ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Vantobra 170 mg nebuliser solution

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each single-dose ampoule of 1.7 ml contains 170 mg tobramycin.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Nebuliser solution.

A clear to slightly yellow solution.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

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

Consideration should be given to official guidance on the appropriate use of antibacterial agents.

4.2 Posology and method of administration

Posology

The dose of Vantobra is the same for all patients within the approved age range, regardless of age or weight. The recommended dose is one ampoule (170 mg/1.7 ml) administered twice daily (i.e. total daily dose is 2 ampoules) for 28 days. The dose interval should be as close as possible to 12 hours and not less than 6 hours. Vantobra is taken in alternating cycles of 28 days. A cycle of 28 days of active therapy (on-treatment period) and 28 days of rest from treatment (off-treatment period) should be maintained.

Missed doses
In case of a missed dose with at least 6 hours remaining until the next dose, the patient should inhale the dose as soon as possible. If less than 6 hours remain to the next planned dose, the patient should wait for the next dose and not inhale more to make up for the missed dose.

Duration of treatment
Treatment should be continued on a cyclical basis for as long as the physician considers the patient is gaining clinical benefit from the treatment taking into account that long-term safety data are not available for Vantobra. If clinical deterioration of pulmonary status is evident, additional or alternative anti-pseudomonal therapy should be considered. See also information on clinical benefit and tolerability in sections 4.4, 4.8 and 5.1.

Special populations

Elderly patients (≥65 years)
There are insufficient data in this population to support a recommendation for or against dose adjustment.

Renal impairment
There are no data in this population to support a recommendation for or against dose adjustment with Vantobra. Please also refer to nephrotoxicity information in section 4.4 and excretion information in section 5.2.

Hepatic impairment
No studies have been performed on patients with hepatic impairment. As tobramycin is not metabolised, an effect of hepatic impairment on the exposure to tobramycin is not expected.

Patients after organ transplantation
Adequate data do not exist for the use of inhaled tobramycin in patients after organ transplantation. No recommendation for or against dose adjustment can be made for patients after organ transplantation.

Paediatric population
There is no relevant use of Vantobra in children below 6 years of age.

Method of administration

Inhalation use.

Vantobra is administered by inhalation using the Tolero nebuliser handset provided in the pack. For detailed instructions on use see section 6.6.

Vantobra must not be administered by any other route or using any other device than the one provided in the pack. The use of an alternative untested nebuliser system may alter the pulmonary deposition of the active substance. And this in turn may alter efficacy and safety of the product.

Where patients are receiving several inhaled medicinal products and chest physiotherapy, it is recommended that Vantobra is used last.

4.3 Contraindications

Hypersensitivity to the active substance and any aminoglycoside or to any of the excipients listed in section 6.1.

4.4 Special warnings and precautions for use

Ototoxicity

Ototoxicity, manifested as both auditory toxicity (hearing loss) and vestibular toxicity, has been reported with parenteral aminoglycosides. Vestibular toxicity may be manifested by vertigo, ataxia or dizziness. Tinnitus may be a sentinel symptom of ototoxicity, and therefore the onset of this symptom warrants caution.

Auditory toxicity, as measured by complaints of hearing loss or by audiometric evaluations, was observed with parenteral aminoglycosides and may be considered also for the inhalation route of administration. In open label studies and post-marketing experience, some patients with a history of prolonged previous or concomitant use of intravenous aminoglycosides have experienced hearing loss. Physicians should consider the potential for aminoglycosides to cause vestibular and cochlear toxicity and carry out appropriate assessments of auditory function during Vantobra therapy.

In patients with a predisposing risk due to previous prolonged systemic aminoglycoside therapy it may be necessary to consider audiological assessment before initiating Vantobra therapy. If a patient reports tinnitus or hearing loss during aminoglycoside therapy, the physician should consider referring them for audiological assessment.

There is an increased risk of ototoxicity in patients with mitochondrial DNA mutations (particularly the nucleotide 1555 A to G substitution in the 12S rRNA gene), even if aminoglycoside serum levels are within the recommended range during treatment. Alternative treatment options should be considered in such patients. In patients with a maternal history of relevant mutations or aminoglycoside induced deafness, alternative treatments or genetic testing prior to administration, should be considered.

Nephrotoxicity

Nephrotoxicity has been associated with parenteral aminoglycoside therapy**.** There was no evidence of nephrotoxicity during clinical trials with inhaled tobramycin and Vantobra. Caution should be exercised when prescribing Vantobra to patients with known or suspected renal dysfunction. According to current clinical practice baseline renal function should be assessed. Urea and creatinine levels should be reassessed after every 6 complete cycles of Vantobra therapy (180 days of nebulised aminoglycoside therapy).

Monitoring of serum tobramycin concentrations

Patients with known or suspected auditory or renal dysfunction should be monitored for serum tobramycin concentrations. If oto- or nephrotoxicity occurs in a patient receiving Vantobra, tobramycin therapy should be discontinued until serum concentration falls below 2 µg/ml.

Serum concentrations greater than 12 µg/ml are associated with tobramycin toxicity and treatment should be discontinued if concentrations exceed this level.

The serum concentration of tobramycin should only be monitored using validated methods. Finger prick blood sampling is not recommended due to the risk of contamination of the sample.

Bronchospasm

Bronchospasm can occur with inhalation of medicinal products and has been reported with the use of nebulised tobramycin. Bronchospasm should be treated as medically appropriate.

The first dose of Vantobra should be used under supervision of a physician, after taking a bronchodilator if this is part of the current regimen for the patient. FEV_1 should be measured before and after nebulisation.

If there is evidence of therapy-induced bronchospasm, the physician should carefully evaluate whether the benefits of continued use of Vantobra outweighs the risks to the patient. If an allergic response is suspected, Vantobra should be discontinued.

Neuromuscular disorders

Vantobra should be used with great caution in patients with neuromuscular disorders such as Parkinsonism or other conditions characterized by myasthenia, including myasthenia gravis, as aminoglycosides may aggravate muscle weakness due to a potential curare-like effect on neuromuscular function.

Haemoptysis

Inhalation of nebulised tobramycin solutions may induce a cough reflex. The treatment with Vantobra in patients with active, severe haemoptysis should be initiated only if the benefits of treatment are considered to outweigh the risks of inducing further haemorrhage.

Development of resistance

The development of antibiotic-resistant P. aeruginosa and superinfection with other pathogens represent potential risks associated with antibiotic therapy. Development of resistance during inhaled tobramycin therapy could limit treatment options during acute exacerbations; this should be monitored.

Other precautions

Patients receiving concomitant parenteral aminoglycoside therapy (or any medicine affecting renal excretion, such as diuretics) should be monitored as clinically appropriate taking into account the risk of cumulative toxicity. This includes monitoring of serum concentrations of tobramycin.

Safety and efficacy have not been studied in patients colonised with *Burkholderia cepacia*.

4.5 Interaction with other medicinal products and other forms of interaction

No interaction studies have been performed. Based on the interaction profile for tobramycin following intravenous and aerosolised administration, concurrent and/or sequential use of Vantobra is not recommended with other medicinal products with nephrotoxic or ototoxic potential, such as:

- amphotericin B, cefalotin, ciclosporin, tacrolimus, polymyxins (risk of increased nephrotoxicity);
- platinum compounds (risk of increased nephrotoxicity and ototoxicity);

Concurrent use of Vantobra with diuretic compounds (such as ethacrynic acid, furosemide, urea or mannitol) is not recommended. Such compounds can enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue (see section 4.4).

Other medicinal products that have been reported to increase the potential toxicity of parenterally administered aminoglycosides include:

- anticholinesterases, botulinum toxin (neuromuscular effects).

In clinical studies patients using inhaled tobramycin continued to take dornase alfa, bronchodilators, inhaled corticosteroids and macrolides. No evidence of drug interactions with these medicines was identified.

4.6 Fertility, pregnancy and lactation

Pregnancy

There are limited data from the parenteral use of tobramycin in pregnant women. There are no adequate data from the use of tobramycin administered by inhalation in pregnant women. Animal studies do not indicate a teratogenic effect of tobramycin (see section 5.3). However, aminoglycosides can cause foetal harm (e.g., congenital deafness and nephrotoxicity) when high systemic concentrations are achieved in a pregnant woman. Systemic exposure following inhalation of Vantobra is very low (see section 5.2). If Vantobra is used during pregnancy, or if the patient becomes pregnant while taking Vantobra, she should be informed of the potential hazard to the foetus.

Vantobra should not be used during pregnancy unless the benefits to the mother outweigh the risks to the foetus or baby.

Breast-feeding

Tobramycin is excreted in human breast milk after systemic administration. The amount of tobramycin excreted in human breast milk after administration by inhalation is not known, though it is estimated to be very low considering the low systemic exposure. Because of the potential for ototoxicity and nephrotoxicity in infants, a decision should be made whether to terminate breast-feeding or discontinue treatment with Vantobra, taking into account the importance of the treatment to the mother.

Fertility

No effect on male or female fertility was observed in animal studies after subcutaneous administration (see section 5.3).

4.7 Effects on ability to drive and use machines

Vantobra has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Summary of the safety profile

In controlled clinical trials with Vantobra the most frequent adverse reactions in cystic fibrosis patients with *P. aeruginosa* infection were cough and dysphonia. Other clinical trials with tobramycin nebuliser solution mention dysphonia and tinnitus as the most frequent undesirable events that were reported in significantly more patients compared to those treated with placebo. The episodes of tinnitus were transient and resolved without discontinuation of tobramycin therapy.

In open label studies and post-marketing experience, some patients with a history of prolonged previous or concomitant use of intravenous aminoglycosides have experienced hearing loss. Parenteral aminoglycosides have been associated with hypersensitivity, ototoxicity and nephrotoxicity (see section 4.4).

Long-term safety data are not available for Vantobra (see also sections 4.2 and 5.1).

Tabulated list of adverse reactions

Adverse drug reactions reported for tobramycin nebuliser solution are listed in Table 1.
Adverse drug reactions are listed according to system organ classes in MedDRA. Within each system organ class, the adverse drug reactions are ranked by frequency, with the most frequent reactions first. Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness. In addition, the corresponding frequency category is provided using the following convention: Very common (≥ 1/10); Common (≥ 1/100 to < 1/10); Uncommon (≥ 1/1,000 to < 1/100); Rare (≥ 1/10,000 to < 1/1,000); Very rare (< 1/10,000).

Table 1 Adverse reactions

System Organ Class	Frequency category	Adverse Reactions
Infections and infestations		
	Rare	Laryngitis
	Very rare	Fungal infection Oral candidiasis
Blood and lymphatic system disorders		
	Very rare	Lymphadenopathy
Immune system disorders		
	Very rare	Hypersensitivity
Metabolism and nutrition disorders		
	Rare	Anorexia
Nervous system disorders		
	Rare	Dizziness Aphonia Headache
	Very rare	Somnolence
Ear and labyrinth disorders		
	Rare	Hearing loss

		Tinnitus
	Very rare	Ear pain Ear disorder
Vascular disorders		
	Rare	Haemoptysis Epistaxis
Respiratory, thoracic and mediastinal disorders		
	Uncommon	Dyspnoea Dysphonia Pharyngitis Cough
	Rare	Asthma Lung disorder Chest discomfort Productive cough Rhinitis Bronchospasm
	Very rare	Hypoxia Hyperventilation Sinusitis
Gastrointestinal disorders		
	Rare	Vomiting Mouth ulceration Nausea Dysgeusia
	Very rare	Diarrhoea Abdominal pain
Skin and subcutaneous tissue disorders		
	Rare	Rash
	Very rare	Urticaria Pruritus
Musculoskeletal and connective tissue disorders		
	Very rare	Back pain
General disorders and administration site conditions		
	Rare	Asthenia Pyrexia Pain Chest pain
	Very rare	Malaise
Investigations		
	Rare	Pulmonary function test decreased

Paediatric population

There was no difference in the safety profile between pediatric and adult patient population treated with Vantobra.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Administration by inhalation results in low systemic bioavailability of tobramycin. Symptoms of aerosol overdose may include severe hoarseness.

In the event of accidental ingestion of Vantobra, toxicity is unlikely as tobramycin is poorly absorbed from an intact gastrointestinal tract.

In the event of inadvertent administration of Vantobra by the intravenous route, signs and symptoms of parenteral tobramycin overdose may occur, including dizziness, tinnitus, vertigo, loss of hearing acuity, respiratory distress and/or neuromuscular blockage and renal impairment.

Acute toxicity should be treated with immediate withdrawal of Vantobra and baseline tests of renal function should be undertaken. Assessment of tobramycin serum concentrations may be helpful in monitoring overdose. In the case of any overdose, the possibility of drug interactions with alterations in the elimination of Vantobra or other medicinal products should be considered.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antibacterials for systemic use, Aminoglycoside antibacterials.
ATC code: J01GB01

Mechanism of action

Tobramycin is an aminoglycoside antibiotic produced by *Streptomyces tenebrarius*. It acts primarily by disrupting protein synthesis leading to altered cell membrane permeability, progressive disruption of the cell envelope and eventual cell death. It is bactericidal at concentrations equal to or slightly greater than inhibitory concentrations.

Breakpoints
Established susceptibility breakpoints for parenteral administration of tobramycin are inappropriate in the aerosolised administration of the medicinal product. Sputum of cystic fibrosis patients exhibits an inhibitory action on the local biological activity of nebulised aminoglycosides. This necessitates sputum concentrations following treatment with aerosolised tobramycin to be ten to twentyfive-fold above the Minimum Inhibitory Concentration (MIC) for both *P. aeruginosa* growth suppression and control of bactericidal activity. In controlled clinical trials, 97% of patients receiving tobramycin nebuliser solution achieved sputum concentrations 10-fold of the highest *P. aeruginosa* MIC cultured from the patient and 95% of patients receiving tobramycin nebuliser solution achieved 25-fold of the highest MIC.

Susceptibility
In the absence of conventional susceptibility breakpoints for the nebulised route of administration, caution must be exercised in defining organisms as susceptible or insusceptible to nebulised tobramycin.

In clinical studies with TOBI, most patients with *P. aeruginosa* isolates with tobramycin MICs < 128 µg/ml at baseline showed improved lung function following treatment with TOBI. Patients with a *P. aeruginosa* isolate with MIC ≥ 128 µg/ml at baseline are less likely to show a clinical response. However, seven of 13 patients

(54%) in the placebo-controlled trials who acquired isolates with MICs of ≥ 128 µg/ml while using TOBI had improvement in pulmonary function.

Based upon *in-vitro* data and/or clinical trial experience, the organisms associated with pulmonary infections in CF may be expected to respond to Vantobra therapy as follows:

Susceptible	*Pseudomonas aeruginosa* *Haemophilus influenzae* *Staphylococcus aureus*
Insusceptible	*Burkholderia cepacia* *Stenotrophomonas maltophilia* *Alcaligenes xylosoxidans*

Treatment with the 28-days on and 28-days off dose regimen in clinical studies showed a small but clear increase in tobramycin, amikacin and gentamicin MICs for *P. aeruginosa* isolates tested. Each additional 6 months of treatment resulted in incremental increases similar in magnitude to that observed in the 6 months of controlled studies. The most prevalent aminoglycoside resistance mechanism seen in *P. aeruginosa* isolated from chronically infected CF patients is impermeability, defined by a general lack of susceptibility to all aminoglycosides. *P. aeruginosa* isolated from CF patients has also been shown to exhibit adaptive aminoglycoside resistance that is characterised by a reversion to susceptibility when the antibiotic is removed.

Other information
There is no evidence that patients treated with up to 18 months with tobramycin nebuliser solution were at a greater risk for acquiring *B. cepacia, S. maltophilia* or *A. xylosoxidans*, than would be expected in untreated patients. *Aspergillus* species were more frequently recovered from the sputum of treated patients; however, clinical sequelae such as Allergic Bronchopulmonary Aspergillosis (ABPA) were reported rarely and with similar frequency as in the control group.

Aerosol characteristics
Table 2: Comparative performance data for the clinical test and reference batches: Vantobra /Tolero nebuliser handset[1], and TOBI/PARI LC PLUS[2].

Performance parameter/ Drug/Device combination*	**Vantobra/Tolero**	**TOBI/PARI LC PLUS**
Total Drug Delivered [mg±SD]	96 ± 4.4	101 ± 8.5
Fine Particle Mass < 5 µm [mg±SD]	72 ± 6.5	65 ± 7.1
Drug Delivery Rate [mg/min]	27 ± 5.0	7 ± 0.9
Mass Median Aerodynamic Diameter [µm ± SD]	3.8 ± 0.3	3.6 ± 0.4
Geometric Standard Deviation ±SD	1.5 ± 0.0	2.3 ± 0.2
Nebulisation Time [min]	3.9 ± 0.6	15.3 ± 0.6

*Results from breath simulation and cascade impactor measurements.
[1] connected with an eBase controller or eFlow *rapid* controller
[2] connected with a PARI Boy SX compressor

The drug delivery rate of Vantobra with the Tolero nebuliser is independent of the breathing pattern applied i.e. adult or child in contrast to the PARI LC PLUS nebuliser.

Clinical efficacy and safety

Limited data from one controlled clinical study over one treatment cycle indicate that the improvement in lung function was maintained above baseline during the 28-day off-treatment period.
As a result of study 12012.101, lung function improvement FEV_1% predicted relative to baseline increased by 8.2 ± 9.4% under Vantobra and by 4.8 ± 9.6% under the reference therapy in the first treatment cycle showing

non-inferior (p=0.0005) efficacy. CFU reduction as an indicator for suppression of P. aeruginosa was comparable for Vantobra and the reference product.

5.2 Pharmacokinetic properties

Absorption and distribution

The systemic exposure to tobramycin after inhalation of Vantobra is expected to emerge primarily from the inhaled portion of the medicinal product as tobramycin is not absorbed to any appreciable extent when administered via the oral route. Inhalation of nebulised tobramycin produces high sputum concentrations and low plasma levels.

For comparative aerosol data please refer to Table 2 in section 5.1

At the end of a 4-weeks dosing cycle of Vantobra (170 mg/1.7 ml twice daily) in cystic fibrosis patients, maximum tobramycin plasma concentrations (Cmax) of 1.27 ± 0.81 µg/ml were reached at approximately one hour after inhalation. Sputum concentrations were higher and more variable with Cmax of 1,951 ± 2,187 µg/g. After administering a single dose of Vantobra 170 mg to healthy volunteers Cmax of 1.1 ± 0.4 µg/ml were reached after a tmax of approximately 4 hours.

Distribution

Less than 10% of tobramycin is bound to plasma proteins.

Biotransformation

Tobramycin is not metabolised and is primarily excreted unchanged in the urine.

Elimination

The elimination of tobramycin administered by the inhalation route has not been studied.

Following intravenous administration, systemically absorbed tobramycin is eliminated by glomerular filtration. The elimination half-life of tobramycin from serum is approximately 2 hours.

Unabsorbed tobramycin following administration by inhalation is probably eliminated primarily in expectorated sputum.

5.3 Preclinical safety data

Non-clinical data reveal that the main hazard for humans, based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential and toxicity to reproduction and development, consists of renal toxicity and ototoxicity. In repeated dose toxicity studies it has been shown that target organs of toxicity are the kidneys and vestibular/cochlear functions. In general, toxicity is seen at higher systemic tobramycin levels than are achievable by inhalation of the recommended clinical dose.

No reproduction toxicology studies have been conducted with tobramycin administered by inhalation. Subcutaneous administration at doses of 100 mg/kg/day in rats and the maximum tolerated dose of 20 mg/kg/day in rabbits during organogenesis was not teratogenic. Teratogenicity could not be assessed at higher parenteral doses in rabbits as they induced maternal toxicity and abortion. Based on available data from animals a risk of toxicity (e.g. ototoxicity) at prenatal exposure levels cannot be excluded. Tobramycin did not impair fertility in male or female rats at subcutaneous doses up to 100 mg/kg/day.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Calcium chloride
Magnesium sulphate
Sulphuric acid (for pH adjustment)
Sodium hydroxide (for pH adjustment)
Water for injections

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products in the nebuliser.

6.3 Shelf life

3 years

The contents of a single-dose ampoule should be used immediately after opening (see section 6.6).

Stability after opening of the sachet: 4 weeks when stored below 25 °C.

6.4 Special precautions for storage

Store in a refrigerator (2 °C – 8 °C).

For storage conditions after first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Vantobra is supplied in polyethylene (PE) ampoules that are packed in sealed aluminium foil sachets (8 ampoules per sachet).

Outer box contains:

- One box with the medicinal product: 56 ampoules with nebuliser solution in 7 sachets.
- One box with the Tolero nebuliser handset.

6.6 Special precautions for disposal and other handling

The contents of one ampoule should be emptied into the medication reservoir of the Tolero nebuliser handset and administered by inhalation until no medicine is left in the reservoir. The Tolero nebuliser handset can be operated either with an eBase controller or with the eTrack control unit. The performance parameters from *in vitro* aerosol characterisation studies are identical for the two controllers.

- Nebulisation should take place in a well ventilated room.
- The nebuliser handset must be kept horizontally during operation.
- The patient should sit in an upright position during inhalation. Inhalation should be performed by applying a normal breathing pattern without interruption.
- The Tolero nebuliser handset must be cleaned and disinfected as described in the instructions for use of the device.

Vantobra is a clear to slightly yellow solution, but some variability in colour may be observed, which does not indicate loss of activity if the product is stored as recommended.

Vantobra solution is a sterile, aqueous preparation for single use only. As it is preservative-free, the contents of the whole ampoule should be used immediately after opening and any unused solution should be discarded. Opened ampoule should never be stored for re-use.

Use a new Tolero nebuliser handset for each treatment cycle (28 days on-treatment) as provided with the medicine.

Any unused medicinal product or waste material should be disposed off in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

PARI Pharma GmbH
Moosstrasse 3
82319 Starnberg
Germany

Tel.: +49 (0) 89 – 74 28 46 - 10
Fax: +49 (0) 89 – 74 28 46 - 30
E-Mail: info@paripharma.com

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1350/001

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 February 2019
Date of latest renewal: 15 September 2023

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency http://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

PARI Pharma GmbH
Lochhamer Schlag 21
82166 Graefelfing
GERMANY

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER BOX

1. NAME OF THE MEDICINAL PRODUCT

Vantobra 170 mg nebuliser solution
tobramycin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ampoule of 1.7 ml contains 170 mg tobramycin.

3. LIST OF EXCIPIENTS

Excipients: sodium chloride, calcium chloride, magnesium sulphate, water for injections, sulphuric acid and sodium hydroxide for pH adjustment.

4. PHARMACEUTICAL FORM AND CONTENTS

Package contains

- One box with 56 ampoules with nebuliser solution in 7 sachets.
- One box with a Tolero nebuliser handset.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read both the package leaflet of Vantobra and the Instructions for Use of the Tolero nebuliser handset before use.

Inhalation use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PARI Pharma GmbH
Moosstrasse 3
82319 Starnberg
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1350/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vantobra 170 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER _ HUMAN READABLE DATA

PC:
SN:
NN:

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

INNER BOX CONTAINING THE MEDICINE

1. NAME OF THE MEDICINAL PRODUCT

Vantobra 170 mg nebuliser solution
tobramycin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ampoule of 1.7 ml contains 170 mg tobramycin.

3. LIST OF EXCIPIENTS

Excipients: sodium chloride, calcium chloride, magnesium sulphate, water for injections, sulphuric acid and sodium hydroxide for pH adjustment.

4. PHARMACEUTICAL FORM AND CONTENTS

Package contains 56 ampoules with nebuliser solution in 7 sachets.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read both the package leaflet of Vantobra and the Instructions for Use of the Tolero nebuliser handset before use.

Inhalation use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PARI Pharma GmbH
Moosstrasse 3
82319 Starnberg
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1350/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Vantobra 170 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER _ HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

SACHET

1. NAME OF THE MEDICINAL PRODUCT

Vantobra 170 mg nebuliser solution
tobramycin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each ampoule of 1.7 ml contains 170 mg tobramycin.

3. LIST OF EXCIPIENTS

Excipients: sodium chloride, calcium chloride, magnesium sulphate, water for injections, sulphuric acid and sodium hydroxide for pH adjustment.

4. PHARMACEUTICAL FORM AND CONTENTS

Contains 8 ampoules.

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read both the package leaflet of Vantobra and the Instructions for Use of the Tolero nebuliser handset before use.

Inhalation use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in a refrigerator.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

PARI Pharma GmbH
Moosstrasse 3
82319 Starnberg
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/18/1350/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER _ HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

AMPOULE

1. NAME OF THE MEDICINAL PRODUCT

Vantobra 170 mg nebuliser solution
tobramycin
Inhalation use

2. NAME OF THE MARKETING AUTHORISATION HOLDER

PARI Pharma GmbH

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Vantobra 170 mg nebuliser solution
tobramycin

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Vantobra is and what it is used for

What Vantobra is
Vantobra contains an antibiotic medicine called tobramycin. It belongs to a class of antibiotic medicines called aminoglycosides.

What Vantobra is used for
Vantobra is used in patients with cystic fibrosis aged 6 years and older to treat lung infections caused by bacteria named *Pseudomonas aeruginosa.*

Pseudomonas aeruginosa is a bacterium that frequently infects the lungs of cystic fibrosis patients at some time during their lives. If the infection is not properly treated, it continues to damage the lungs, causing further problems with breathing.

How Vantobra works
When you inhale Vantobra, the antibiotic can enter directly into your lungs to fight the bacteria causing the infection. It works by disrupting the production of proteins that the bacteria need to build their cell walls. This damages the bacteria and eventually kills them.

2. What you need to know before you use Vantobra

Do not use Vantobra:
- if you are allergic (hypersensitive) to tobramycin, to any type of aminoglycoside antibiotics, or to any of the other ingredients of Vantobra (listed in section 6).

If this applies to you, tell your doctor before using Vantobra.

Warnings and precautions
Talk to your doctor if you have ever had any of the following conditions:

- hearing problems (including noises in your ears and dizziness);
- kidney problems;
- chest tightness;
- blood in your sputum (the substance you cough up);
- muscle weakness that lasts or becomes worse over time, a symptom mostly related to conditions such as myasthenia (muscle weakness) or Parkinson's disease.

If any of these apply to you, tell your doctor before using Vantobra.

If you have problems with your hearing or kidney function, your doctor may take blood samples to monitor the amount of Vantobra in your system.

If you or your maternal family members have a mitochondrial mutation disease (a genetic condition) or loss of hearing due to antibiotic medicines, you are advised to inform your doctor or pharmacist before you take this medicine; certain mitochondrial mutations may increase your risk of hearing loss with this product. Your doctor may recommend genetic testing before administration of Vantobra.

Inhaling medicines can cause chest tightness due to narrowing of the airways, and this can happen with Vantobra. Your doctor may ask you to use other appropriate medicines to widen the airways before using Vantobra.

Strains of *Pseudomonas* can become resistant to treatment with an antibiotic over time. This means that Vantobra may not work as well as it should over time. Talk to your doctor if you are concerned about this.

If you are also taking tobramycin or another aminoglycoside antibiotic by injection, it may increase the risk of side effects and your doctor will monitor for these as appropriate.

Children
The medicine is not intended for use in children under 6 years of age.

Other medicines and Vantobra
Tell your doctor or a pharmacist if you are taking or have recently taken any other medicines, including medicines obtained without a prescription.

You should not take the following medicines while you are using Vantobra:
- furosemide, a diuretic ("water tablet");
- other medicines with diuretic potential such as urea or mannitol;
- other medicines which may harm your kidneys or hearing:
    - amphotericin B, cefalotin, polymyxins (used to treat microbial infections), ciclosporin, tacrolimus (used to reduce the activity of immune system). These medicines may harm the kidneys;
    - platinum compounds such as carboplatin and cisplatin (used to treat some forms of cancer). These medicines may harm the kidneys or hearing.

The following medicines can increase the risks of harmful effects occurring if they are given to you while you also take tobramycin or another aminoglycoside antibiotic given by injection:
- anticholinesterases such as neostigmine and pyridostigmine (used to treat muscle weakness), or botulinum toxin. These medicines may cause muscle weakness to appear or become worse.

If you are taking one or more of the above medicines, talk to your doctor before you use Vantobra.

You should not mix or dilute Vantobra with any other medicine in your Tolero nebuliser handset which is provided together with Vantobra.
If you are taking several different treatments for cystic fibrosis, you should take them in the following order:

1. Bronchodilator therapy, such as salbutamol

2. Chest physiotherapy
3. Other inhaled medicines
4. Vantobra
   Please check this order with your doctor as well.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before using this medicine.

It is not known whether inhaling this medicine while you are pregnant causes side effects. When they are given by injection, tobramycin and other aminoglycoside antibiotics can cause harm to an unborn child, such as deafness and kidney problems.

If you are breast feeding, you should talk to your doctor before using this medicine.

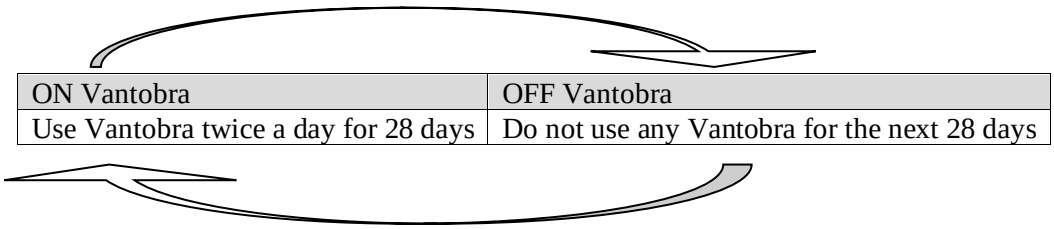
Driving and using machines
Vantobra is not expected to affect your ability to drive or use machines.

3. How to use Vantobra

Always use this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

The recommended dose is <u>two</u> ampoules each day (one in the morning and one in the evening) for 28 days.

- The dose is the same for all persons aged 6 years and older.
- Inhale by mouth the full content of one ampoule in the morning, and one ampoule in the evening using the Tolero nebuliser handset.
- It is best to have an interval as close as possible to 12 hours between doses, but this interval must be <u>at least 6 hours</u>.
- After you have used your medicine for 28 days, you then have a 28-day break, during which you do not inhale any Vantobra. You then start another course after the break (as illustrated).
- It is important that you keep using the medicine twice each day during your 28 days on treatment, and that you keep to the <u>28-day on / 28-day off cycle</u>.



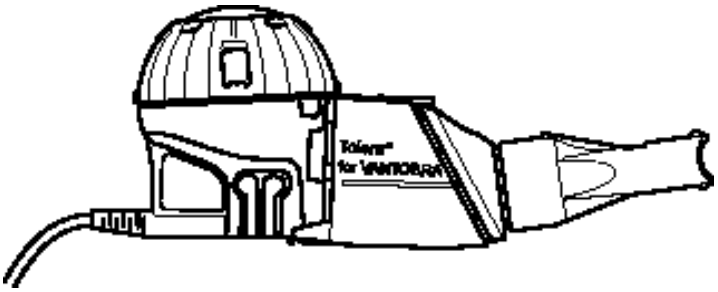
ON Vantobra	OFF Vantobra
Use Vantobra twice a day for 28 days	Do not use any Vantobra for the next 28 days

Repeat cycle

Continue using Vantobra on this cyclical basis for as long as your doctor tells you.
If you have questions about how long to use Vantobra, talk to your doctor or pharmacist.

Preparing Vantobra for inhalation

- Use Vantobra only with the Tolero nebuliser handset shown in the picture below to make sure you inhale the correct dose. Do not use the Tolero nebuliser handset for any other medicine**.**
- Read the Instructions for Use provided with the handset device before use.



- Make sure you have an eTrack or eBase controller to connect the Tolero nebuliser handset. The respective controller can be prescribed by your physician or purchased separately.
- Wash your hands thoroughly with soap and water.
- Remove one ampoule of Vantobra from the aluminium foil sachet just before inhalation.
- Keep the rest of the medicine refrigerated in the original box.
- Lay out all the pieces of your Tolero nebuliser handset on a clean, dry paper or cloth towel. Make sure the nebuliser handset is on a flat, stable surface.
- Assemble the Tolero nebuliser handset as illustrated in the Instructions for Use of the handset device.
- Hold the ampoule upright and tap lightly before twisting off the head part to avoid spilling. Empty the contents of one ampoule into the medication reservoir of the nebuliser handset.
- Begin your treatment sitting in an upright position, in a well ventilated room. Hold the nebuliser handset horizontally and breath normally through your mouth. Avoid breathing through your nose. Continue to inhale and exhale comfortably until the treatment is finished. When all of the medicine has been delivered, you will hear the “treatment complete” tone.
- If you need to interrupt your treatment for any reason, press and hold the On/Off button for one full second. To re-start the treatment, press and hold the On/Off button again for one full second to resume treatment.
- The Tolero nebuliser handset must be cleaned and disinfected as described in the instructions for use of the device.
- Use a new Tolero nebuliser handset for each treatment cycle (28 days on-treatment) as provided with the medicine.

Do not use an alternative untested nebuliser system because it may alter the amount of medicine reaching the lungs. This in turn may alter how well the medicine works and its safety.

If you use more Vantobra than you should
If you inhale too much Vantobra you may get a very hoarse voice. Tell your doctor as soon as possible. If Vantobra is swallowed, it is unlikely to cause severe problems as tobramycin is poorly absorbed from the stomach, but you should still tell your doctor as soon as possible.

If you forget to use Vantobra
If you forget to use Vantobra and there are at least 6 hours to your next dose, use your dose as soon as you can. Otherwise, wait for your next dose. Do not use a double dose to make up for a forgotten dose.

If you stop using Vantobra
Do not stop using Vantobra unless your doctor tells you to do so, as your lung infection may not be controlled sufficiently and may become worse.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Some side effects can be serious
- chest tightness with difficulty in breathing (rare, affecting up to 1 in 1,000 people)
- allergic reactions including hives and itching (very rare, affecting up to 1 in 10,000 people).

If you experience any of these, stop using Vantobra and tell your doctor straight away.

People with cystic fibrosis have many symptoms of the disease. These may still occur while using Vantobra, but should not be as frequent or worse than before.

If your underlying lung disease seems to become worse while you are using Vantobra, tell your doctor straight away.

Other side effects may include:
Uncommon (may affect up to 1 in 100 people)
- shortness of breath
- voice alteration (hoarseness)
- increased cough
- sore throat

Rare (may affect up to 1 in 1,000 people)
- laryngitis (inflammation of the voice box that can cause voice alteration, sore throat and difficulty swallowing)
- Loss of voice
- headache, weakness
- nosebleed, runny nose
- ringing in the ears (normally transient), hearing loss, dizziness
- coughing up blood, producing more sputum than normally, chest discomfort, asthma, fever
- taste disturbances, feeling sick (nausea), mouth ulcers, being sick (vomiting), loss of appetite
- rash
- chest pain or general pain
- worsening of lung function test results

Very rare (may affect up to 1 in 10,000 people)
- fungal infections of the mouth or throat, such as thrush
- swelling of lymph glands
- sleepiness
- ear pain, ear problems
- hyperventilating, low oxygen levels in your blood, sinusitis
- diarrhoea, pain in and around the stomach
- red pustules, papules on the skin
- nettle rush, itching
- back pain
- generally feeling unwell

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Vantobra

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the ampoule or the sachet or box after EXP. The expiry date refers to the last day of that month.

Store in a refrigerator (2°C - 8°C). If you don't have a refrigerator available (such as when you are transporting your medicine) you can store the box with the medicine (even if sachets are opened) below 25°C for up to 4 weeks. If the product has been stored at room temperature for longer than 4 weeks, it has to be disposed according to local requirements.

Do not use this medicine if you notice that it has become cloudy, or if there are particles in the solution.

Never store an opened ampoule. Once opened an ampoule should be used immediately, and any remaining product should be discarded.

Do not throw away any medicines via household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help to protect the environment.

6. Contents of the pack and other information

What Vantobra contains

- The active substance is tobramycin. One ampoule contains 170 mg of tobramycin as a single dose.
- The other ingredient(s) (excipient(s)) are: sodium chloride, calcium chloride, magnesium sulphate, water for injections, sulphuric acid and sodium hydroxide for pH adjustment.

What Vantobra looks like and contents of the pack
Vantobra nebuliser solution is provided in a ready-to-use ampoule.

Vantobra is a clear to slightly yellow coloured solution which can vary to a darker yellow. This does not change how Vantobra works provided that the storage instructions have been followed.

Ampoules are packed in sachets, one sachet contains 8 ampoules which correspond with 4 days of treatment.

Vantobra is available together with a Tolero nebuliser handset. It is supplied in a box that contains two inner boxes, one with the medicine (56 ampoules with nebuliser solution in 7 sachets), and one with the nebuliser handset. A package is sufficient for one treatment cycle of 28 days.

Marketing Authorisation Holder and Manufacturer

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Other sources of information

Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.