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Summary of the risk management plan (RMP) for Vantobra (tobramycin)

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This is a summary of the risk management plan (RMP) for Vantobra, which details the measures to be taken in order to ensure that Vantobra is used as safely as possible. For more information on RMP summaries, see here.

This RMP summary should be read in conjunction with the EPAR summary and the product information for Vantobra, which can be found on Vantobra's EPAR page.

Overview of disease epidemiology

Vantobra is an antibiotic used to treat long-term lung infection caused by the bacteria *Pseudomonas aeruginosa* in patients aged six years and over who have cystic fibrosis. Cystic fibrosis is an inherited, long-term debilitating and life-threatening disease in which there is an accumulation of thick mucus in the lungs that allows bacteria to grow more easily, causing infections. *P. aeruginosa* is a frequent cause of infections in cystic fibrosis patients.

Cystic fibrosis affects approximately 0.3 people in 10,000 in the European Union. Approximately 20% of patients with cystic fibrosis aged below 5 years are infected with *P. aeruginosa*; the prevalence of *P. aeruginosa* infections increases with age, and by the age of 25 to 34 years approximately 80% of patients with cystic fibrosis are infected with *P. aeruginosa*.

Summary of treatment benefits

Vantobra is a 'hybrid medicine'. It contains the active substance tobramycin, which is the same active substance as that of the reference medicinal product, Tobi. Both medicines are available as a nebuliser solution. However, Vantobra differs from Tobi by having a higher concentration of the active substance and is inhaled using a different type of nebuliser.

Tobramycin has been used for several years to treat *P. aeruginosa* infection in patients with cystic fibrosis and the applicant submitted data from the literature to support the use of Vantobra.

In addition, the applicant conducted a 'bioequivalence' study in 58 patients with cystic fibrosis aged 6 years and above to determine whether Vantobra produces similar levels of the active substance in the body as the reference medicine, Tobi. The results of the study showed that Vantobra can be considered comparable to Tobi.

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Unknowns relating to treatment benefits

There are currently no data on benefits in children aged below 6 years.

Summary of safety concerns

Important identified risks

Risk	What is known	Preventability
Cough	Although cough is a common symptom in patients with cystic fibrosis, it is also known to occur following administration of nebulised medications. Cough was reported in clinical trials with Vantobra as an uncommon side effect (occurring in up to 1 patient in 100).	The patient should discuss any worsening of cough with their doctor. Treatment with Vantobra may be stopped and an alternative treatment should be used if cough leads to severe bronchospasm (excessive contraction of the airway muscles), or haemoptysis (coughing up blood).
Bronchospasm (excessive contraction of the airway muscles)	Bronchospasm is known to occur following administration of nebulised medications and has been reported with the use of nebulised tobramycin. So far, no cases of Vantobra-related bronchospasm have been reported.	The patient should discuss any sign of bronchospasm with their doctor. The doctor should prescribe a bronchodilator (a medicine that widens the airways in the lungs) as part of the treatment and the first dose of Vantobra should be given under medical supervision. Lung function (FEV_1) should be measured before and after nebulisation. If bronchospasm occurs, the doctor should evaluate whether the benefits of continuing treatment outweigh the risks.
Haemoptysis (coughing up blood)	Haemoptysis is usually mild and self-limiting in patients with cystic fibrosis and is mostly related to infection. Haemoptysis with a large amount of blood loss (over 240 ml), though infrequent, may be life threatening.	The patient should discuss any sign of haemoptysis with their doctor. Treatment with Vantobra should be carefully considered in patients with severe haemoptysis because of the risk of inducing further bleeding.

Important potential risks

Risk	What is known
Nephrotoxicity (damage to the kidneys)	Nephrotoxicity is a well-known effect of tobramycin when given via routes other than inhalation (e.g. into a vein). It can be assumed that if the tobramycin in Vantobra passes into the bloodstream from the lung, it could have similar effects to other tobramycin

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Risk	What is known
	products, which may include effects on the kidneys. Kidney function should therefore be assessed before and during Vantobra treatment. Treatment should be stopped if blood levels of tobramycin are too high. Hydration may help prevent nephrotoxicity.
Ototoxicity (damage to the ears)	Tobramycin has been shown to cause damage to the ears in 0.5% to 25% of patients. For intravenous (into a vein) tobramycin, hearing loss was observed in up to 33% of the patients (in six studies). No complete hearing loss has been observed for inhaled tobramycin. However, impaired hearing and vertigo have been reported. Patients should discuss any sign of ototoxicity (such as hearing loss, ringing in the ears and dizziness) with their doctor and hearing tests should be carried out.
Fetal harm (harm to the unborn child)	Animal studies do not show a risk of harm to the fetus, but high blood concentrations of tobramycin in a pregnant woman could potentially cause fetal harm (e.g. deafness or kidney damage). Data from the use of inhaled tobramycin in pregnant women are insufficient to draw any conclusions. If pregnancy is planned or if the patient is pregnant, she should tell her doctor and the benefits of treatment should be weighed against the risks. Tobramycin levels should be measured and consideration given to either stopping the treatment or reducing the dose at least during the first three months of pregnancy.
Pathogen resistance: decreased *P. aeruginosa* susceptibility to tobramycin (medicine may no longer be effective against certain bacteria)	Bacterial resistance to antibiotics like tobramycin is widespread. In clinical studies with Tobi some patients needed higher blood concentrations of tobramycin to benefit from treatment, which is a possible sign of bacterial resistance. This effect cannot be excluded with Vantobra. Doctors should follow official guidance on the appropriate use of antibiotics when prescribing Vantobra.
Potential drug-drug interactions	Side effects of tobramycin may be increased by some medicines if taken at the same time as tobramycin. These include: certain medicines used to treat fungal or bacterial infections such as amphotericin B, cefalotin and polymyxins (i.e. colistimethate) and some medicines that reduce the activity of the immune system, such as ciclosporin and tacrolimus, all of which increase the risk of damage to kidneys; platinum compounds such as cisplatin, which increase the risk of damage to ears and kidneys; anticholinesterases such as rivastigmine (used to treat dementia), or medicines such as botulinum toxin, which increase the risk of neuromuscular effects (effects on muscles). Concurrent use of these medicines with Vantobra is not recommended. If there are no alternatives, patients taking these medicines should have their blood levels of tobramycin routinely monitored and they should be routinely

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Risk	What is known
	checked for signs of ear or kidney damage.
Off-label use in children below 6 years of age	Vantobra is approved only for patients aged 6 years or older. It is recommended that prescribers adhere to the instructions in the product information.
Bacterial growth in the Tolero nebuliser handset	The Tolero nebuliser is the nebuliser that is used with Vantobra. Vantobra must not be used with any other nebuliser. Nebulisers are potential reservoirs for bacterial growth, particularly if they are not adequately cleaned. Bacterial growth in nebulisers could lead to infection of the respiratory tract in cystic fibrosis patients. The instructions for using the nebuliser should be strictly adhered to.

Missing information

Risk	What is known
Individuals after transplantation	Lung transplantation has become a treatment option for progressive respiratory failure in patients with cystic fibrosis. However, there are inadequate data on the use of Tobi and Vantobra in patients after organ transplantation. No recommendation for or against dose adjustment can be made for them.
Pregnancy or breastfeeding	There is little information available on the use of Vantobra in pregnant or breastfeeding women. It is known that antibiotics of this group may cause harm to the unborn child (e.g. deafness and kidney damage) when high blood concentrations are found in a pregnant woman. However, inhalation of a medicine leads to lower blood concentrations compared with oral (by mouth) or intravenous (into a vein) administration. When given into a vein, tobramycin passes into breast milk. It is not known to what extent tobramycin given by inhalation passes into breast milk, though the amount is estimated to be very low. If Vantobra is used during pregnancy, or if the woman becomes pregnant while taking Vantobra, she should be informed of the potential harm to the unborn child. A decision should be made whether to discontinue treatment with Vantobra, taking into account the importance of the treatment to the mother. See information on 'fetal harm' in the section on 'important potential risks'.
Disease severity different from clinical trial populations (e.g. patients with FEV_1 below 25%)	There are currently no data available for patients with poor lung function (showing an FEV_1 lung test result below 25%). FEV_1, (or forced expiratory volume in one second) is a measure of lung function and is the maximum volume of air the patient can breathe out in one second.
Individuals who were	Information on the safety in patients previously treated with aminoglycoside

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Risk	What is known
treated with aminoglycosides (antibiotics similar to Vantobra) before Vantobra treatment	antibiotics (the group of antibiotics to which Vantobra belongs) is currently not available. Such patients may have an increased risk of developing ear or kidney damage and should therefore undergo medical tests before starting Vantobra treatment.

Summary of risk minimisation measures by safety concern

All medicines have a summary of product characteristics (SmPC) which provides physicians, pharmacists and other healthcare professionals with details on how to use the medicine and also describes the risks and recommendations for minimising them. Information for patients is available in lay language in the package leaflet. The measures listed in these documents are known as 'routine risk minimisation measures'.

The SmPC and the package leaflet are part of the medicine's product information. The product information for Vantobra can be found on Vantobra's EPAR page.

Planned post-authorisation development plan

A post-authorisation development plan is currently not planned.

Summary of changes to the risk management plan over time

Not applicable.

This summary was last updated in 03-2015.

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