NHS
Pan Mersey
Area Prescribing Committee

AZITHROMYCIN tablets for prevention of exacerbations of COPD and bronchiectasis in selected high-risk patients

The Pan Mersey Area Prescribing Committee recommends the prescribing of azithromycin tablets in selected high-risk patients, when recommended by a respiratory specialist, for the prevention of exacerbations in COPD and bronchiectasis.

AMBER following specialist recommendation

The Pan Mersey Area Prescribing Committee recommends azithromycin tablets for the prevention of exacerbations in COPD and bronchiectasis in selected patients, when recommended by a respiratory specialist. This is an off-label use and informed patient consent should be sought before prescribing. The specialist should clearly communicate that this discussion has taken place and the daily dose in the letter to the GP. Azithromycin has anti-inflammatory, immunomodulatory and lung remodelling properties in chronic airways disease.

The British Thoracic Society guideline for the use of long-term macrolides in adults with respiratory disease, 2020[1], recommends long term macrolide therapy for patients with COPD with more than three acute exacerbations requiring steroid therapy and at least one exacerbation requiring hospital admission per year to reduce exacerbation rate. Long term macrolide therapy is also recommended to reduce exacerbations in patients with bronchiectasis with high exacerbation rates (i.e., 3 or more per year).

The recommended starting dose for COPD is 500mg azithromycin three times weekly. If gastrointestinal adverse effects occur at this dose, a dose reduction to 250mg three times weekly could be considered if macrolide therapy has been of clinical benefit.

For bronchiectasis, the azithromycin dosing regimens with the greatest supportive evidence to reduce exacerbation rates are 500 mg three times a week and 250mg daily. A starting dose of azithromycin 250 mg three times a week could be used to minimise side effect risk with subsequent titration according to clinical response.

Azithromycin capsules are significantly more expensive than tablets; therefore tablets should be prescribed where possible.

For patients with both COPD and bronchiectasis, treatment success is determined by a reduction in exacerbations. All patients should be reviewed by the GP after a 6-month trial to establish the overall risk/benefit. However, a longer period of treatment up to 12 months may be required to establish significant effects. The specialist will inform the GP of the treatment goal in terms of reduction of exacerbations and the follow up action if this goal is not achieved. The specialist will also inform the patient that the GP will carry out the review and decide if treatment should continue.

Azithromycin does not significantly affect the hepatic cytochrome P450 system. It is not believed to undergo the pharmacokinetic drug interactions as seen with erythromycin and other macrolides. Hepatic cytochrome P450 induction or inactivation via cytochrome-metabolite complex does not occur with azithromycin.[2]

Note: Patients who are not eligible for treatment under this statement may be considered on an individual basis where their GP or consultant believes exceptional circumstances exist that warrant deviation from the rule of this policy. In this situation, follow locally defined processes.

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APC administration provided by Midlands and Lancashire Commissioning Support Unit

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Effectiveness

Two randomised controlled trials BAT[3] and EMBRACE[4] found that, compared with placebo, azithromycin reduced the rate of pulmonary exacerbations needing antibiotics in adults with non-cystic fibrosis bronchiectasis over 6-12 months. The trials showed that azithromycin reduces exacerbations in the short term compared with placebo, but the evidence for other outcomes was unclear.

The BTS guidelines identified six meta-analyses and nine RCTs for the use of long-term therapy in COPD patients. GOLD 2019 and NICE NG115 (2018) were also considered. NICE NG115[5] suggests using azithromycin, usually 250mg three times weekly in COPD patients who have optimised non-pharmacological management and inhaled therapies and have 4 or more exacerbations per year or prolonged exacerbations or exacerbations resulting in hospitalisation. The BTS guidelines suggest a starting dose of 500mg three times weekly.

Safety

Long term safety has not been established as published trial data does not extend to greater than 1 year.

Clinicians should consider the arrhythmogenic potential (due to QT-interval prolongation) of azithromycin, particularly in those patients already taking medications that could prolong the QT interval and perform a baseline ECG prior to initiation. The largest trial to date excluded patients with tachycardia, prolonged QT interval and patients taking medications that could prolong the QT interval[6]

Nausea, vomiting, abdominal discomfort, and diarrhoea are common side-effects. Hepatotoxicity and rash occur less frequently. Hearing loss (usually reversible) occurs commonly after long-term therapy with azithromycin[7].

Azithromycin is contraindicated if there is hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any excipients listed in the SPC.

Microbiologists across the locality have been consulted and the general consensus of opinion is that azithromycin for prevention of exacerbation should not lead to bacterial resistance; however, consideration should be paid to the possibility of macrolide resistance.

Cost

Azithromycin capsules are significantly more expensive than tablets; therefore, tablets should be prescribed where possible.

It is not possible to estimate patient numbers for this indication, however, this intervention is likely to be cost neutral due to the reduction in non-elective hospital attendance.

<u>Annual Costs[8] (if tablets prescribed)</u>

250mg 3 times per week = £46.41

250mg daily = £108.59

500mg 3 times per week = £51.48 (using 500mg tablets)

(Capsules 250mg 3 times/week = £395.42, 250mg daily = £922.64, 500mg 3 times/week = £790.83).

Patient factors

No dose adjustment necessary in patients with mild to moderate renal impairment but caution is advised in patients with severe renal impairment (**eGFR**< 10mL/min) as systemic exposure to azithromycin may be increased.

Use with caution in patients with significant hepatic disease. and those taking medication which may prolong the QT interval.

LFTs and ECG should be performed at baseline.

Although full information on the risk this poses is not available patients should be advised of the potential for hearing loss after long term use.

Prescribing information

Opinion on dosing in this condition is varied, with a dose range of between 250mg to 500mg three times per week to 250mg daily, as per consultant recommendation.

Azithromycin does not significantly affect the hepatic cytochrome P450 system and is not believed to undergo the pharmacokinetic drug interactions as seen with erythromycin and other macrolides. Please refer to the Summary of Product Characteristics (SPC)[2] for further information.

Implementation notes

Azithromycin can be prescribed in primary care following recommendation by a respiratory specialist. The specialist should advise the GP of the daily dose and communicate that patient consent has been obtained. The specialist will inform the GP of the treatment goal in terms of reduction of exacerbations and the follow up action if this goal is not achieved – using template letter here. This information will be specific to each individual patient.

References

1. Smith D et al. British Thoracic Society guideline for the use of long-term macrolides in adults with respiratory disease. Thorax 2020;**75**:370–404.
2. SPC Azithromycin accessed 26/8/20
3. Altenburg J et al. (2013) Effect of azithromycin maintenance treatment on infectious exacerbations among patients with non-cystic fibrosis bronchiectasis: the BAT randomized controlled trial. JAMA 309:1251–9
4. Wong C et al. (2012) Azithromycin for prevention of exacerbations in non-cystic fibrosis bronchiectasis (EMBRACE): a randomised, double-blind, placebo-controlled trial. Lancet 380:660–7
5. NICE NG115 Chronic obstructive pulmonary disease in over 16s: diagnosis and management December 2018
6. Albert RK et al. Azithromycin for prevention of exacerbations of COPD, N Eng J Med 2011;365:689-98.
7. British National Formulary. (Accessed via nice.org.uk 26/8/20)
8. National Health Service England and Wales. Drug Tariff. August 2020: accessed 26/8/20