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.

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 Yellow Card Scheme Website: http://www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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

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

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