Use of prophylactic azithromycin in adults with COPD
Prescribing support guide

Amber Initiation

RECOMMENDED FOR RESTRICTED USE in certain patients with COPD following initiation and initial management (minimum of 3 months) by a respiratory specialist with continuation in primary care

Inclusion criteria (per NG 115): COPD patients who:

- do not smoke **and**
- have optimised non-pharmacological management and inhaled therapies, relevant vaccinations and (if appropriate) have been referred for pulmonary rehabilitation **and**
- continue to have 1 or more of the following, particularly if they have significant daily sputum production:
  - frequent (typically 4 or more per year) exacerbations* with sputum production
  - prolonged exacerbations with sputum production
  - exacerbations resulting in hospitalisation.

Exclusion criteria: children, cystic fibrosis, other lung pathologies, mycobacterial infections, previous allergy to macrolides, abnormal QTc, pregnancy, breast feeding.

*Exacerbation – a sustained worsening of a person's symptoms from their usual stable state (beyond normal day-to-day variations) which is acute in onset. Commonly reported symptoms are worsening breathlessness, cough, increased sputum production and change in sputum colour.

All patients should have had their pharmacological and non-pharmacological therapy optimised prior to initiating treatment with azithromycin:

•Smoking cessation • Vaccinations • Chest clearance advice, consider mucolytic therapy • Pulmonary rehab referral
•Optimised inhaler choice and dose • Correct inhaler technique • Personalised self-management plan

Baseline evaluation by respiratory specialist:

- **Spirometry/Lung function**
- **Document the nature & frequency of exacerbations** including:
  - increased breathlessness, new sputum production or increased volume, the purulent nature of the sputum
- **CT chest** (to exclude bronchiectasis and other lung pathologies)
- **FBC, Liver function tests (LFT) & U+E** - Avoid azithromycin in severe liver disease; use with caution in severe renal disease (eGFR<10ml/min); correct any electrolyte disturbance before starting treatment (particularly hypokalaemia or hypomagnesaemia)
- **Sputum culture & sensitivity** (including tuberculosis culture), to identify other possible causes of persistent/recurrent infection that may need treatment e.g. antibiotic-resistant organisms, atypical mycobacteria or Pseudomonas aeruginosa
- An electrocardiogram (**ECG**) to rule out prolonged QTc interval. If QTc is >450ms for men & >470ms for women, this is considered a contraindication to initiating therapy. Avoid azithromycin and consider referral to electrophysiology /cardiology. Caution if low serum potassium or concomitant medicines that prolong the QTc interval. See: BNF or SPS guidance
- **Assess for azithromycin interactions** with concomitant medications & review for **contraindications or cautions** in use. See: BNF Azithromycin
- **Consider audiometry** referral especially if pre-existing audiological disease (note - British Thoracic Society (BTS) guidelines list hearing or balance problems as a relative contra-indication to macrolide therapy)
- **Note the following measures**: Spirometry/ Lung function, number of exacerbation in past 12 months, clinical wellbeing ((m)MRC dyspnoea scale, COPD scoring tools e.g. COPD Assessment Test (CAT)), baseline hepatic function (LFTs), QTc interval from ECG

Treatment initiation by respiratory specialist:

- Before starting therapy, patients should be counselled about the benefits and risks (potential adverse effects including gastro-intestinal upset, hearing and balance disturbances, cardiac effects and microbiological resistance)
- **Document informed patient consent** (this is an off-label use)
- Dose: oral azithromycin 250mg three times a week (Monday, Wednesday, Friday)
- **Give advice to patients to stop medication and seek advice if they notice hearing impairment or signs of tinnitus**
- Prescribe to ensure **supply** is in place until 3 month review
- GP to be notified that treatment has commenced and provided with above baseline information

Treatment initiation by respiratory specialist (continued . .)

- Arrange **to recheck LFTs and ECG within 2 months** after starting azithromycin treatment. (If new liver dysfunction or QTc prolongation is present treatment should be stopped)
- For people who are taking prophylactic azithromycin and are still at risk of exacerbations, ensure a non-macrolide antibiotic is available to keep at home as part of their exacerbation action plan (See NG114)
- It is not necessary to stop prophylactic azithromycin during an acute exacerbation of COPD unless another antibiotic with potential to affect the QT interval has also been prescribed (refer to SPS guidance for further information)

3 month review by respiratory specialist and transfer of prescribing to GP:

- **Assess response to and tolerability of treatment**. **Consider** - Spirometry/ Lung function, number of exacerbations, clinical wellbeing ((m)MRC, COPD scoring tools e.g. CAT), adherence to therapy, and any adverse effects, (ensure ECG & LFTs checked after initiation have been **reviewed & actioned appropriately**)
- Only continue treatment if the continued benefits outweigh the risks
- **If no benefit is seen:** treatment should be stopped and the GP notified.
- **If benefit demonstrated & patient free from adverse reactions:** continue and review in 6 months.
- Issue a prescription for 1 month supply.
- Contact GP to notify them of the outcome of the review and ask them to take over prescribing.
  Clinic letter from specialist should highlight:
  - Assessment of any potential adverse effects including QT prolongation and hearing impairment
  - Response to treatment
  - Reason for continuation of treatment and ongoing treatment plan
  - Contact details for responsible specialist via secretary or via specialist e-mail address

9 month & ongoing review by respiratory specialist:

- **Assess response to and tolerability of treatment. Consider** - symptoms, exacerbations, LFTs, adherence to therapy
- **If no benefit is seen:** treatment should be stopped and the GP notified
- **If benefit demonstrated & patient free from adverse reactions:** Continue treatment. The patient will require **annual specialist review** to confirm ongoing azithromycin treatment is appropriate.
- Consider **trial off antibiotics** in summer months and advise GP if appropriate, as some patients may only require azithromycin in winter months due to seasonal variations

GP responsibilities:

- GP to contact specialist if further information/guidance is required, prior to accepting prescribing responsibility.
- Treatment should be reviewed every 6 months and reassessed for efficacy & side effects.
- NICE do not make any recommendations about ongoing monitoring for those on prophylactic azithromycin but the BTS guideline suggests that checking LFTs every 6 months is good practice. This would be mandatory for any patients with other risk factors (e.g. pre-existing liver disease or those taking other hepatotoxic medications).*
- GP to seek specialist advice as needed (see below).

* Since liver is the principal route of elimination for azithromycin, it should be used with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin. Some patients may have had pre-existing hepatic disease or may have been taking other hepatotoxic medicinal products.
In case of signs and symptoms of liver dysfunction, such as rapid developing asthenia associated with jaundice, dark urine, bleeding tendency or hepatic encephalopathy, liver function tests / investigations should be performed immediately. Azithromycin administration should be stopped if liver dysfunction has emerged.

GP to seek specialist advice in the following situations:

- Patient experiences adverse effects
- Patient has a recurrent or non-resolving exacerbation whilst on azithromycin, except where there is a clear reason e.g. acute viral infection
- Patient non-adherence with optimal therapy (e.g. inhalers, oral medication)
- Patient has not had specialist review at 3 & 9 months after initiation of azithromycin, or at regular intervals not exceeding 12 months thereafter
- Significant drug interaction with essential therapy (including medicines that prolong the QTc interval – refer to SPS guidance for further information)

References: BNF (BNF British National Formulary - NICE); NICE guideline [NG115] Chronic obstructive pulmonary disease in over 16s: diagnosis and management**; NICE CKS** Chronic obstructive pulmonary disease: Antibiotics **(link); British Thoracic Society guideline for the use of long-term macrolides in adults with respiratory disease.** Smith D, Du Rand I, Addy CL, *et al.* Thorax 2020;75:370–404 (link); **SPS/UKMI.** What issues should be considered regarding drug-induced QT prolongation? Medicines Q&As, Jan 2020 **(link);** Birmingham, Sandwell, Solihull and environs Joint Formulary document, June 2019 (link); Azithromycin 250 Film-coated Tablets -SmPC, April 2022 **(link)**

Version 1.1	**Approved by** HMMC May 2022 & WEMOPB June 2022	**Review date:** The recommendation is based upon the evidence available at the time of publication. This recommendation will be reviewed upon request in the light of new evidence becoming available.	**Superseded version** 1.0