

Protocol Cardiff & Vale (C&V) Corporate Medicines Management Group (c MMG) Tobramycin nebuliser solution 300mg/5ml (Tobi ®) CV 48 300mg/4ml (Bramitob®) For the treatment of adults and children aged 6 years and older with cystic fibrosis This document should be read in conjunction with the current Summary of Product Characteristics(SPC) http://emc.medicines.org.uk	
1. Licensed Indications	Long-term management of chronic pulmonary infection due to <i>Pseudomonas aeruginosa</i> in cystic fibrosis (CF) patients aged 6 years and older.
2. Therapeutic use & Background	<p>The choice of antibiotics for cystic fibrosis is based on the susceptibility patterns of the micro-organism and the patient's ability to tolerate different drugs. In the UK only two antibiotics are licensed for administration by nebulisation; colistin and tobramycin. Tobramycin is considered suitable for patients chronically colonised with <i>Pseudomonas aeruginosa</i> and whose lung function (FEV₁) continues to decline (measured as greater than or equal to 1%per year) or who have needed more than one course of IV antibiotics in previous year, despite compliance with the standard current practice of nebulised colistin (2MU), or if colistin is not tolerated.</p> <p>The Cochrane Collaboration review of nebulised anti-pseudomonal antibiotics for CF in May 2003¹ concluded that, "Nebulised anti-pseudomonal antibiotic treatment improves lung function. However, more evidence, from longer duration trials, is needed to determine if this benefit is maintained as well as to determine the significance of development of antibiotic resistant organisms. Safety and efficacy have been assessed in controlled and open label studies for up to 96 weeks (12 cycles), but have not been studied in patients < 6 years of age, patients with FEV₁ <25% or >75% predicted, or patients colonised with <i>Burkholderia cepacia</i>.</p>
3. Contraindications	<ul style="list-style-type: none"> Patients with known or suspected renal, auditory, vestibular or neuromuscular dysfunction, or with severe, active haemoptysis. Known hypersensitivity to any aminoglycoside. <p>Pregnancy: Tobramycin should not be used unless the benefits to the mother outweigh the risks to the foetus or baby.</p> <p>Breast-feeding: Because of the potential for ototoxicity and nephrotoxicity with tobramycin in infants, a decision should be made whether to terminate nursing or discontinue Tobramycin therapy.</p>
4. Typical Dosage Regimen (Adults)	<p>The recommended dose for adults and children is one ampoule (300mg) nebulised twice daily for 28 days. Dosage is not adjusted for weight.</p> <p>The dose interval should be as close as possible to 12 hours and not < 6 hours.</p> <p>After 28 days of therapy, patients should stop Tobramycin therapy for the next 28 days.</p> <p>A cycle of 28 days of active therapy and 28 days of rest from treatment should be maintained. The specialist may recommend use of Colistin during the 'rest' month.</p> <p>Tobramycin is inhaled whilst the patient is sitting or standing upright and breathing normally through the mouthpiece of the nebuliser. Nose clips may help the patient breathe through the mouth. The patient should continue their standard regimen of chest physiotherapy. The use of appropriate bronchodilators should continue as thought clinically necessary. Where patients are receiving several different respiratory therapies it is recommended that they are taken in the following order: bronchodilator, chest physiotherapy, other inhaled medicinal products, and finally Tobramycin.</p> <p>All dose adjustments will be undertaken by specialist unless directions have been specified in the medical letter to the GP.</p>
5. Drug	Concurrent and/or sequential use with other drugs with nephrotoxic or ototoxic potential should be avoided. Some diuretics can enhance aminoglycoside toxicity. Tobramycin

¹ Ryan G, Mukhopadhyay S, Singh M. Nebulised anti-pseudomonal antibiotics for cystic fibrosis. *Cochrane Database of Systematic Reviews* 2003, Issue 3. Art. No.: CD001021. DOI: 10.1002/14651858.CD001021..

Interactions	<p>should not be administered concomitantly with furosemide, urea or mannitol. No interactions have been noted when Tobramycin was taken concomitantly with dornase alfa, inhaled corticosteroids, beta agonists, and other oral or parenteral antipseudomonal antibiotics.</p> <p>For a comprehensive list consult the British National Formulary or Summary of Product Characteristics.</p>																
<p>6. Adverse drug Reactions</p> <p>Any serious reaction to an established drug should be reported to CHM.</p>	<p>Although nephrotoxicity has been associated with parenteral aminoglycoside therapy, there was no evidence of nephrotoxicity during clinical trials with Tobramycin.</p> <table border="1" data-bbox="411 383 1503 786"> <thead> <tr> <th data-bbox="411 383 730 416">Occurrence</th> <th data-bbox="735 383 1358 416">Adverse effect</th> <th data-bbox="1362 383 1503 416">Action</th> </tr> </thead> <tbody> <tr> <td data-bbox="411 423 730 506">Respiratory system - uncommon</td> <td data-bbox="735 423 1358 506">Voice alteration (including hoarseness), dyspnoea, increased cough, pharyngitis.</td> <td data-bbox="1362 423 1503 786" rowspan="5">Seek Specialist advice</td> </tr> <tr> <td data-bbox="411 512 730 629">Respiratory system - rare</td> <td data-bbox="735 512 1358 629">Bronchospasm, chest tightness, cough, shortness of breath, lung disorder, increased sputum, asthma haemoptysis, decreased lung function, laryngitis,</td> </tr> <tr> <td data-bbox="411 636 730 696">ENT rare - very rare</td> <td data-bbox="735 636 1358 696">Epistaxis, rhinitis Ear disorder, ear pain.</td> </tr> <tr> <td data-bbox="411 703 730 757">Special senses - rare</td> <td data-bbox="735 703 1358 757">Tinnitus, taste perversion, hearing loss, aphonia.</td> </tr> <tr> <td data-bbox="411 763 730 786">Skin -rare</td> <td data-bbox="735 763 1358 786">Rash.</td> </tr> </tbody> </table> <p>For a comprehensive list, or if significance of possible adverse event uncertain, consult product literature, BNF or contact specialist.</p> <p>The patient should be advised to report any of the following signs or symptoms without delay: Tinnitus or hearing loss.</p>			Occurrence	Adverse effect	Action	Respiratory system - uncommon	Voice alteration (including hoarseness), dyspnoea, increased cough, pharyngitis.	Seek Specialist advice	Respiratory system - rare	Bronchospasm, chest tightness, cough, shortness of breath, lung disorder, increased sputum, asthma haemoptysis, decreased lung function, laryngitis,	ENT rare - very rare	Epistaxis, rhinitis Ear disorder, ear pain.	Special senses - rare	Tinnitus, taste perversion, hearing loss, aphonia.	Skin -rare	Rash.
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7. Baseline investigations	<p>To be undertaken by specialist centre:</p> <p>Rate of decline of FEV₁ (% predicted) over last 6-12 months. FEV₁, sputum culture and sensitivities, renal function, weight. Pure tone audiometry may be considered in patients with a predisposing risk .</p>																
8. Monitoring	<p>TO BE UNDERTAKEN BY SPECIALIST CENTRE</p> <p>Specialist reviews typically include documentation of physiotherapy regime, general well-being score and CF symptom score.</p> <p>At 1 month after starting treatment FEV₁ , sputum culture and sensitivities, renal function ,</p> <p>At 3 after starting treatment FEV₁ , sputum culture and sensitivities</p> <p>At 6 months Patients will continue treatment provided that there is an improvement of FEV₁ after the first month of treatment of over 7% OR the rate of decline of FEV₁ over the first 6 months is improved, and the patient is compliant with treatment.</p> <p>At 12 months Patients will continue treatment provided that the rate of decline of FEV₁ is consistently improved and/or there is a reduction in IV antibiotic use and the patient is compliant and there is an improvement in weight gain and well-being.</p> <table border="1" data-bbox="411 1574 1503 1977"> <thead> <tr> <th data-bbox="411 1574 722 1664">Monitoring parameters & Frequency</th> <th data-bbox="727 1574 967 1664">Laboratory results & responsibility</th> <th data-bbox="971 1574 1503 1664">Action to be taken if abnormal result identified by GP</th> </tr> </thead> <tbody> <tr> <td data-bbox="411 1671 722 1883">Creatinine and electrolytes after every 6 completed cycles – Once yearly</td> <td data-bbox="727 1671 967 1883">Creatinine >100 µmol/l By specialist</td> <td data-bbox="971 1671 1503 1883">Stop drug and discuss. If there is evidence of nephrotoxicity, all tobramycin therapy should be discontinued until trough tobramycin serum levels fall below 2µg/ml. Seek specialist's advice before reintroducing treatment.</td> </tr> <tr> <td data-bbox="411 1890 722 1977">Audiology only if patient reports tinnitus or hearing loss</td> <td data-bbox="727 1890 967 1977">By primary care or specialist</td> <td data-bbox="971 1890 1503 1977">Stop drug and discuss.</td> </tr> </tbody> </table>			Monitoring parameters & Frequency	Laboratory results & responsibility	Action to be taken if abnormal result identified by GP	Creatinine and electrolytes after every 6 completed cycles – Once yearly	Creatinine >100 µmol/l By specialist	Stop drug and discuss. If there is evidence of nephrotoxicity, all tobramycin therapy should be discontinued until trough tobramycin serum levels fall below 2µg/ml. Seek specialist's advice before reintroducing treatment.	Audiology only if patient reports tinnitus or hearing loss	By primary care or specialist	Stop drug and discuss.					
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9. Pharmaceutical	<p>The ampoules should be stored in a refrigerator at 2 to 8°C. Intact ampoules may be stored at up to 25°C for up to 28 days.</p>																

aspects	The nebuliser solution is ready to use, doesn't froth and is preservative free. The contents of one ampoule should be emptied into the nebuliser and administered by inhalation over approximately a 15-minute period using a hand-held PARI LC PLUS reusable nebuliser with a suitable compressor. Suitable compressors are those which, when attached to a PARI LC Plus nebuliser, deliver a flow rate of 4 to 6 L/min and/or a back pressure of 110-217 kPa. An e-flow nebuliser may also be used.
10. Specialist centre contact information	If stopping medication or needing advice please contact: Adults: Dr I Ketchell 02920 715382 Or Physiotherapists 02920 711711 bleep 989 (0830am to 1630pm Monday to Friday). CF Pharmacist 02920715261 Paediatrics: Dr I Doull 02920 744891 or Physiotherapists 02920 745250
11. Criteria for shared care	Prescribing responsibility will only be transferred when <ul style="list-style-type: none"> ▪ Treatment is for a specified indication and duration. ▪ Treatment has been initiated and established by the cystic fibrosis specialist. ▪ The patient's initial reaction to and progress on the drug is satisfactory. ▪ The GP has agreed in writing in each individual case that shared care is appropriate. ▪ The patient's general physical, mental and social circumstances are such that he/she would benefit from shared care arrangements.
12. Responsibilities of specialist centre	<ul style="list-style-type: none"> ▪ Determine when initiation of treatment with Tobramycin is appropriate. ▪ Supervise the initial dose of Tobramycin (risk of bronchospasm) and monitor response to treatment as above. ▪ Undertake monitoring. ▪ Ensure that the patient has an adequate supply of medication (usually 28 days) until shared care arrangements are in place. ▪ Respond to GP request to review the patient due to adverse effects of therapy. <p>Provide GP with:</p> <ul style="list-style-type: none"> ▪ Initiation letter (which includes diagnosis, relevant clinical information and baseline results, treatment to date and treatment plan, duration of treatment before consultant review). ▪ Details of outpatient consultations, ideally within 14 days of seeing the patient, including electrolyte result when taken and presence/absence of auditory symptoms. ▪ Advice on when to stop Tobramycin therapy. ▪ Inform GP if patient does not attend outpatient appointment <p>Provide patient/carer with:</p> <ul style="list-style-type: none"> ▪ Suitable nebuliser / compressor. ▪ Information on the potential benefits and side effects of treatment. ▪ Details of the necessary monitoring, storage and administration requirements for Tobramycin.
13. Responsibilities of primary care	<ul style="list-style-type: none"> ▪ To prescribe according to this protocol. ▪ Symptoms or results are appropriately actioned, recorded and communicated to specialist centre when necessary. ▪ Report to, and seek advice from, the specialist on any aspect of patient care which is of concern or may affect treatment (including potential non-compliance). ▪ Stop treatment on advice of the specialist

14. Responsibilities of patients	<ul style="list-style-type: none"> ▪ Ensure they have a clear understanding of their treatment including how to store and administer the nebuliser solution. ▪ To attend hospital and GP clinic appointments, <u>failure to attend will result in medication being stopped.</u> ▪ To report adverse effects to their specialist or GP. 			
15. Additional Responsibilities	Any serious reaction to an established drug should be reported to Yellow Card Centre Wales using the Yellow Card system.			
16. Supporting Documentation	Patient information leaflet			
17. Patient monitoring booklet	Not needed			
19. Guideline date.	Date of approval March 2015		20. Guideline review date March 2018	