INFORMATION

Within the pan-Dorset Formulary “traffic light” system azithromycin has been classified as red. This Shared Care Guidance has been prepared to support the transfer of prescribing of long-term azithromycin from secondary to primary care (“amber”) within a shared care arrangement and is intended to apply to adults with bronchiectasis experiencing three or more exacerbations per year requiring antibiotic therapy.

Macrolides have been shown to have anti-inflammatory as well as antibiotic properties. Two small trials have demonstrated that treating patients with azithromycin can significantly reduce the number of exacerbations in patients with non-cystic fibrosis bronchiectasis. This use of azithromycin is off-label.

NICE has published an Evidence Summary on this topic https://www.nice.org.uk/advice/esuom38/chapter/Full-evidence-summary

AREAS OF RESPONSIBILITY FOR SHARED CARE

This shared care agreement outlines suggested ways in which the responsibilities for managing the prescribing of azithromycin for bronchiectasis can be shared between the specialist setting and the patient’s GP (if different). GPs are invited to participate. If the GP is not confident to undertake these roles, then he or she is under no obligation to do so. In such an event, the total clinical responsibility for the patient for the diagnosed condition remains with the specialist. If a specialist asks the GP to prescribe this drug, the GP should reply to this request as soon as practicable.

Sharing of care assumes communication. The intention to share care is usually explained to the patient by the doctor initiating treatment. It is important that patients are consulted about treatment and are in agreement with it.

The doctor who prescribes the medication legally assumes clinical responsibility for the drug and the consequences of its use.

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<th>Specialist Responsibilities</th>
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Specialist Responsibilities

11 After a 6-month trial, review patient and decide whether to continue treatment. Reflect on symptoms, exacerbation frequency and clinical outcomes such as spirometry.

12 Treatment should be discontinued if the patient becomes pregnant.

13 Advise GP on antibiotics to be prescribed in case of an acute exacerbation.

General Practitioner Responsibilities

1 To contact the referring consultant without delay if they do not wish to enter into a shared care agreement.

2 To continue prescriptions of azithromycin ensuring prescriptions include an end date of 6-months post initiation.

3 Where review of the patient by a respiratory consultant establishes that the patient requires longer term therapy ensure length of treatment required is clear.

4 To liaise with the consultant regarding any complications of treatment or as necessary.

5 To check for possible drug interactions when newly prescribing or stopping concurrent medication especially with regard to QT prolongation. See Interactions section below.

Patient's role (or that of carer)

1 Report to the specialist or GP if he or she does not have a clear understanding of the treatment.

2 Attend appropriate consultant and GP appointments.

3 Share any concerns in relation to treatment with azithromycin.

4 Use written and other information on the medication.

5 Seek help urgently if suffering suspected side effects, or otherwise unwell.

SUPPORTING INFORMATION

Dosage and Administration

500 mg once daily on Monday, Wednesday and Friday.

A reduced dose (250 mg) may be considered by the respiratory consultant in individual patient circumstances.

Azithromycin should always be prescribed as TABLETS as they are cheaper than capsules, see Drug Costs below.

Contraindications

The use of this product is contraindicated in patients with hypersensitivity to azithromycin, erythromycin, any macrolide or ketolide antibiotic, or to any of the excipients.

Cautions

As with erythromycin and other macrolides, rare serious allergic reactions, including angioedema and anaphylaxis (rarely fatal), have been reported. Some of these reactions with azithromycin have resulted in recurrent symptoms and required a longer period of observation and treatment.

Since liver is the principal route of elimination for azithromycin, the use of azithromycin should be undertaken with caution in patients with significant hepatic disease. Cases of fulminant hepatitis potentially leading to life-threatening liver failure have been reported with azithromycin (see section 4.8). 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.

In patients receiving ergot derivatives, ergotism has been precipitated by coadministration of some macrolide antibiotics. There are no data concerning the possibility of an interaction between ergot and azithromycin. However, because of the theoretical possibility of ergotism, azithromycin and ergot derivatives should not be co-administered.

As with any antibiotic preparation, observation for signs of super-infection with non-susceptible organisms, including fungi is recommended. 

_Clostridium difficile_ associated diarrhea (CDAD) has been reported with use of nearly all antibacterial agents, including azithromycin, and may range in severity from mild diarrhea to fatal colitis. Treatment with antibacterial agents alters the normal flora of the colon leading to overgrowth of _C. difficile_.

_C. difficile_ produces toxins A and B which contribute to the development of CDAD. Hypertoxin producing strains of _C. difficile_ cause increased morbidity and mortality, as these infections can be refractory to antimicrobial therapy and may require colectomy. CDAD must be considered in all patients who present with diarrhea following antibiotic use. Careful medical history is necessary since CDAD has been reported to occur over two months after the administration of antibacterial agents.

In patients with severe renal impairment (GFR <10 ml/min) a 33% increase in systemic exposure to azithromycin was observed.

Prolonged cardiac repolarization and QT interval, imparting a risk of developing cardiac arrhythmia and torsades de pointes, have been seen in treatment with macrolides including azithromycin. Therefore, as the following situations may lead to an increased risk for ventricular arrhythmias (including torsade de pointes) which can lead to cardiac arrest, azithromycin should be used with caution in patients with ongoing pro-arrhythmic conditions (especially women and elderly patients) such as patients:

- With congenital or documented QT prolongation
- Currently receiving treatment with other active substances known to prolong QT interval such as antiarrhythmics of class IA (quinidine and procainamide) and class III ( dofetilide, amiodarone and sotalol); antipsychotic agents such as pimozide; antidepressants such as citalopram; and fluoroquinolones such as moxifloxacin and levofloxacin
- With electrolyte disturbance, particularly in cases of hypokalaemia and hypomagnesaemia
- With clinically relevant bradycardia, cardiac arrhythmia or severe cardiac insufficiency

Exacerbations of the symptoms of myasthenia gravis and new onset of myasthenia syndrome have been reported in patients receiving azithromycin therapy (see section 4.8).

**Side effects**

Nausea, vomiting, abdominal discomfort, and diarrhoea anorexia, dyspepsia, flatulence, dizziness, headache, malaise, paraesthesia, arthralgia, disturbances in taste and vision; _less commonly_ constipation, gastritis, chest pain, oedema, anxiety, sleep disturbances, hypoesthesia, leucopenia, photosensitivity; _rarely_ agitation; also reported syncope, convulsions, smell disturbances, interstitial nephritis, acute renal failure, thrombocytopenia, haemolytic anaemia, tongue discoloration Generally reversible hearing loss (sometimes with tinnitus) can occur after large doses of a macrolide; it occurs commonly after long-term therapy with azithromycin

**Interactions**

_Antacids_
In a pharmacokinetic study investigating the effects of simultaneous administration of antacid with azithromycin, no effect on overall bioavailability was seen although peak serum concentrations were reduced by approximately 25%. In patients receiving both azithromycin and antacids, the drugs should not be taken simultaneously.

**Digoxin (P-gp substrates)**
Concomitant administration of macrolide antibiotics, including azithromycin, with P-glycoprotein substrates such as digoxin, has been reported to result in increased serum levels of the P-glycoprotein substrate. Therefore, if azithromycin and P-gp substrates such as digoxin are administered concomitantly, the possibility of elevated serum concentrations of the substrate should be considered.

**Ergot**
Due to the theoretical possibility of ergotism, the concurrent use of azithromycin with ergot derivatives is not recommended.

**Zidovudine**
*Single* 1000 mg doses and multiple 1200 mg or 600 mg doses of azithromycin had little effect on the plasma pharmacokinetics or urinary excretion of zidovudine or its glucuronide metabolite. However, administration of azithromycin increased the concentrations of phosphorylated zidovudine, the clinically active metabolite, in peripheral blood mononuclear cells. The clinical significance of this finding is unclear, but it may be of benefit to patients.

Azithromycin does not interact significantly with 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. Pharmacokinetic studies have been conducted between azithromycin and the following drugs known to undergo significant cytochrome P450 mediated metabolism.

**Atorvastatin**
Coadministration of atorvastatin (10 mg daily) and azithromycin (500 mg daily) did not alter the plasma concentrations of atorvastatin (based on a HMG CoA-reductase inhibition assay). However, post-marketing cases of rhabdomyolysis in patients receiving azithromycin with statins have been reported.

**Coumarin-Type Oral Anticoagulants**
There have been reports received in the post-marketing period of potentiated anticoagulation subsequent to co-administration of azithromycin and coumarin-type oral anticoagulants. Although a causal relationship has not been established, consideration should be given to the frequency of monitoring prothrombin time when azithromycin is used in patients receiving coumarin-type oral anticoagulants.

**Cyclosporin**
Caution should be exercised before considering concurrent administration of these drugs. If co-administration of these drugs is necessary, cyclosporin levels should be monitored and the dose adjusted accordingly.

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This list is not exhaustive. The manufacturer’s summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contraindications, warnings, side-effects and drug interactions.

**Drug costs:**
Drug Tariff December 2016

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<th>Pack size</th>
<th>Cost</th>
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<tr>
<td>Azithromycin 250 mg capsules</td>
<td>6</td>
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<td>Azithromycin 500 mg tablets</td>
<td>3</td>
<td>£1.32</td>
<td>£0.44</td>
</tr>
</tbody>
</table>

References

1. Non-cystic fibrosis bronchiectasis: long-term azithromycin ESUOM38. NICE Evidence Summary 2014  
   [https://www.nice.org.uk/advice/esuom38/chapter/Full-evidence-summary](https://www.nice.org.uk/advice/esuom38/chapter/Full-evidence-summary)
2. Summary of Product Characteristics Sandoz Azithromycin 250 mg tablets  
   [http://www.medicines.org.uk/emc/medicine/26131#PRODUCTINFO](http://www.medicines.org.uk/emc/medicine/26131#PRODUCTINFO)
3. BNF online Azithromycin, accessed online October 2016

First developed by: Respiratory Working Group November 2016  
Reviewed by: Respiratory Working Group February 2017  
Approved by: DMAG March 2017  
Review date: March 2019 or sooner if there is new evidence.