TOBI Podhaler based on own and/or published data.
- In the light of the above, to further justify why the applicant considers Tobramycin VVB clinically superior in a substantial portion of the target population to the orphan-designated medicinal product TOBI Podhaler.

Difference in the incidence of adverse events

A higher percentage of TIP- than TIS-treated patients reported AEs (90.3% versus 84.2%, $p < 0.05$). Cough (not including productive cough) was the most frequently reported AE throughout the entire study period (TIP: 48.4%; TIS: 31.1%) despite being present in the same proportion of patients (42%) in both groups as a baseline symptom. The frequency of severe cough events was also higher in TIP group (2.6% versus 1.9%). In addition, 3.9% (12/308) of TIP-treated patients discontinued due to cough vs 1% (2/209) of TIS-treated patients. Cough events were suspected by the investigator as being related to study drug in 25.3% and 4.3% of patients in the TIP and TIS group, respectively.

Other treatment-related AEs more commonly reported in the TIP group were dysphonia (13.6% vs 3.8%) and dysgeusia (3.9% vs 0.5%). Results of audiology performed in a subpopulation of patients (TIP: 78 [25.3%]; TIS: 45 [21.5%]) revealed that a higher proportion of TIP-treated patients (25.6%; 20/78) than TIS-treated patients (15.6%; 7/45) experienced a decrease from baseline in any audiology test frequency at any visit.

¹ Konstan MW, Flume PA, Kappler M, Chiron R, Higgins M, Brockhaus F, Zhang J, Angyalosi G, He E, Geller DE (2011). Safety, efficacy and convenience of tobramycin inhalation powder in cystic fibrosis patients: The EAGER trial. *J Cyst Fibros.* 10(1):54-61.

² Geller DE, Nasr SZ, Piggott S, He E, Angyalosi G, Higgins M (2014). Tobramycin inhalation powder in cystic fibrosis patients: response by age group. *Respir Care.* 59(3):388-98.

Post hoc subgroup analyses of EAGER data compared the safety profiles of TIP and TIS in children, adolescents, and adults. The overall discontinuation rates for TIP were 3.6% in the children (≥ 6 to < 13 years), 18.2% in the adolescents (≥ 13 to < 20 years), and 32.7% in the adults (≥ 20 years), while the discontinuation rates with TIS were 16.7% in the children and adolescents, and 18.9% in the adults. Fewer adolescents and adults on TIS discontinued study medication as a result of AEs, compared with those on TIP (9.1% on TIS discontinued vs 17.3% on TIP). Although fewer children receiving TIP discontinued the treatment, the overall number of children in EAGER study was small, and thus no definite conclusion about this subpopulation can be drawn.

Post hoc analysis of AEs profile in different age groups confirmed the results that were originally observed in EAGER study, i.e., any AE and cough, dysphonia and dysgeusia were more frequent among TIP-treated patients across all age groups.

The higher cough rate observed with TOBI Podhaler may be due to a higher powder deposition in the throat in comparison to nebuliser products. The importance of cough as AE for a powder formulation was already acknowledged during the assessment of TOBI Podhaler, and it is recommended that alternative treatment with the nebuliser solution is considered for patients using TOBI Podhaler who experience continued therapy-induced cough.

It is therefore established that there is a portion of the target population who cannot use powder inhalator due to the development of intolerance. For these patients, tobramycin nebuliser solution is an alternative.

The differences in terms of safety (in terms of tolerability) observed in the EAGER trial between the nebuliser solution and the inhalation powder, favouring the nebuliser solution regarding the occurrence of cough and discontinuation of treatment, are relevant and support the claim of greater safety (in terms of tolerability), *as per* article Article 8(3)(c) of Regulation (EC) No 141/2000, of Tobramycin VVB in those patients who develop intolerance to TOBI Podhaler. This is particularly illustrated by the differences in the discontinuation rates due to AEs (13% for the inhalation powder vs. 8% for the nebuliser solution), development of cough as an adverse drug related event (25% for the inhalation powder vs. 4% for the nebuliser solution) and dysphonia rates (13% for the inhalation powder vs. 4% for the nebuliser solution). These observations were replicated in post-hoc analyses of different age groups.

Greater safety in a substantial portion of the target population

Having established that there is a portion of the target population who cannot use powder inhalator due to the development of intolerance and that for these patients the tobramycin nebuliser solution is a safer alternative, in order for a conclusion on clinical superiority to be drawn CHMP needed to assess whether these patients correspond to a substantial portion of the target population.

Considering the data from EAGER study and its post-hoc analyses, the difference in overall discontinuations is nearly 9% and difference in discontinuations due AEs is ~5% in favour of Tobramycin nebuliser solution. The difference is even more pronounced in the adult cystic fibrosis patient population (14% difference in overall discontinuations and 8% - in discontinuations due to AEs). According to the European Cystic Fibrosis Society Patient Registry, 48.0% of cystic fibrosis patients in the 20 European countries presenting data are over 18 years of age³.

Local respiratory intolerability to the dry powder inhalation can manifest itself through symptoms such as cough, and result in discontinuation of treatment. In the EAGER study, cough described as an adverse drug related event was observed in 25% of patients on the inhalation powder vs. 4% of patients on the nebuliser solution. The post hoc subgroup analysis of EAGER trial data confirmed the

³ European Cystic Fibrosis Society (ECFS) Patient registry annual data report 2008-2009 v. 03.2012.

differences in the rates of incidence of cough in all age groups. The smallest difference was observed in the adult population (45% powder inhalation vs 34% nebuliser solution). This is in line with fact that cough is described as a 'very common' adverse reaction in association with TOBI Podhaler, which means that it occurs with a frequency of at least 10%.

When taken together, these elements allow to estimate that at least 10% of the target population may not be able to use TOBI Podhaler due to intolerance. For these patients, the nebuliser solution is a safer alternative (in terms of tolerability) and 10% is considered by CHMP to be a substantial portion of the target population.

Overall, in the context of the claim of clinical superiority based on a greater safety according to Article 8(3)(c) of Regulation (EC) No 141/2000 read in combination with Article 3(3)(d)(2) of Regulation (EC) No 847/2000, CHMP considered that a substantial portion of the target population experiences greater safety (in terms of tolerability) with Tobramycin VVB in terms of the incidence of cough and treatment discontinuation, as compared to TOBI Podhaler.

Therefore the CHMP concluded that the clinical relevance of the abovementioned differences between Tobramycin VVB and TOBI Podhaler demonstrates the clinical superiority of Tobramycin VVB over TOBI Podhaler based on greater safety in a substantial portion of the target population.

During the discussion, CHMP also noted the differences in terms of inhalation time between Tobramycin VVB and Tobi Podhaler. However, CHMP concluded that these differences are not relevant in the context of the claim of clinical superiority based on greater safety as the patients constituting a substantial portion of the target population are intolerant to Tobi Podhaler and cannot use therefore Tobi Podhaler.

Grounds for positive opinion

Whereas:

- The Committee considered the notification of the referral initiated by the Reference Member State Lithuania under Article 29(4) of Directive 2001/83/EC where the Concerned Member State Poland raised objections to the granting of the marketing authorisation;
- The Committee reviewed the responses submitted by the applicant to address the issues raised with regard to the claim for clinical superiority of Tobramycin VVB vs. TOBI Podhaler;
- The Committee was of the view that the data support the claim for clinical superiority of Tobramycin VVB versus TOBI Podhaler based on greater safety in a substantial portion of the target population, as per Article 8(3)(c) of Regulation (EC) No 141/2000 read in combination with Article 3(3)(d)(2) of Regulation (EC) No 847/2000;
- The Committee therefore considered that, in the context of Article 8(3) of Regulation (EC) No 141/2000, clinical superiority of Tobramycin VVB over TOBI Podhaler in a substantial portion of the target population can be established.

The CHMP issued a positive opinion by consensus recommending the granting of the marketing authorisation and of the summary of product characteristics, labelling and package leaflet as per the final versions achieved during the Coordination group procedure as mentioned in Annex III of the CHMP opinion.