

**Public Assessment Report  
for paediatric studies submitted in accordance  
with Article 46 of Regulation (EC) No1901/2006, as  
amended**

**Tobi Nebulizer Solution  
(Tobramycin)**

**UK/W/0089/pdWS/001**

**Marketing Authorisation Holder:  
Novartis, UK**

<b>Rapporteur:</b>	UK
<b>Finalisation procedure (day 120):</b>	22 June 2016

## ADMINISTRATIVE INFORMATION

Invented name of the medicinal product:	Tobi Nebulizer Solution
INN (or common name) of the active substance(s):	Tobramycin
MAH:	Novartis, UK
Currently approved Indication(s)	Long-term management of chronic pulmonary infection due to <i>Pseudomonas aeruginosa</i> in cystic fibrosis (CF) patients aged 6 years and older.
Pharmaco-therapeutic group (ATC Code):	J01GB01
Pharmaceutical form(s) and strength(s):	Nebulizer Solution 300mg/5ml

## **I. EXECUTIVE SUMMARY**

No SmPC and PL changes are proposed.

## **II. RECOMMENDATION**

The results of this study are not directly related to the safety or efficacy of tobramycin. However, contamination of the device used for delivery of the drug can have adverse consequences. Improper cleaning of device is not unexpected however this can be influenced by a number of other independent factors such as patient/ carer education, accessibility to clean water/ disinfectants, as well as patient/carers compliance in following the instructions for cleaning the equipment.

The study was carried out in Brazil only, and therefore the relevance in a European setting cannot be definitely determined.

Therefore no further action is proposed at the current time, although it is expected that the MAH will consider these findings in the next phase of development.

It is considered that the benefit/risk balance remains positive in the approved indications at present.

## **III. INTRODUCTION**

The present paediatric data is submitted by the MAH in accordance with Article 46 of Regulation (EC) No1901/2006, as amended, on medicinal products for paediatric use.

The objective of this Critical Expert Overview is to provide a summary of the findings obtained from one study which included paediatric population. This study, (last patient last visit on 11 Dec 2014) was a non-interventional, observational study to evaluate the microbial contamination profile of nebulizers of patients on treatment with antibiotic inhalation therapy for chronic lung colonization with of *Pseudomonas Aeruginosa* (Pa).

The aim of study was to evaluate the microbiological contamination profile of the nebulizer device and therefore no drug, including tobramycin, was involved in this study.

### About the product

TOBI is indicated for the long-term management of chronic pulmonary infection due to *Pseudomonas aeruginosa* in cystic fibrosis (CF) patients aged 6 years and older.

TOBI is supplied for use via inhalation and is not for parenteral use.

The recommended dose for adults and children is one ampoule twice daily for 28 days. The dose interval should be as close as possible to 12 hours and not less than 6 hours. After 28 days of therapy, patients should stop TOBI therapy for the next 28 days. A cycle of 28 days of active therapy and 28 days of rest from treatment should be maintained.

## *Paediatric population*

The safety and efficacy of TOBI in children below 6 years has not been established. Currently available data are described in section 5.1 of the SPC but no recommendation on posology are made.

## **IV. SCIENTIFIC DISCUSSION**

### **1. Introduction**

The MAH submitted a final report for:

- Study: Microbiological contamination profile of nebulizers used in the treatment of chronic lung colonization by *P. aeruginosa* in cystic fibrosis patients

### **2. Clinical study(ies)**

#### **➤ Description**

##### Objective(s)

To evaluate microbiological contamination profile of nebulizers of patients under inhaled antibiotic therapy for the treatment of chronic lung colonization by *P.aeruginosa*. In addition, to estimate frequency of contamination specifically by *P.aeruginosa* and different types of bacteria and fungi, the profile of nebulizers use and cleaning, and its association with socio-demographic characteristics and clinical characteristics of cystic fibrosis patients in Brazil.

##### Rationale and background

Home nebulizers are widely used by CF patients. Contamination of this equipment has been studied and estimates can reach 68.8%. It is known that most patients do not properly follow the nebulizer's cleaning instructions, however, few Brazilian studies related to this issue are available.

##### Study design

Cross-sectional.

Study was conducted in 7 study sites.

Inclusion criteria:  $\geq 6$  years old; disease confirmed by sweat chloride test  $>60$  mEq/dl or evidence of  $\geq 2$  copies of genetic mutation; therapy with inhaled antibiotics due to chronic lung colonization by *P.aeruginosa*; between D21 and D28 from the off period; nebulizers' brand PARI® and compressor, PRONEB®; same nebulizer since at least 3 consecutive months; ability to answer the interview; and informed consent/assent.

Exclusion criteria: not use nebulizer for inhaled antibiotic therapy for  $>30$  days; on period of inhaled antibiotic therapy; sharing nebulizer with other people; participation in a similar study in the last 12 months; and currently participating of a clinical study.

### Subjects and study size, including dropouts

Considering a projected frequency of contamination of 63.8%, 80 patients would provide a 95% CI with a margin of error of 10.5%. However, 77 patients were included, which provided 95% CI with a margin of error of 10.7%.

### Variables and data sources

Data were obtained from medical charts, interview and results from swab of nebulizer parts. A database was constructed with the following variables: culture of swab samples; clinical data about CF; sociodemographic data; nebulizer use characteristics; nebulizer cleaning methods.

## ➤ **Results**

Nebulizers' samples have shown a contamination frequency of 71.6%. Bacterial and fungal contamination were observed in 56.0% and 45.3% of the cases, respectively. Most common pathogens isolated were: *Stenotrophomonas maltophilia* (6.8%), *Chryseobacterium indologenes* (6.8%), *Pseudomonas putida* (8.1%), *Non-albicans Candida* spp. (21.6%) and Environmental Contaminant Fungus (12.2%).

High frequency of nebulizers' cleaning was observed (97.4%) and most reported methods were: lathering and rinsing with tap water (66.2%), only tap water (60.8%) and immersion in boiling water (52.7%). Final model regarding cleaning characteristics and positivity of culture included only cleaning under tap water as a risk factor to increase the chance of contamination (OR=4.29; 95%CI=1.13-16.28; p=0.03).

## **3. Discussion on clinical aspects**

The applicant states that previous reports of nebulizers' contamination in Brazil described lower estimates when compared to the frequency described in this study. Differences can possibly be attributed to the presence of lung contamination. A wide variety of bacteria were isolated, following the same pattern previously reported, however, most frequent species differ across the studies. Presence of fungal contamination is less explored in the literature. Although a high frequency of nebulizer cleaning was observed, adoption of non-recommended methods was reported. Association between nebulizer cleaning and presence of contamination is not clearly investigated in the literature and the only associated factor previously described was the frequency of cleaning, which was not present in the final model proposed in this study.

The rapporteur asked clarification in the following issues:

1. Please state if there was a correlation between nebulizer contamination to signs and symptoms of secondary infections in the study population.
2. Please discuss if contamination data from Europe are available and to what extent the data obtained from the Brazil study are transferable to the situation in Europe.
3. Please state if any risk minimisation measures are required to improve device cleanliness e.g. the compliance for the cleaning procedure of the device.

#### 4. Assessment of responses

The following response was received from the applicant.

##### Question 1

Please state if there was a correlation between nebuliser contamination to signs and symptoms of secondary infections in the study population.

MAH response:

Swab samples were only collected from the nebuliser equipment for bacterial and fungal pathogens for analysis. Neither swab samples nor sputum samples for culture were collected from patients as part of this study. Signs and symptoms of secondary infection were not part of the data collected for this study. Therefore, based on the results of this study, MAH is unable to comment on a correlation between nebuliser contamination to signs and symptoms of secondary infections in the study population.

##### Rapporteur's comments

As the study did not include collection of data for the signs and symptoms of secondary infection, no correlation can be evaluated. However this is an important consideration and the MAH is encouraged to evaluate this in any future studies planned, whether in adults or children.

**Point resolved.**

##### Question 2

Please discuss if contamination data from Europe are available and to what extent the data obtained from the Brazil study are transferable to the situation in Europe.

MAH response:

Based on a review of the available literature, contamination data are available from Europe, Brazil, US, and Israel. Similar to the current study, these studies assessed pathogens isolated from various nebuliser parts, but not all studies assessed pathogens isolated from patients. Only one study involved genotyping of similar pathogens isolated from both the nebuliser and patients. Thus, in most cases the results were inconclusive regarding a possible correlation between pathogens isolated from the nebuliser and its corresponding parts and pathogens isolated from patients.

In study various nebuliser cleaning methods were reported. One of the most common cleaning methods noted in the study for the nebuliser and its parts was cleaning with tap water. A model was carried out to assess the association between cleaning methods and the frequency of culture positivity. Cleaning with tap water was reported by 60.8% of patients and this was the only factor found to be associated with an increased chance of contamination of the nebuliser (4.29%; 95% CI: 1.13–16.28;  $p=0.03$ ).

The most common bacterial pathogen isolated was *Pseudomonas putida*, which was isolated from at least one part of the nebuliser in 14.3% of samples. The next most common bacterial pathogens isolated were *Stenotrophomonas maltophilia* and *Chryseobacterium indologenes*, in 11.9% of samples from at least one part of the nebuliser. Non-mucoid *Pseudomonas aeruginosa* was isolated in at least one part of the nebuliser in 4.8% of samples and mucoid *P. aeruginosa* was not isolated in any sample. Fungi were isolated in 45.9% of samples from at least one part of the nebuliser and non-albicans *Candida* species was the most common fungus isolated.

To assess if these data are transferable a Pubmed literature search was conducted using the following search terms “cystic fibrosis” and “contamination” and “nebulisers. Relevant findings from this literature search will be discussed.

i. Studies discussing contamination potentially associated with tap water cleaning

A study conducted in the United Kingdom (UK), evaluated 89 inpatient nebulisers for evidence of *S. maltophilia*. Of these, 9 (10.1%) yielded 14 strains of *S. maltophilia*. Environmental samples (from the hospital wards) were obtained and positive sources for *S. maltophilia* included taps, sink drains and water samples, though none of the environmental isolates shared a genotype with any of the nebuliser isolates. None of the patients with *S. maltophilia* isolated from their nebuliser equipment had a positive sputum culture for this bacterium, although it was noted that routine sputum cultures did not use a selective medium to isolate *S. maltophilia*. So, the presence of low numbers of this bacterium in sputum samples may have been missed. (Denton et al, 2003).

A study conducted in the UK evaluated if water filters decreased the transmission of *S. maltophilia* to the atomiser chamber of the nebuliser. Two taps delivering water contaminated with *S. maltophilia* were identified. One tap was fitted with a water filter and the nebuliser atomiser chambers were rinsed repeatedly either in filtered or unfiltered water from these taps. *S. maltophilia* was recovered from all of the nebuliser atomiser chambers rinsed in the unfiltered tap water after 3 weeks. Atomiser chambers rinsed in filtered water remained uncontaminated for up to 8 weeks (Woodhouse et al, 2008).

ii. Studies assessing device contamination and patient sputum without genotyping

A study conducted in France in 53 patients evaluated the contamination of delivery systems after an aerosol therapy session in patients with cystic fibrosis (CF) and chronic *P. aeruginosa* infection. Inclusion criteria required that patients were receiving treatment with Pulmozyme®, and an exclusion criterion was administration of anti-pseudomonal antibiotics via the nebuliser in the prior 2 weeks. The inhaled medication administered during this study was Pulmozyme and sputum was collected immediately after nebulisation and sent for culture as well as samples from the nebuliser equipment were collected and sent for culture. Also, sample from 44 nebulisers and nebuliser equipment were collected and sent for culture. *P. aeruginosa* was isolated from 38%, *S. aureus* from 31.8%, and yeast (not otherwise specified) from 13.6% of nebulisers. Congruence between sputum culture organisms other than *P. aeruginosa* and those found in the nebuliser were evaluated for *Staphylococcus* species only, and there was no relationship between the type of bronchial colonization and contamination of the equipment (Vassal et al, 2000).

An early study conducted in the US and Canada evaluated contamination of nebuliser equipment in 36 CF patients. Eighty-six percent of these patients were colonized with *P. aeruginosa*. Nine patients had contaminated equipment and all 9 were chronically colonized with *P. aeruginosa*. A total of 317 samples were collected from the nebuliser equipment and for the majority of these samples (75%) no pathogens were isolated. Of the pathogens that were isolated, 20 were *Pseudomonas* species, of which 4 were identified as *P. putida*. Other *Pseudomonas* organisms also included *P. aeruginosa* nontypable; *Pseudomonas* serotypes 03, 010, and 011; *P. fluorescens*; *P. maltophilia*; and *P. testosteroni*. There was no concordance between pathogens isolated from the equipment and pathogens isolated from patients, with the exception of one *Pseudomonas* species which was isolated from both the nebuliser and the patient's sputum. It was noted that all contaminated nebulisers were either not cleaned or cleaned only with tap water (Pitchford et al, 1987).

A study conducted in Israel evaluated microbial contamination of nebulisers and patient's sputum, nebuliser cleaning techniques and the relationship to bacterial contamination.

Twenty-nine patients were evaluated and 19 (65.5%) patients had contaminated nebuliser equipment. *Pseudomonas* species were the most frequent contaminants and were cultured from 10 nebulisers (34.5%). All 10 of these patients had chronic *P. aeruginosa* airway infection and this was compared with 7 patients with chronic *P. aeruginosa* airway infection who did not have *Pseudomonas* cultured from the nebuliser. The authors concluded that without genotyping they could not be sure that the *Pseudomonas* isolated from the patients' airways was the same as that isolated from their nebuliser. *Klebsiella* species were the second most common contaminant and were cultured from the nebulisers of 7 patients (24.1%). None of these patients had *Klebsiella* cultured from their sputum. *Proteus* species, *Enterobacter* species, *Acinetobacter* species, coagulase negative *Staphylococcus* species, and *Micrococcus luteus* were found to be heavy contaminants in two nebulisers each, but these pathogens were not found in the sputum of respective patients. *Candida albicans* was cultured from 5 nebulisers and from the sputum of 3 patients. Of the 19 contaminated nebulisers, only 4 (21.1%) had been cleaned after each use. In contrast, 7 of the 10 (70.0%) uncontaminated nebulisers were cleaned after each use. Of the 29 patients, 14 cleaned the nebuliser with water, 13 with soap and water, one with alcohol, and one with water and vinegar. There seemed to be no significant difference in cleaning or drying technique between clean nebulisers and those contaminated with *Pseudomonas* or other organisms. It was noted that cleaning with tap water appeared adequate, though these patients also air dried their equipment which seemed to help decrease the rate of contamination (Blau et al, 2006).

iii. Study assessing device contamination and patient sputum with genotyping

A study conducted in Brazil evaluated the nebuliser equipment of 40 CF patients to describe the pathogens found in home nebulisers and in respiratory samples from CF patients. All of these patients were being treated with inhaled Pulmozyme and 40% were being treated with an inhaled antibiotic (not specified). Prior colonization (sputum) profiles from these patients revealed *Staphylococcus aureus* (>30%), *P. aeruginosa* (>30% of patients), methicillin-resistant *S. aureus* (10%), and both *Burkholderia cepacia* and *S. maltophilia* (1% each). *P. putida* was not cultured from patients. Amongst these 40 patients, contamination of any part of their nebulisers was detected in 23 cases (57.5%). *P. putida* was isolated from the nebuliser equipment in 7 cases, *P. aeruginosa* in 3 cases, *S. maltophilia* and *B. cepacia* in 2 cases each, and *S. aureus* in 1 case. Yeasts were isolated from the nebuliser equipment in 12 cases. In 4 cases, the same organism was detected in sputum culture and in the nebuliser sample culture. In 2 cases the bacteria belonged to the *Pseudomonas* genus and the other 2 were part of the *Staphylococcus* species. Genetic analysis of the isolates showed that they were unrelated strains. After standardized instructions regarding the cleaning and disinfection of home nebulisers had been provided, the number of contaminated nebuliser cases dropped to 10 (25%) (Zuana et al, 2014).

## **Conclusion**

Overall, although cleaning with tap water has been recommended (Rosenfeld et al, 2001) with the exception of the study by Blau et al, the previously described studies demonstrate that there may be a higher risk of contamination of nebuliser equipment if cleaning with tap water is the only cleaning method used.

Studies which evaluated pathogens isolated both in nebuliser equipment and sputum cultures in general demonstrated low concordance between pathogens isolated in the nebuliser equipment and sputum. In the Zuana et al study in which genotyping was performed, the strains that were isolated from the nebuliser equipment were not the same strains isolated from the patient. Therefore, there is inconclusive evidence on whether there is a correlation between nebuliser contamination and the pathogens harboured by CF patients.



### Rapporteur's comments

Due to varying information collected during different studies, no definitive conclusions can be made.

**Point resolved.**

### Question 3

Please state if any risk minimisation measures are required to improve device cleanliness e.g. the compliance for the cleaning procedure of the device.

MAH response:

The instructions for use and for cleaning the nebuliser are to wash all parts with warm water and liquid dish soap, rinse nebuliser parts thoroughly with warm water and shake out water and air dry parts on a lint-free towel. Instructions for disinfection of the nebuliser are also provided in the PARI instructions for use.

Device functionality has been established during development and is ensured by testing during manufacture and subsequent testing prior to use. Since the mechanism of the device is mechanical in nature, it is independent from external influences such as heat or physical stress. Malfunction of the device is often reported in relation with insufficient training of the patient in appropriate handling of the device. The instructions for use provide clear guidance and steps, like inspecting capsule after inhalation; this would allow detecting a device failure.

Additionally, each monthly commercial pack contains a reserve inhaler, for use in case the inhaler gets damaged or wet.

Section "3. How to use Tobi" of the UK leaflet (dated March 2013) provides the following instruction to patients: "Please remember to clean and disinfect your nebuliser after treatment according to the manufacturer's instructions. You should never use a dirty or clogged nebuliser. You should not share your nebuliser with other people."

The cumulative patient exposure since the first launch of TOBI was estimated to be approximately 133,656.01 patient-treatment-years. A review of reports of medical device incidents did not reveal any patterns or other safety information relevant to the benefit-risk assessment for TOBI. A critical analysis of the efficacy and safety data revealed that the overall benefit-risk profile of TOBI remains favourable (TOBI PSUR 3).

Thus, MAH believes that given the adequacy of the instructions in the currently approved patient leaflet in the Reference Member State and Concerned Member States, there are no additional risk minimization measures required to improve device cleanliness. MAH continues to monitor all adverse events including those events resulting from device as part of the company's routine pharmacovigilance and safety surveillance measures.

### Rapporteur's comments

The current instructions are considered adequate.

**Point resolved.**

## **V. MEMBER STATES OVERALL CONCLUSION AND RECOMMENDATION**

### **➤ Overall conclusion**

The results of the present study do not have any direct impact on the safety or efficacy of tobramycin. Device contamination can have adverse consequences. However the previously raised questions cannot be answered definitely as appropriate data to answer these, were not collected.

Therefore no further action is proposed at the current time, although it is expected that the MAH will consider these findings in the next phase of development.

It is considered that the benefit/risk balance remains positive in the approved indications at present.

### **➤ Recommendation**

No changes to the SPC/PIL are proposed, no further action required.