20 November 2014
EMA/CHMP/701057/2014 - adopted
Committee for Medicinal Products for Human use (CHMP)

CHMP Type II Group of variations assessment report

Invented name: TOBI Podhaler

International non-proprietary name: TOBRAMYCIN

Procedure No. EMEA/H/C/002155/II/0027/G

Marketing authorisation holder (MAH): Novartis Europharm Ltd

Rapporteur, type of application and status of the report during the procedure	
CHMP Rapporteur:	Johann Lodewijk Hillege
PRAC Rapporteur:	Sabine Straus
This application is in the area of:	Clinical RMP
eCTD sequences related to the procedure:	
☒	The relevant sections of this Assessment Report were endorsed by the PRAC on 6 November 2014

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Assessment Timetable / Steps taken for the assessment

Timetable	Actual dates
Start of procedure:	21 September 2014
CHMP Rapporteur Assessment Report	20 October 2014
PRAC Rapporteur Assessment Report	20 October 2014
Committees comments on PRAC Rapp Advice	24 October 2014
PRAC Meeting, adoption of PRAC Assessment Overview and Advice	6 November 2014
CHMP comments	10 November 2014
Opinion	20 November 2014

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1. Background information on the procedure

1.1. Requested group of variations

Pursuant to Article 7.2 of Commission Regulation (EC) No 1234/2008, Novartis Europharm Ltd submitted to the European Medicines Agency on 5 September 2014 an application for a group of variations.

The following changes were proposed:

Variations requested		**Type**	**Annexes affected**
A.1	A.1 - Administrative change - Change in the name and/or address of the MAH	Type IAin	I, IIIA and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to reflect data from study CTBM100C2401 (in fulfilment of MEA 010). Update of the RMP to reflect the study conclusion.

In addition, update of the product information to reflect the change of address of the MAH.

The requested group of variations proposed amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

1.2. Rationale for the proposed changes

In this variation application the MAH has submitted the clinical study report from study CTBM100C2401, "A single arm, open label, multicentre, Phase IV trial to assess long-term safety of tobramycin inhalation powder (TIP) in patients with Cystic Fibrosis". Study CTBM100C2401 was conducted as a post-authorization measure (PAM) for TOBI Podhaler (MEA 010) with the aim of addressing the need for long-term data. With the submission of this Clinical Study Report this commitment is considered to be fulfilled.

Based on the availability of this long-term data, the MAH proposes to remove the statement "Long-term safety data are not available for TOBI Podhaler" from each of the relevant sections of the Summary of Product Characteristics (SmPC). In addition, the Risk Management Plan (RMP) is proposed to be updated to reflect that long-term safety data are no longer considered to be missing information.

Information on paediatric requirements

The application included an EMA Decision (P/0177/2014) on the agreement of a paediatric investigation plan (PIP).

The PIP P/0177/2014 was completed.

The PDCO issued an opinion on compliance for the PIP P/0177/2014.

2. Overall conclusion and impact on the benefit/risk balance

The newly submitted data on safety provided by the MAH are consistent with the known safety profile and are considered not to change the overall benefit/risk of TOBI Podhaler.

The MAH proposal to remove the statement that long-term data are not available for TOBI Podhaler in sections 4.2, 4.4 and 4.8 of the SmPC and relevant section of the package leaflet is acceptable.

With the submission of the Clinical Study Report study CTBM100C2401, MEA 010 is considered to be fulfilled.

Significance of paediatric studies

The CHMP is of the opinion that study CTBM100C2302, which is contained in the agreed Paediatric Investigation Plan, which is completed, and has been completed after 26 January 2007, is considered as significant (as mentioned in the assessment report of the initial marketing authorisation).

3. Recommendations

Based on the review of the submitted data, this application regarding the following changes:

Variations requested		**Type**	**Annexes affected**
A.1	A.1 - Administrative change - Change in the name and/or address of the MAH	Type IAin	I, IIIA and IIIB
C.I.4	C.I.4 - Change(s) in the SPC, Labelling or PL due to new quality, preclinical, clinical or pharmacovigilance data	Type II	I

Update of sections 4.2, 4.4 and 4.8 of the SmPC in order to reflect data from study CTBM100C2401 (in fulfilment of MEA 010). Update of the RMP to reflect the study conclusion.

In addition, update of the product information to reflect the change of address of the MAH.

☒ is recommended for approval.

The requested group of variations leads to amendments to the Summary of Product Characteristics, Labelling and Package Leaflet and to the Risk Management Plan (RMP).

Furthermore, the CHMP reviewed at the time of initial marketing authorisation application the available paediatric data of studies subject to the agreed Paediatric Investigation Plan P/0177/2014 and the results of these studies are reflected in the Summary of Product Characteristics (SmPC) and, as appropriate, the Package Leaflet.

In accordance with Article 45(3) of Regulation (EC) No 1901/2006, significant studies in the agreed paediatric investigation plan P/0177/2014 have been completed after the entry into force of that Regulation.

4. Scientific discussion

4.1. Introduction

TOBI Podhaler contains the active substance tobramycin, which is an aminoglycoside antibiotic produced by *Streptomyces tenebrarius* that acts primarily by disrupting protein synthesis leading to altered cell membrane permeability, progressive disruption of the cell envelope and eventual cell death. It is indicated for the suppressive therapy of chronic pulmonary infection due to *Pseudomonas aeruginosa* in patients with cystic fibrosis aged 6 years or older.

The EURD for tobramycin is 29 October 1973. The International Birth Date of TOBI Podhaler is 25 Nov 2010 (Chile) and was first authorized in the EU on 20 July 2011.

Not applicable

4.2. Clinical Safety and Efficacy aspects

The MAH completed study TBM100C2410: A single arm, open-label, multicenter, Phase IV trial to assess long term safety of tobramycin inhalation powder (TIP) in patients with Cystic Fibrosis. The primary objective of the study was to provide long-term safety data of TIP over 6 cycles of treatment. Secondary objectives were assessment of the efficacy of TIP over 6 cycles of treatment as measured by the relative change in FEV1 % predicted, FVC % predicted and FEF25-75 % predicted from baseline to the end of the dosing periods (Visits 3, 5, 7, 9, 11 and 13) of each cycle and at the end of the final off-treatment period (Visit 14).

Study design
This study was an open label, single arm study in patients suffering from cystic fibrosis, aged 6 years and older, with FEV1 in the range 25 - 75% predicted, who have chronic pulmonary infection with *P. aeruginosa* (confirmed within the last 6 months and at screening). The study consisted of a 14 - 28 days screening period to test/re-confirm the presence of *P. aeruginosa*, a baseline visit, followed by the treatment phase of 6 cycles. Each cycle consisted of 28 days on-treatment period followed by 28 days off-treatment period. Total duration of treatment was up to 48 weeks with a total of 14 visits: 9 site visits and 5 telephone calls. Patients had a site visit at the end of each on-treatment period and the end of the final off-treatment period. The study was planned to recruit approximately 150 patients, with the aim of at least 50% of them are 18 years or older.

4.2.1. Results

Sample size was 157 patient of which 96 patients (61.1%) completed the study (6 cycles of TIP treatment). The demographic characteristics of the population showed the majority of patients included in the study were male (61.8%) and ≥ 20 years of age (mean age of 28 years).

The mean FEV1 % predicted at baseline was 50.2%. Patients on average had a sputum density of 7.6 log10 CFUs of P. aeruginosa at baseline (sum of all biotypes) and 26.1% had baseline MIC values > 8 µg/ml. A total of 58% of patients were on chronic macrolide therapy. Overall the study population was experienced to inhaled TOBI or TIP use with 72% having previous experience with TOBI and 5.7% having previous experience with TIP.

Efficacy results

On average, FEV1 % predicted remained stable during the course of the study with a non-significant 1.9% relative decrease from baseline after 6 cycles of TIP treatment. The mean relative change from baseline showed a decrease of 3.1% for FVC % predicted and an increase of 4.3% for FEF25-75 % predicted after 6 cycles of TIP treatment.

After 6 cycles of TIP treatment, a 1.4 log reduction in colony forming units (CFUs) was observed for mucoid biotype of P. aeruginosa and a 1.2 log reduction for the sum of all biotypes ($p<0.001$). At the end of study visit, the recovery of CFUs returned to baseline, as expected for the end of an offtreatment phase.

At study end (off-treatment), 18% of patients had no change in tobramycin MIC (minimum inhibitory concentration) from baseline, 43% experienced at least a 2-fold increase in tobramycin MIC, and 27% had at least a 4-fold increase. For patients with a baseline MIC ≤ 8 µg/ml, 16.9% had an increase to a MIC > 8 µg/ml.

Overall, 103 patients (65.6%) were treated with a new anti-pseudomonal antibiotic during the study (43.3% oral use, 45.9% IV use and 5.7% inhaled use). Patients with baseline tobramycin MIC > 8 µg/ml reported higher use of new anti-pseudomonal antibiotic as compared to those with baseline tobramycin MIC ≤8 µg/ml (31/41 patients, 75.6% vs. 72/115 patients 62.6%).
Patients with chronic macrolide use reported higher use of new anti-pseudomonal antibiotic overall as compared to those without chronic macrolide. Similarly patients with prior inhaled TOBI use reported higher use of new anti-pseudomonal antibiotic overall as compared to those without prior inhaled TOBI use

Safety results

As the primary study endpoint, 85.4% of patients experienced one or more AEs regardless of relationship to study drug. There were no deaths in this study.
SAEs were experienced by 31.2% of patients and the most common events were infective pulmonary exacerbation of CF (24.8%) and hemoptysis (3.2%). Most frequent AEs were infective pulmonary exacerbation of cystic fibrosis (55.4%), cough (23.6%) and hemoptysis (22.9%). A total of 29 patients (18.5%) discontinued the study due to AEs. Four patients (2.5%) discontinued study drug due to SAEs.

Thirty patients (19.1%) discontinued the study drug due to an AE, regardless of study drug relationship. The most common AEs leading to discontinuation were cough and infective pulmonary exacerbations of cystic fibrosis (9 patients or 5.7% each), chest discomfort and hemoptysis (4 patients (2.5%) each), dyspnea and wheezing (3 patients (1.9%) each) and bronchospasm (2 patients, 1.3%).

There was no signal of clinically significant bronchospasm (airway reactivity) observed based on relative change of FEV1 % predicted from baseline to each post-baseline site visit.
Post-inhalation events were reported by 37.8% of patients on Day 1 of Cycle 1 and subsequently decreased over time to between 21% and 22% during Cycles 4, 5, and 6. Most post inhalation events were cough and generally of short duration with a mean time ranging from 0.3 to 3.3 minutes. The incidence of post inhalation events ongoing at completion of visit was low (range: 0% in Cycle 1 and Cycle 6 to 2.5% in Cycle 2). Overall, cough was the most reported event at all time points.

4.2.2. Discussion

The completed single arm, open-label, multicenter, Phase IV trial to assess long term safety of tobramycin inhalation powder (TIP) in patients with Cystic Fibrosis shows that TIP was reasonably well tolerated. The reported AEs and the AE frequencies are consistent with the known safety profile.

A high number of patients were treated with a new anti-pseudomonal antibiotic during the study. Resistance development is an important potential risk for TIP, in line with the RMP. No hard conclusions can be made from the observed change in tobramycine MIC values as FEV1 % predicted remained stable and the observed sustained suppressive effect of Tobi Podhaler on P. aeruginosa.
Overall, the provided data do not indicate that efficacy of TOBI Podhaler decreases with long-term use however there is a suggestion of a slight decrease of efficacy after the 4th cycle. Yet the data is not sufficiently robust to conclude this.

The detailed assessment of the results of the study TBM100C2410 is available in a separate assessment report (EMA/H/C/002155/0000)

The MAH proposes to remove the statement that long-term data are not available for TOBI Podhaler in sections 4.2, 4.4 and 4.8 of the SmPC based on the availability of long-term data from study TBM100C2410.

This is accepted.

4.3. Risk management plan

The MAH submitted an updated RMP version 6.0, dated 12 Aug 2014 with this application.

The RMP has been updated to reflect the results of the completed study TBM100C2410 and to reflect that long-term data are no longer considered to be missing data. In addition, many minor textual amendments have been made.

☒ The content of the updated RMP proposed by the MAH contains the following elements (new wording underlined, deleted wording ~~in strikethrough~~):

Safety concerns

Table 1: Summary of the Safety Concerns

Important identified risks	Cough
	Bronchospasm
	Hemoptysis
Important potential risks	Nephrotoxicity
	Ototoxicity
	Fetal harm
	Decreased *P aeruginosa* susceptibility to tobramycin (MIC)
	Potential drug-drug interactions with diuretics and other drugs affecting renal clearance, nephrotoxic, neurotoxic and ototoxic drugs (class effect of parenteral use of aminoglycosides)
~~Important~~ **Missing information**	Patients with moderate or severe renal failure not included in clinical trials
	Patients on diuretics and other drugs affecting renal clearance, nephrotoxic, neurotoxic and ototoxic drugs (class effect of parenteral use of aminoglycosides) generally not included in clinical trials
	Patients post organ-transplantation not included in clinical trials
	~~Potential adverse effects of long term use (other than listed as potential risks)~~
	Pregnant or lactating females
	Patients with disease severity different from that studied in clinical trials
	Patients with co-morbidities (i.e., severe hepatic impairment).
	Effects of medications prior to treatment (e.g., steroids, other antibiotics)
	Demographics of risk for aminoglycoside-related deafness in both Caucasians and Non-Caucasians
	Handling of the T-326 Inhaler in young pediatric patients

Considering that no new safety concerns have been identified in the completed study TBM100C2410, the removal of long term safety as a missing information in accepted..

Pharmacovigilance plan

Table 2: On-going and planned studies in the post-authorisation pharmacovigilance development plan

Study/activity Type, title and category (1-3)	Objectives	Safety concerns addressed	Status (planned, started)	Date for submission of interim or final Reports (planned or actual)
~~CTBM100C2401~~	~~Study C2401 is a single arm, open-label, multicenter, Phase IV trial to assess long term safety of tobramycin inhalation powder (TIP) in patients with CF, to obtain safety data from longer term exposure in adult patients (6 treatment cycles [48 weeks]).~~	~~Potential adverse effects of long-term use.~~	~~Started~~	~~Final CSR 31 Dec 2014~~
C~~TBM100C~~2407	To determine if decreased susceptibility to tobramycin is increasing in *Pseudomonas aeruginosa* from cystic fibrosis (CF) patients. Monitor resistance to: meropenem, imipenem, ceftazidime, aztreonam and ciprofloxacin. Evaluate the emergence of the following treatment emergent pathogens: *Staphylococcus aureus, Stenotrophomonas maltophilia, Achromobacter xylosoxidans*, and *Burkholderia* spp. Evaluate clinical outcomes in the first year (change in lung function, respiratory and non-respiratory hospitalizations, mortality and use of new anti-pseudomonal antibiotics) in patients using TOBI Podhaler compared to a cohort using other FDA-approved inhaled anti-pseudomonal antibiotics.	Decreased susceptibility of Pseudomonas aeruginosa to tobramycin (MIC)	Planned	Planned annual interim reports May-2016 –to May-2020. Planned CSR covering 1928-1 – July-2021. Planned CSR covering 1928-2 – July-2017.
A prospective observational study in cystic fibrosis patients with chronic respiratory Pseudomonas aeruginosa infection treated with TOBI® Podhaler™ (tobramycin inhalation powder) or other FDA approved inhaled anti-pseudomonal antibacterial drugs. This study is proposed by Novartis to fulfill FDA Post-marketing requirement 1928-1 and FDA Post-marketing requirement 1928-2 (see section 10.4.3). Category 2				

*Category 1 are imposed activities considered key to the benefit risk of the product.
Category 2 are Specific Obligations in the context of a marketing authorisation under exceptional circumstances under Article 14(8) of Regulation (EC) 726/2004 or in the context of a conditional marketing authorisation under Article 14(7) of Regulation (EC) 726/2004.
Category 3 are required additional PhV activity (to address specific safety concerns or to measure effectiveness of risk minimisation measures)

Routine pharmacovigilance is sufficient to identify and characterise the risks of the product.

Risk minimisation measures

Table 3: Summary table of Risk Minimisation Measures

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Important identified risk		
Cough	This risk is adequately addressed and communicated in the SmPC (see Annex 2). Special warnings and precautions for use (Section 4.4 of the SmPC) Undesirable effects (Section 4.8 of the SmPC).	None
Bronchospasm	This risk is adequately addressed and communicated in the SmPC (see Annex 2) Special warnings and precautions for use (Section 4.4 of the SmPC) Undesirable effects (Section 4.8 of the SmPC).	None
Hemoptysis	This risk is adequately addressed and communicated in the SmPC (see Annex 2) Special warnings and precautions for use (Section 4.4 of the SmPC) Undesirable effects (Section 4.8 of the SmPC).	None
Important potential risks		
Nephrotoxicity	This risk is adequately addressed and communicated in the SmPC (see Annex 2) Special warnings and precautions for use (Section 4.4 of the SmPC).	None
Ototoxicity	This risk is adequately addressed and communicated in the SmPC (see Annex 2) Special warnings and precautions for use (Section 4.4 of the SmPC) Undesirable effects (Section 4.8 of the SmPC).	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
Fetal harm	This risk is adequately addressed and communicated in the SmPC (see Annex 2) Fertility, pregnancy and lactation (Section 4.6 of the SmPC).	None
Decreased *P aeruginosa* susceptibility to tobramycin (MIC)	This risk is adequately addressed and communicated in the SmPC (see Annex 2) Special warnings and precautions for use (Section 4.4 of the SmPC).	None
Potential drug-drug interactions with diuretics and other drugs affecting renal clearance, nephrotoxic, neurotoxic and ototoxic drugs (class effect of parenteral use of aminoglycosides).	This risk is adequately addressed and communicated in the SmPC (see Annex 2). Special warnings and precautions for use (Section 4.4 of the SmPC).	None
~~Important~~ **Missing information**		
Patients with moderate or severe renal failure not included In clinical trials	This is adequately addressed and communicated in the SmPC (see Annex 2) Posology and method of administration (Section 4.2 of the SmPC).	None
Patients on diuretics and other drugs affecting renal clearance, nephrotoxic, neurotoxic and ototoxic drugs (class effect of parenteral use of aminoglycosides) generally not included in clinical trials.	This is adequately addressed and communicated in the SmPC (see Annex 2) Interaction with other medicinal products and other forms of interaction (Section 4.5 of the SmPC).	None
Patients post organ-transplantation not included in clinical trials	Posology and method of administration (Section 4.2 of the SmPC) (see Annex 2).	None
~~Potential adverse effects of long-term use (other than listed as potential risks)~~	~~Should routine pharmacovigilance activities and/or open- label study (CTBM100C2401) uncover additional data, this risk will be communicated through will be communicated through the IB and SPC and additional risk minimization activities may be proposed if necessary.~~	~~None~~
Pregnant or lactating females	This risk is adequately addressed and communicated in the SmPC (see Annex 2) Fertility, pregnancy and lactation	None

Safety concern	Routine risk minimization measures	Additional risk minimization measures
	(Section 4.6 of SmPC).	
Patients with disease severity different from that studied in clinical trials	Should routine pharmacovigilance activities uncover additional data, this risk will be communicated through the IB and SmPC and additional risk minimization activities may be proposed if necessary.	None
Patients with co-morbidities (i.e., severe hepatic impairment)	This risk is adequately addressed and communicated in the SmPC (see Annex 2) Posology and method of administration (Section 4.2 of the SmPC).	None
Effects of medications prior to treatment (e.g., steroids, other antibiotics)	Should routine pharmacovigilance activities uncover additional data; this risk will be communicated through the IB, and SmPC and additional risk minimization activities may be proposed if necessary.	None
Demographics of risk for aminoglycoside-related deafness in both Caucasians and Non-Caucasians	Should routine pharmacovigilance activities uncover additional data; this risk will be communicated through the IB, and SmPC and additional risk minimization activities may be proposed if necessary.	None
Handling of the T-326 Inhaler in young pediatric patients	This risk is adequately addressed and communicated in the SmPC (see Annex 2) Posology and method of administration (Section 4.2 of the SmPC).	None

The proposed risk minimisation measures are sufficient to minimise the risks of the product in the proposed indication(s).

Elements for a public summary of the RMP

The elements for a public summary of the RMP required revision following the conclusion of the procedure.

Tis part of the RMP has been updated appropriately.

Annexes

The annexes have been updated appropriately.

Overall conclusion on the RMP

☒ The changes to the RMP are acceptable.

4.4. Changes to the Product Information

As a result of this group of variations, the MAH proposed to remove the statement that long-term data are not available for TOBI Podhaler in sections 4.2, 4.4 and 4.8 of the SmPC based on the availability of long-term data from study TBM100C2410. The Package Leaflet (PL) is updated accordingly. These changes are accepted.

Please refer to Attachment 1 which includes all proposed changes to the Product Information.

5. Attachments

1. Product Information (changes highlighted) as adopted by the CHMP on 20 November 2014