VI.2.1 Overview of disease epidemiology

Cystic fibrosis(CF) is an inherited disease characterized by the buildup of thick, sticky mucus that can damage many of the body's organs. The disorder's most common signs and symptoms include progressive damage to the respiratory system and chronic digestive system problems. The features of the disorder and their severity vary among affected individuals.[29] This abnormal mucus can clog the airways, leading to severe problems with breathing and further facilitating chronic bacterial infections, which may start in infancy.[30]

Chronic bacterial infection in CF patients varies over time. Patients are initially infected with Staphylococcus aureus and Haemophilus influenza, and then by Pseudomonas aeruginosa. Chronic P. aeruginosa infection usually occurs during adolescence, when most patients (60%–80%) are colonized. Cystic fibrosis affects approximately 0.8 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.[4]

VI.2.2 Summary of treatment benefits

Aminoglycosides and especially tobramycin are clinically effective against P. aeruginosa when administrated intravenously or by nebulization in patients with CF. Tobramycin is a bactericidal aminoglycoside antibiotic with demonstrated activity against gram-negative microorganisms. It works by disrupting protein synthesis and irreversibly binding the 30S bacterial ribosome, thus leading to alterations in cell membrane permeability and, eventually, cell death.[30]

Tobramycin SUN is a solution for inhalation that allows for targeted antibiotic delivery to the lungs and is indicated for maintenance therapy in cystic fibrosis patients infected with P. aeruginosa.

Studies demonstrate that cyclical treatment with Tobramycin solution for inhalation is associated with an increase in respiratory function and a decrease in sputum density in cystic fibrosis patients. Additional benefits include fewer hospitalizations and a decreased need for systemic antibiotics.[31]

The EarLy Inhaled Tobramycin for Eradication (ELITE) trial showed that treatment with Tobramycin inhalation solution (TIS) for 28 days is effective for treating early P aeruginosa infection, and extending TIS treatment to 56 days does not provide notable additional improvements. Over 90% of randomized patients in the 28-day and 56-day TIS groups had negative cultures for P aeruginosa 1 month after the end of treatment, and the majority of these patients remained free from infection for up to 27 months. The results were similar in sputum and non-sputum producers and were unaffected by the patient’s baseline characteristics (age, lung function and first versus recurrent infection).[2]

VI.2.3 Unknowns relating to treatment benefits

No or very limited information is available regarding treatment benefits of Tobramycin nebuliser in patients below the age of 06 years. There are insufficient data to support a recommendation for use in population with disease severity different from clinical trial populations (e.g. patients with FEV1 < 25% and in population previously treated with aminoglycosides (antibiotics similar to tobramycin). As tobramycin is not metabolized in the liver, an effect of hepatic impairment on the exposure to tobramycin is not expected. Adequate data do not exist for the use of Tobramycin nebuliser solution in pregnant or breastfeeding women and in patients after organ transplantation.

VI.2.4 Summary of safety concerns

A summary is given in table below and a full list of side-effects is available in the SmPC.

Important identified risks

Risk	Known Information	Preventability
1. Cough [Cough]	Although cough is a common symptom in patients with cystic fibrosis, it is also known that inhalation of nebulised solutions may induce a cough reflex. Cough was reported as most commonly occurring side effect (occurring in up 10 % patients).	The patient should discuss any worsening of cough with their doctor. Treatment with Tobramycin nebulisation 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).
2. Excessive contraction of airway muscles [Bronchospasm]	Bronchospasm can occur with inhalation of medicinal products and has been reported with nebulised tobramycin.	The patient should discuss any sign of bronchospasm with their doctor. The first dose of Tobramycin should be given under supervision, using a pre-nebulisation bronchodilator (a medicine that widens the airways in the lungs). FEV1 should be measured before and after nebulisation. Evidence of bronchospasm in the presence of bronchodilator therapy may indicate an allergic response. If an allergic response is suspected nebulised tobramycin should be discontinued. Bronchospasm should be treated as medically appropriate.
3. Coughing up blood [Haemoptysis]	Haemoptysis is usually mild and self-limiting in patients with cystic fibrosis and is mostly related to infection.	The patient should discuss any sign of haemoptysis with their doctor. The use of nebulised tobramycin in patients with active, severe haemoptysis should be undertaken only if the benefits of treatment are considered to outweigh the risks of inducing further haemorrhage.

Important potential risks

Risk	What is known (Including reason why it is considered a potential risk)
4. Damage to the kidney [Nephrotoxicity]	Nephrotoxicity has been associated with parenteral aminoglycoside therapy; however there was no evidence of nephrotoxicity during clinical trials with tobramycin nebulized solution. High serum tobramycin concentrations are related to nephrotoxicity. It can be assumed that if the tobramycin in nebulised solution passes into the bloodstream from the lung, it could have similar effects to other tobramycin The product should be used with caution in patients with known or suspected renal dysfunction and serum concentrations of tobramycin should be monitored. Baseline renal function should be assessed and urea and creatinine levels should be reassessed after every 6 complete cycles of nebulised tobramycin therapy (180 days).[32]
5. Damage to the ears [Ototoxicity]	Ototoxicity, manifested as both auditory and vestibular toxicity, has been reported with parenteral aminoglycosides. Vestibular toxicity may be manifested by vertigo, ataxia or dizziness. Ototoxicity, as measured by complaints of hearing loss or by audiometric evaluations. No complete hearing loss has been observed for inhaled tobramycin. The mechanism leading to the development of irreversible vestibular injury from exposure to aminoglycosides appears to be through the excessive production of oxidative free radicals. This production and subsequent toxicity appears to be a time-dependent process and is unrelated to dose or serum concentration. 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. Patients with hearing loss frequently reported tinnitus. Caution should be exercised when prescribing nebulised tobramycin therapy to patients with known or suspected auditory or vestibular dysfunction. Physicians should consider an audiological assessment for patients who show any evidence of auditory dysfunction, or who are at increased risk for auditory dysfunction. Minimizing the duration of exposure to aminoglycosides is recommended to reduce the risk from this form of drug toxicity.[33]
6. Harm to the unborn child [Fetal harm]	There are no adequate data from the use of tobramycin administered by inhalation in pregnant women. Preclinical data reveal that the main hazard for humans, based on studies of safety pharmacology, repeated dose toxicity, toxicity to reproduction, consists of renal toxicity and ototoxicity.

Risk	What is known (Including reason why it is considered a potential risk)
	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.
7. Medicine may no longer be effective against certain bacteria [Pathogen resistance: Decreased P. aeruginosa susceptibility to tobramycin]	Bacterial resistance to antibiotics like tobramycin is widespread. There is a theoretical risk that patients being treated with nebulised tobramycin may develop P. aeruginosa isolates resistant to intravenous tobramycin. However, the clinical studies showed that a microbiological report indicating in vitro drug resistance did not necessarily preclude a clinical benefit for the patient. P. aeruginosa isolated from CF patients has been shown to exhibit adaptive aminoglycoside resistance that is characterized by a reversion to susceptibility when the antibiotic is removed.
8. Interaction with water pills, and other medicine that may affect kidney function of medicine with toxic effects on brain and ears **[**Potential drug-drug interactions with diuretics and other drugs affecting renal clearance, nephrotoxicity, neurotoxic and ototoxic drugs (class effects of parenteral use of aminoglycosides)]	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 Tobramycin 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 checked for signs of ear or kidney damage.
9. Use in unapproved age group (children less than 6 year old) [Off-label use in children below 6 years of age]	Off-label use is use for medical purpose of a product not in accordance with the authorized product information. Tobramycin is approved only for patients aged 6 years or older. It is recommended that prescribers adhere to the instructions in the product information.

Missing Information

Risk	Known Information
10. Administration after transplant [Use in 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 Tobramycin in patients after organ transplantation. No dosing recommendations can be made for this subpopulation based on available data.

11. Administration in pregnant and nursing women [Use during pregnancy or breastfeeding]	There is little information available on the use of Tobramycin 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 Tobramycin is used during pregnancy, or if the woman becomes pregnant while taking Tobramycin, she should be informed of the potential harm to the unborn child. A decision should be made whether to discontinue treatment with Tobramycin, taking into account the importance of the treatment to the mother.
12. Administration in patients with more severe diseases stage [Use in population with disease severity different from clinical trial populations (e.g. patients with FEV1 below 25%)]	There are currently no data available for patients with poor lung function (showing an FEV1 lung test result below 25%). FEV1, (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. No dosing recommendations can be made for this subpopulation based on available data.
13. Use in population previously treated with aminoglycosides [Administration in patients previously treated with antibiotics similar to tobramycin)]	Information on the safety in patients previously treated with aminoglycoside antibiotics (the group of antibiotics to which Tobramycin 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 Tobramycin treatment. No dosing recommendations can be made for this subpopulation based on available data.
14. Administration in patients with severe impaired liver function [Use in patients with severe hepatic impairment]	There is currently no data available for use in patients with severe hepatic impairment. As tobramycin is not metabolized, an effect of hepatic impairment on the exposure to tobramycin is not expected. No dosing recommendations can be made for this subpopulation based on available data.

15. Administration in patients with moderate and severe impaired kidney function [Use in patients with moderate to severe renal failure]	There is little information available on the use of Tobramycin in patient with renal impairment. The elimination of tobramycin administered by the inhalation route has not been studied. Renal function is expected to affect the exposure to tobramycin, however data is not available as patients with serum creatinine 2 mg/dL (176,8 μmol/L) or more or blood urea nitrogen (BUN) 40 mg/dL or more were not included in clinical studies. The product should be used with caution in patients with known or suspected renal dysfunction and serum concentrations of tobramycin should be monitored. No dosing recommendations can be made for this subpopulation based on available data.
16. Administration in patients under treatment with water pills, or other medicines with toxic effects on kidney, brain or ears [Use in patients on diuretics and other drugs affecting renal clearance, nephrotoxic, neurotoxic and ototoxic drugs (class effect of parenteral use of aminoglycosides) generally not included in clinical trials]	Limited data is available regarding the use of Tobramycin in combination with water pills, or other medicines with toxic effects on kidney, brain or ears. Aminoglycoside drug like Tobramycin should not be given concurrently with potent diuretics (water pills), such as ethacrynic acid and furosemide. Some diuretics themselves cause ear damage and intravenously administered diuretics enhance aminoglycoside toxicity by altering antibiotic concentrations in serum and tissue Concurrent and sequential use of other neurotoxic and/or nephrotoxic antibiotics, particularly other aminoglycosides (e.g., amikacin, streptomycin, neomycin, kanamycin, gentamicin, and paromomycin), cephaloridine, viomycin, polymyxin B, colistin, cisplatin, and vancomycin, should be avoided.
17. Effects of medications prior to treatment (e.g., steroids, other antibiotics [Effects of medications prior to treatment (e.g., steroids, other antibiotics]	There are currently limited data available regarding the effect of administration of other medication before initiation of Tobramycin therapy. In several studies patients that use of inhaled/systemic antipseudomonal antibiotics, dornase alfa or inhaled steroids or macrolides antibiotics before initation of Tobramycin were not enrolled. Although in some clinical studies that assess the efficacy and safety, patients taking tobramycin concomitantly with dornase alfa, β-agonists, inhaled corticosteroids, and other oral or parenteral anti-pseudomonal antibiotics, has a similar adverse experience profile with those of the control group.[34-35]
18. Different group of people characteristics related to the risk of deafness following the use of antibiotics similar to tobramycin [Demographics of risk for aminoglycoside-related deafness in both Caucasians and Non-Caucasians]	There currently no demographic data available on the risk of aminoglycosides deafness in both Caucasian and non-Caucasian patients. It is known that in some individuals there is an unusual susceptibility to amynoglycoside ear damage and hearing loss, due to an inherited mitochondrial DNA mutation known as A1555G. This susceptibility is passed on genetically through the mother and occurs in as many as 17% of individuals with hearing loss after aminoglycoside exposure. Some Non Caucasian population (e.g. Asian patients) with this defect have more rapid and severe effects of aminoglycoside related deafness.

	Aminoglycoside-induced hearing impairment appears to be particularly common in some EU countries The A1555G mutation appears to be highly prevalent among Spanish deaf individuals where it is found in 27% of multigeneration families (with and without aminoglycoside exposure. So, careful evaluation of family history is important and may prevent many cases of aminoglycoside related defaness. In addition, it has been suggested that high-risk populations (eg. patients with cystic fibrosis, a family history of amynoglycosidess hearing loss, and immune dysfunction) should be screened for this mutation.[36-39]

VI.2.5 Summary of risk minimisation activities by safety concern

Summary of Product Characteristics (SmPC) of Tobramycin SUN 300 mg/5 ml nebuliser solution provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL) for patients.

For all of the above mentioned risks, the routine risk minimisation measures as presented in proposed SmPC and PL for Tobramycin SUN 300 mg/5 ml nebuliser solution are considered sufficient and no additional risk minimisation measures are proposed by Sun Pharma for the safety concerns identified with Tobramycin.

VI.2.6 Planned post-authorization development plan

None

VI.2.7 Summary of changes to the risk management plan over time

Version	Date	Safety Concerns	Comment
1.0	22-Jul-15	***Important identified risks:*** 1. Cough 2. Bronchospasm 3. Haemoptysis ***Important potential risks*** 4. Nephrotoxicity 5. Ototoxicity 6. Foetal harm 7. Pathogen resistance: decreased P. Aeruginosa susceptibility to tobramycin 8. Off-label use in children below 6 years of age 9. Potential drug-drug interactions with diuretics and other drugs affecting renal clearance, nephrotoxicity, neurotoxic and ototoxic drugs (class effects of parenteral use of aminoglycosides) ***Missing information*** 10. Use in individuals after transplantation 11. Use during pregnancy or breastfeeding	New RMP issue for new NL/DCP.

Version	Date	Safety Concerns	Comment
		12. Use in population with disease severity different from clinical trial populations 13. Use in population previously treated with aminoglycosides 14. Use in patients with severe hepatic impairment 15. Use in patients with renal impairment (moderate to severe renal failure)	
1.1 (current)	04-Aug-16	***Important identified risks*** 1. Cough 2. Bronchospasm 3. Haemoptysis ***Important potential risks*** 4. Nephrotoxicity 5. Ototoxicity 6. Foetal harm 7. Pathogen resistance: decreased P. Aeruginosa susceptibility to tobramycin 8. Off-label use in children below 6 years of age 9. Potential drug-drug interactions with diuretics and other drugs affecting renal clearance, nephrotoxicity, neurotoxic and ototoxic drugs (class effects of parenteral use of aminoglycosides) ***Missing information*** 10. Use in individuals after transplantation 11. Use during pregnancy or breastfeeding 12. Use in population with disease severity different from clinical trial populations 13. Use in population previously treated with aminoglycosides 14. Use in patients with severe hepatic impairment 15. Use in patients with moderate to severe renal failure 16. Use in patients on diuretics and other drugs affecting renal clearance, nephrotoxic, neurotoxic and ototoxic drugs (class effect of parenteral use of aminoglycosides) generally not included in clinical trials 17. Effects of medications prior to treatment (e.g., steroids, other antibiotics) 18. Demographics of risk for aminoglycoside-related deafness in both Caucasians and Non-Caucasians	Following day 70 Assessment Report of RMS NL (Procedure no: NL/H/3504/001-002/DC) the summary of safety concerns was brought in line with reference product. The following missing information were added: • *Use in patients on diuretics and other drugs affecting renal clearance, nephrotoxic, neurotoxic and ototoxic drugs (class effect of parenteral use of aminoglycosides) generally not in-cluded in clinical trials , Effects of medications prior to treatment (e.g., steroids, other antibiotics)* • *Demographics of risk for aminoglycoside-related deaf-ness in both Caucasians and Non-Caucasians* Part III, Part V and Part VI were also amended in line with changes performed in the summary of safety concerns. Taking into consideration GVP module V requirement for a hybrid application the missing modules from Part II have been added. Annex 2 was updated with revised SmPC and PL.

Version	Date	Safety Concerns	Comment
			Annex 12 was amended with new reference citations.