Non-cystic fibrosis bronchiectasis: long-term azithromycin

Evidence summary
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Key points from the evidence

The content of this evidence summary was up-to-date in November 2014. See summaries of product characteristics (SPCs), British national formulary (BNF) or the MHRA or NICE websites for up-to-date information.

Summary

Two randomised controlled trials (BAT: Altenburg J et al. 2013; n=89 and EMBRACE: Wong C et al. 2012; n=141) found that, compared with placebo, azithromycin reduced the rate of pulmonary exacerbations needing antibiotics in adults with non-cystic fibrosis bronchiectasis over 6 to 12 months. However, the evidence for other outcomes is unclear and the improvement in exacerbations must be balanced against the risk of experiencing adverse events and the development of antibiotic resistance.

Gastrointestinal adverse events occur very commonly with azithromycin treatment (incidence 1 in 10 or more). However, in the trials few people discontinued treatment due to adverse events. There is little published evidence to determine the efficacy and safety of azithromycin when used for non-cystic fibrosis bronchiectasis for more than 6 to 12 months.

Regulatory status: off-label. The topic was prioritised because there is uncertainty about the balance of risks and benefits when azithromycin is used long-term for non-cystic fibrosis bronchiectasis.
**Effectiveness**

- In BAT and EMBRACE, azithromycin was statistically significantly better than placebo in reducing exacerbations needing antibiotics.

- Azithromycin improved forced expired volume in 1 second (FEV$_1$) statistically significantly more than placebo in BAT. However, there was no significant difference between the groups in changes in pre-bronchodilator FEV$_1$ in EMBRACE.

- In BAT, St George's Respiratory Questionnaire (SGRQ) total scores improved statistically significantly more in the azithromycin group, compared with the placebo group. The difference was also clinically significant. However, in EMBRACE, there was no significant difference between the groups in change in SGRQ total score.

**Safety**

- In BAT and EMBRACE, azithromycin was generally well-tolerated and few people discontinued treatment due to adverse events.

- The summary of product characteristics for Zithromax capsules reports that diarrhoea, abdominal pain, nausea and flatulence occur very commonly with azithromycin treatment (incidence 1 in 10 or more).

- Azithromycin should be used with caution in people with a predisposition to QT interval prolongation.

- Concerns have been raised over the emergence of macrolide resistance during long-term azithromycin treatment.

**Patient factors**

- Children were not included in the BAT and EMBRACE trials. A study in 89 indigenous Australian, Maori and Pacific Island children with non-cystic fibrosis bronchiectasis found that azithromycin reduced the risk of exacerbations compared with placebo, but may not be applicable to the UK population.

- The optimal dose, frequency and treatment duration is unclear. In BAT, azithromycin 250 mg daily was used for 12 months, compared with azithromycin 500 mg 3 times weekly for 6 months in EMBRACE.

**Resource implications**

According to the Drug Tariff (October 2014), excluding VAT, azithromycin costs:

- £1.78 for 3 x 500 mg tablets
- £1.97 for 4 x 250 mg tablets
- £15.00 for 6 x 250 mg capsules
- £4.06 for 15 ml, £6.10 for 22.5 ml or £11.04 for 30 ml x 200 mg/5 ml suspension.
Introduction and current guidance

Bronchiectasis is a permanent dilatation and thickening of the airways associated with chronic cough, sputum production, bacterial colonisation and recurrent infection (NICE Clinical knowledge summary: bronchiectasis).

NICE has not published a clinical guideline on non-cystic fibrosis bronchiectasis. The British Thoracic Society guideline for non-CF bronchiectasis, which has been accredited by NICE, advises that long-term oral or nebulised antibiotics should be considered in adults with non-cystic fibrosis bronchiectasis who have 3 or more exacerbations per year that need antibiotic therapy, or who have fewer exacerbations that are causing significant morbidity. The antibiotic regimen should be determined by sputum microbiology. Similar advice is given for children.

The guideline notes that macrolide antibiotics may have disease-modifying activity and preliminary data suggest the need for a large randomised controlled trial. Since the guideline was published in 2010, randomised controlled trials on the use of macrolides for this condition have been published. This evidence summary considers the evidence for the safety and efficacy of long-term azithromycin in non-cystic fibrosis bronchiectasis.

Full text of Introduction and current guidance.

Product overview

Azithromycin is a macrolide antibiotic. In the UK, it is licensed for treating certain infections (bronchitis, community-acquired pneumonia, sinusitis, pharyngitis and tonsillitis, otitis media, skin and soft tissue infections and uncomplicated genital infections due to Chlamydia trachomatis) when they are known or likely to be due to one or more susceptible microorganisms (see summaries of product characteristics for azithromycin, for example, Zithromax capsules).

Although azithromycin is generally used for short courses only for its antibacterial properties, in common with some other macrolides, it also has anti-inflammatory properties. Therefore, it has been used for longer periods in chronic inflammatory conditions such as cystic fibrosis and non-cystic fibrosis bronchiectasis (Altenburg J et al. 2011). Use of azithromycin for non-cystic fibrosis bronchiectasis is off-label.

A NICE evidence summary on the off-label use of long-term azithromycin for cystic fibrosis is also available.
Consideration should be given to official guidance regarding the appropriate use of antibacterial agents. NICE is developing guidelines on Antimicrobial stewardship (expected March 2015) and Antimicrobial resistance – changing risk-related behaviours (expected March 2016).

Evidence review

- This evidence summary is based on 2 randomised, double-blind, placebo-controlled trials that assessed the efficacy of long-term azithromycin for treating non-cystic fibrosis bronchiectasis, BAT (Altenburg J et al. 2013; n=89) and EMBRACE (Wong C et al. 2012; n=141).

- Both trials included adults with confirmed non-cystic fibrosis bronchiectasis who had experienced pulmonary exacerbations requiring antibiotic treatment in the previous year (at least 3 in BAT and at least 1 in EMBRACE). In BAT, participants were randomised to receive azithromycin 250 mg daily or placebo for 12 months and, in EMBRACE, participants were randomised to receive azithromycin 500 mg 3 times weekly or placebo for 6 months. Participants in EMBRACE were followed for a further 6 months after the trial ended.

- In BAT, statistically significantly fewer people taking azithromycin had at least 1 exacerbation needing antibiotic treatment over 12 months, compared with people taking placebo (46.5% compared with 80.0% respectively; absolute risk reduction 33.5%, 95% confidence interval [CI] 14.1% to 52.9%; p value not reported). Three people would need to be treated with azithromycin for 12 months to maintain clinical stability in 1 person.

- In EMBRACE, in the 6-month treatment period, the rate of exacerbations needing antibiotics was statistically significantly lower with azithromycin compared with placebo (0.59 per patient compared with 1.57 per patient respectively; relative risk [RR] 0.38, 95% CI 0.26 to 0.54; p<0.0001). The benefits persisted for a further 6 months without treatment.

- A statistically significant improvement in percent of predicted FEV₁ of 4.52% was seen at 12 months in the azithromycin group in BAT, compared with the placebo group (p=0.047). Changes in pre-bronchodilator FEV₁ from baseline to 6 and 12 months did not differ significantly between the groups in EMBRACE.

- In BAT, the improvement in SGRQ total scores was both statistically and clinically significant in the azithromycin group, compared with the placebo group (p=0.046). The mean change in SGRQ total score at 6 and 12 months did not differ significantly between azithromycin and placebo in EMBRACE.
In BAT, 42% of people in both the azithromycin and placebo groups experienced an adverse event. In EMBRACE, 83% of people taking azithromycin and 93% of people taking placebo experienced an adverse event. One person in BAT and 2 people in EMBRACE discontinued azithromycin treatment due to a suspected adverse event. Overall, azithromycin was reported to be generally well tolerated.

The *summary of product characteristics for Zithromax capsules* reports that diarrhoea, abdominal pain, nausea and flatulence occur very commonly with azithromycin treatment (incidence 1 in 10 or more). In common with other macrolides, azithromycin should be used with caution in people with a predisposition to QT interval prolongation (including electrolyte disturbances and concomitant use of drugs that prolong the QT interval). Reversible hearing loss can occur after long-term therapy with azithromycin (*British national formulary*, October 2014).

Development of macrolide resistance was reported in both studies. However, the clinical implications of macrolide resistance are unclear.

There is concern that long-term use of azithromycin in individuals with occult or active nontuberculous mycobacteria infection could lead to resistance, which might complicate its treatment (*US Cystic fibrosis pulmonary guidelines*, 2013). Specialists involved in the production of this evidence summary have suggested that people with non-cystic fibrosis bronchiectasis who are selected for long-term azithromycin treatment should be screened for nontuberculous mycobacterial infection.

Both trials were placebo-controlled. The numbers of patients included in the trials were small, meaning that analysis of some outcomes may have been underpowered. In BAT, azithromycin 250 mg daily was used for 12 months, whereas azithromycin 500 mg 3 times weekly for 6 months (plus 6 months follow-up) was used in EMBRACE. These differences mean the optimal dose, frequency and treatment duration of azithromycin is unclear. Also, there is little published evidence to determine the efficacy and safety of azithromycin when used for non-cystic fibrosis bronchiectasis for more than 6 to 12 months. Both trials included adults only from non-UK populations (the Netherlands and New Zealand) and the results may not be generalisable to children with non-cystic fibrosis bronchiectasis.

A randomised controlled trial (*Valery PC et al. 2013*) has compared azithromycin (30 mg/kg weekly, maximum 600 mg) and placebo in indigenous Australian, Maori and Pacific Island children (*n*=89; mean age 4 years) with non-cystic fibrosis bronchiectasis. Over a mean of 20.7 months, children taking azithromycin were statistically significantly less likely to have pulmonary exacerbations than those taking placebo (*RR* 0.50, 95% *CI* 0.35 to 0.71; *p*<0.0001).
However, the results of this study may not be applicable to the children in the UK. No children or young people aged over 8 years were included in the study.

- The trials show that long-term azithromycin reduces exacerbations in the short term compared with placebo, but the evidence for other outcomes is unclear. The improvement in exacerbations must be balanced against the risk of experiencing adverse events and the development of macrolide-resistance.

Full text of Evidence review.

**Context and estimated impact for the NHS**

Costs of 6 months' treatment with azithromycin 250 mg daily are £89.63 for tablets, £455.00 for capsules and between £369.46 and £507.84 for suspension (Drug Tariff, October 2014).

Costs of 6 months' treatment with azithromycin 500 mg 3 times weekly are £46.28 or £76.83 for tablets, £390.00 for capsules and between £316.68 and £475.80 for suspension (Drug Tariff, October 2014).

Full text of Context and estimated impact for the NHS.

**Information for the public**

A plain English summary is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with non-cystic fibrosis bronchiectasis who are thinking about trying long-term azithromycin.
About this evidence summary

‘Evidence summaries: unlicensed or off-label medicines’ summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, but this summary is not NICE guidance.

Full evidence summary

Introduction and current guidance

Bronchiectasis is a permanent dilatation and thickening of the airways associated with chronic cough, sputum production, bacterial colonisation, and recurrent infection. It is associated with a wide range of diseases (for example, previous lower respiratory tract infection, immune deficiency, congenital airway abnormality and aspiration injury) but often the cause is unknown. Chronic inflammation of the airways destroys the elastic and muscular components of the bronchi, and the surrounding contractile lung tissue widens the airways. Mucus collecting in the dilated airways is prone to further infection, resulting in a cycle of recurrent infection and progressive airway injury (NICE Clinical knowledge summary: bronchiectasis).

The prognosis for bronchiectasis varies widely. Most people have few or no symptoms and a normal life expectancy. More severe disease results in daily symptoms, progressive loss of lung function, and a reduced life expectancy. The prognosis is worse if the person smokes, has extensive disease or frequent exacerbations, or if their lungs are colonised by Pseudomonas aeruginosa (NICE Clinical knowledge summary: bronchiectasis).

NICE has not published a clinical guideline on non-cystic fibrosis bronchiectasis. According to the British Thoracic Society guideline for non-CF bronchiectasis, which has been accredited by NICE, treatments for non-cystic fibrosis bronchiectasis include airway clearance using physiotherapy, pulmonary rehabilitation, antibiotics, bronchodilators (beta-2 agonists and anticholinergics) and surgery. The guideline recommends that antibiotic courses should be given for exacerbations that
present with an acute deterioration and worsening symptoms (cough, increased sputum volume or change of viscosity, increased sputum purulence with or without increasing wheeze, breathlessness or haemoptysis) and/or systemic illness. Sputum culture is recommended to guide antibiotic therapy.

The British Thoracic Society advises that long-term oral or nebulised antibiotics should be considered for adults with non-cystic fibrosis bronchiectasis who have 3 or more exacerbations per year that need antibiotic therapy, or who have fewer exacerbations that are causing significant morbidity. The antibiotic regimen should be determined by sputum microbiology. Similar advice is given for children.

The British Thoracic Society guideline for non-CF bronchiectasis notes that macrolides may have disease-modifying activity and preliminary data suggest the need for a large randomised controlled trial. Since the guideline was published in 2010, randomised controlled trials on the use of macrolides for this condition have been published. This evidence summary considers the evidence for the safety and efficacy of long-term azithromycin in non-cystic fibrosis bronchiectasis.

**Product overview**

**Drug action**

Azithromycin is a macrolide antibiotic. Although it is generally used in short courses for its antibacterial properties, in common with some other macrolides, it also has anti-inflammatory properties. It may also interfere with the protective biofilm of *P. aeruginosa* and the adherence of *P. aeruginosa* to epithelial cells. Therefore, it has been used for longer periods in conditions such as cystic fibrosis and non-cystic fibrosis bronchiectasis (Altenburg J et al. 2011).

A NICE evidence summary on the use of long-term azithromycin for cystic fibrosis is also available.

**Regulatory status**

In the UK, azithromycin is licensed for treating certain infections (bronchitis, community-acquired pneumonia, sinusitis, pharyngitis and tonsillitis, otitis media, skin and soft tissue infections and uncomplicated genital infections due to *Chlamydia trachomatis*) when they are known or likely to be due to one or more susceptible microorganisms (see summaries of product characteristics for azithromycin, for example, Zithromax capsules).

Azithromycin is administered as a single daily dose. In children and young people over 45 kg and adults, the dose is usually 500 mg daily for 3 days (except for uncomplicated genital infections).
Suspensions are available for children and young people weighing less than 45 kg and the dose is 10 mg/kg daily for 3 days. However, azithromycin is not licensed for use in children aged under 6 months (see summaries of product characteristics for azithromycin, for example, Zithromax capsules and suspension).

Use of azithromycin for non-cystic fibrosis bronchiectasis is off-label.

In line with the guidance from the General Medical Council (GMC), it is the responsibility of the prescriber to determine the clinical need of the patient and the suitability of using azithromycin outside its authorised indications.

The summaries of product characteristics for azithromycin advise that consideration should be given to official guidance regarding the appropriate use of antibacterial agents. NICE is developing guidelines on Antimicrobial stewardship (expected March 2015) and Antimicrobial resistance – changing risk-related behaviours (expected March 2016).

**Cost**

According to the Drug Tariff (October 2014), excluding VAT, azithromycin costs:

- £1.78 for 3 x 500 mg tablets
- £1.97 for 4 x 250 mg tablets
- £15.00 for 6 x 250 mg capsules
- £4.06 for 15 ml, £6.10 for 22.5 ml or £11.04 for 30 ml x 200 mg/5 ml suspension.

**Evidence review**

This evidence summary is based on 2 randomised controlled trials (BAT and EMBRACE) that assessed the efficacy of long-term azithromycin for treating non-cystic fibrosis bronchiectasis. Other studies identified by searches performed for the evidence summary were excluded because they were either very small or were not applicable to the UK population. A further study has been completed but not yet published (NCT02107274).

**The BAT trial** (Altenburg J et al. 2013)
• **Design:** The Bronchiectasis and long-term Azithromycin Treatment (BAT) trial was a randomised, double-blind, placebo-controlled trial in 89 outpatients in 14 hospitals in the Netherlands.

• **Population:** The trial included people aged 18 years or over (mean 62 years) who had non-cystic fibrosis bronchiectasis (diagnosed by plain bronchography or high-resolution computed tomography). Other inclusion criteria were at least 3 lower respiratory tract infections treated with antibiotics, and at least 1 sputum culture of 1 or more bacterial respiratory pathogens in the preceding year. Patients were excluded if they had received more than 4 weeks of macrolide therapy in the previous 3 months, oral or intravenous courses of corticosteroids within 30 days of screening, or any antimicrobial treatment for a lower respiratory tract infection in the last 2 weeks. The use of long-term maintenance antibiotics or low-dose steroids was permitted during the trial.

• **Intervention and comparison:** Following randomisation to oral azithromycin 250 mg daily (n=45) or matching placebo (n=44), patients were observed for 2 weeks for clinical stability before they started their allocated treatment. The method of allocation described suggests that this was concealed although it is not explicitly stated in the methods. Patients were followed up every 3 months for 12 months and completed weekly diary cards.

• **Outcomes:** The primary outcome was the number of people having at least 1 infectious exacerbation over 12 months. An infectious exacerbation was defined as an increase in respiratory symptoms requiring antibiotic treatment. The original protocol required the inclusion of antibiotic- and steroid-treated events; however, before the primary outcome was analysed, this was amended to omit a small number of events not treated with antibiotics. Secondary outcomes included lung function, sputum bacteriology, inflammatory markers, symptom scores, quality of life and adverse events. Symptoms were measured using the lower respiratory tract infection visual analogue scale (LRTI-VAS), a symptom score specifically designed to investigate common symptoms in people with bronchiectasis. This scale is currently being validated for use in bronchiectasis by the trial's research group. On the LRTI-VAS scale, 5 symptoms are each scored from 1 to 10 (where 10 indicates more severe symptoms) and added together to obtain a total score. It is unclear how many points constitute a clinically significant change on this scale. Health-related quality of life was measured using the St George’s Respiratory Questionnaire (SGRQ). On this validated scale, 76 items in 3 domains are scored separately and added together to give a total score from 0 to 100, with 0 indicating no impairment of quality of life. According to the NICE full guideline on COPD (NICE guideline CG101), a difference of 4 points or more on the SGRQ scale is considered clinically significant. Statistical analysis was performed on data from the modified intention-to-treat
population, defined as all randomised participants who received at least 1 dose of study drug. The investigators stated that the trial was not powered to analyse adverse events.

Table 1 Summary of the BAT trial (Altenburg J et al. 2013)

<table>
<thead>
<tr>
<th></th>
<th>Azithromycin 250 mg daily</th>
<th>Matching placebo</th>
<th>Analysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Randomised</td>
<td>n=45</td>
<td>n=44</td>
<td></td>
</tr>
<tr>
<td><strong>Efficacy</strong>^a</td>
<td>n=43</td>
<td>n=40</td>
<td></td>
</tr>
<tr>
<td>Mean number of exacerbations after 12 months</td>
<td>0.84 per patient</td>
<td>2.05 per patient</td>
<td>Difference 1.21 per patient p&lt;0.001</td>
</tr>
<tr>
<td>Number of people with at least 1 exacerbation in 12 months</td>
<td>46.5% (20/43)</td>
<td>80.0% (32/40)</td>
<td>NNT for treatment with azithromycin to maintain clinical stability in 1 person = 3</td>
</tr>
<tr>
<td><strong>Selected secondary outcomes:</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Change in health-related quality of life scores (SGRQ)</td>
<td>-6.09 per 6 months (improvement)</td>
<td>-2.06 per 6 months (improvement)</td>
<td>Difference 8.06 at 12 months p=0.046</td>
</tr>
<tr>
<td>Change in % predicted FEV₁</td>
<td>+1.03 per 3 months (improvement)</td>
<td>-0.10 per 3 months (deterioration)</td>
<td>Difference 4.52 at 12 months p=0.047</td>
</tr>
<tr>
<td>Change in symptom scores (LRTI-VAS)</td>
<td>-1.11 per 3 months (improvement)</td>
<td>-0.056 per 3 months (improvement)</td>
<td>Difference 4.216 at 12 months p=0.047</td>
</tr>
<tr>
<td><strong>Safety</strong></td>
<td>n=43</td>
<td>n=40</td>
<td></td>
</tr>
<tr>
<td>Patients reporting adverse events</td>
<td>41.9% (18/43)</td>
<td>42.5% (17/40)</td>
<td>The trial was not powered to detect differences between the treatments in adverse events</td>
</tr>
<tr>
<td>Patients reporting diarrhoea</td>
<td>20.9% (9/43)</td>
<td>2.5% (1/40)</td>
<td></td>
</tr>
<tr>
<td>Patients reporting abdominal pain</td>
<td>18.6% (8/43)</td>
<td>2.5% (1/40)</td>
<td></td>
</tr>
</tbody>
</table>
The EMBRACE trial (Wong C et al. 2012)

- **Design:** The Effectiveness of Macrolides in patients with BRonchiectasis using Azithromycin to Control Exacerbations (EMBRACE) trial was a randomised, double-blind, placebo-controlled trial in 141 patients in 3 centres in New Zealand.

- **Population:** The trial included people aged 18 years or over (mean 60 years) who had non-cystic fibrosis bronchiectasis (diagnosed by high-resolution computed tomography) and at least 1 pulmonary exacerbation requiring antibiotics in the preceding year. Patients were excluded if they had received more than 3 months of macrolide therapy in the previous 6 months, or had a positive culture of nontuberculous mycobacteria in the past 2 years or at screening.

- **Intervention and comparison:** Patients were randomised to receive oral azithromycin 500 mg daily (n=71) or matching placebo (n=70) on 3 days (Monday, Wednesday and Friday) every week for 6 months. Allocation was concealed. Patients were asked to complete a daily symptom diary and were followed up for a further 6 months. Clinic visits were at 1, 3, 6, 9 and 12 months with monthly telephone calls between visits.

- **Outcomes:** The 3 co-primary outcomes were rate of exacerbations in the first 6 months, pre-bronchodilator FEV₁, and SGRQ total score at 6 months. An exacerbation was defined as an increase in, or new onset of, more than 1 pulmonary symptom (sputum volume, sputum purulence or dyspnoea) needing treatment with antibiotics. Treatment of exacerbations was at the discretion of patients’ GPs but they were asked to avoid using macrolide antibiotics. Secondary outcomes included time to first exacerbation, rate of symptom-based exacerbations, lung function, exercise capacity, sputum bacteriology, inflammatory markers, SGRQ total score at 12 months and adverse events. A symptom-based exacerbation was defined as an increase in, or new onset of, more than 1 pulmonary symptom reported on the daily diary card and an increase of at least 1 point (on a 5-point scale) in the mean of the 3 symptom scores from the daily diary card on 2 consecutive days, compared with the same calculation 1 week earlier. Exercise capacity was assessed using the 6-minute walking test, for which the NICE full guideline on COPD considers a distance of 50 m to be clinically significant. All analyses were by intention-to-treat.
Table 2 Summary of the EMBRACE trial (Wong C et al. 2012)

<table>
<thead>
<tr>
<th>Randomised</th>
<th>Azithromycin 500 mg 3 times weekly</th>
<th>Matching placebo</th>
<th>Analysisa</th>
</tr>
</thead>
<tbody>
<tr>
<td>Efficacy</td>
<td>n=71</td>
<td>n=70</td>
<td>RR 0.38</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>95% CI 0.26 to 0.54</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td>p&lt;0.0001</td>
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</tbody>
</table>

Primary outcome 1: rate of exacerbations in 6 months

- Azithromycin: 0.59 per patient
- Placebo: 1.57 per patient

Primary outcome 2: change in pre-bronchodilator FEV₁ at 6 months and 12 months

- Azithromycin: 0.00 L
- Placebo: -0.04 L

Primary outcome 3: Change in health-related quality of life scores (SGRQ) at 6 months

- Azithromycin: -5.17
- Placebo: -1.92

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### Selected secondary outcomes:

<table>
<thead>
<tr>
<th></th>
<th>Group 1</th>
<th>Group 2</th>
<th>Relative Risk</th>
<th>95% Confidence Interval</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rate of exacerbations in 12 months</strong></td>
<td>1.58 per patient</td>
<td>2.73 per patient</td>
<td>RR 0.58</td>
<td>95% CI 0.46 to 0.74</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td><strong>Median time to first exacerbation in 12 months</strong></td>
<td>239 days (95% CI 190 days to 331 days)</td>
<td>85 days (95% CI 52 days to 113 days)</td>
<td>RR 0.44</td>
<td>95% CI 0.29 to 0.65</td>
<td>p&lt;0.0001</td>
</tr>
<tr>
<td><strong>Change in exercise capacity (6MWT) at 12 months</strong></td>
<td>1.19 m</td>
<td>-5.28 m</td>
<td>No significant difference</td>
<td>Difference 6.48</td>
<td>95% CI -11.28 to 24.22</td>
</tr>
<tr>
<td><strong>Change in health-related quality of life scores (SGRQ) at 12 months</strong></td>
<td>-2.89</td>
<td>-4.71</td>
<td>No significant difference</td>
<td>Difference 1.82</td>
<td>95% CI -0.27 to 6.32</td>
</tr>
</tbody>
</table>

### Safety

<table>
<thead>
<tr>
<th></th>
<th>Group 1 (n=71)</th>
<th>Group 2 (n=70)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Patients reporting serious adverse events</strong></td>
<td>5.6% (4/71)</td>
<td>12.9% (9/70)</td>
<td>Significance of difference not reported</td>
</tr>
<tr>
<td><strong>Patients reporting adverse events</strong></td>
<td>83.1% (59/71)</td>
<td>92.3% (65/70)</td>
<td>Significance of difference not reported</td>
</tr>
<tr>
<td><strong>Patients reporting gastrointestinal adverse events</strong></td>
<td>26.8% (19/71)</td>
<td>12.9% (9/70)</td>
<td>p=0.005</td>
</tr>
<tr>
<td>Patients reporting diarrhoea</td>
<td>18.3% (13/71)</td>
<td>5.7% (4/70)</td>
<td>Significance of difference not reported</td>
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<tr>
<td>----------------------------</td>
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<td>----------------------------------------</td>
</tr>
<tr>
<td>Patients reporting nausea or vomiting</td>
<td>12.7% (9/71)</td>
<td>7.1% (5/70)</td>
<td>Significance of difference not reported</td>
</tr>
<tr>
<td>Patients reporting epigastric discomfort</td>
<td>6.8% (5/71)</td>
<td>1.4% (1/70)</td>
<td>Significance of difference not reported</td>
</tr>
</tbody>
</table>

Abbreviations: 6MWT, 6-minute walking test; CI, confidence interval; FEV₁, forced expired volume in 1 second; L, litre; p, p value; RR, relative risk; SGRQ, St George's Respiratory Questionnaire.

All analyses were by intention-to-treat.

Clinical effectiveness

Exacerbations

In BAT (Altenburg J et al. 2013), statistically significantly fewer people taking azithromycin 250 mg daily had at least 1 exacerbation over 12 months, compared with people taking placebo (46.5% compared with 80.0% respectively; absolute risk reduction 33.5%, 95% confidence interval [CI] 14.1% to 52.9%; p value not reported). Three people would need to be treated with azithromycin for 12 months to maintain clinical stability in 1 person.

In EMBRACE (Wong C et al. 2012), in the 6-month treatment period, the rate of exacerbations requiring antibiotic treatment was statistically significantly lower with azithromycin 500 mg 3 times weekly, compared with placebo (0.59 per patient compared with 1.57 per patient respectively; relative risk [RR] 0.38, 95% CI 0.26 to 0.54; p<0.0001). The benefits persisted for a further 6 months without treatment. Over 12 months, the annual rate of exacerbations was 1.58 per patient in the azithromycin group and 2.73 per patient in the placebo group (RR 0.58, 95% CI 0.46 to 0.74; p<0.0001).

In EMBRACE, over 12 months, the median time to the first exacerbation was 239 days in the azithromycin group, compared with 85 days in the placebo group (RR 0.44, 95% CI 0.29 to 0.65; p<0.0001). There was no significant difference between the groups in the annual rate of symptom-based exacerbations (worsening of symptoms compared to the previous week), or the time to the first symptom-based exacerbation over 6 or 12 months.
Lung function

In BAT ([Altenburg J et al. 2013](#)), a statistically significant improvement in percent of predicted FEV\textsubscript{1} (1% at 3 months and 4% at 12 months) was seen in the azithromycin group, compared with the placebo group (p=0.047).

Changes in pre- and post-bronchodilator FEV\textsubscript{1} from baseline to 6 and 12 months did not differ significantly between the groups in EMBRACE ([Wong C et al. 2012](#)).

Health-related quality of life

In BAT ([Altenburg J et al. 2013](#)), SGRQ total scores improved statistically significantly more in the azithromycin group, compared with the placebo group (p=0.046). The average difference between the groups was 4 points per 6 months (8 points at 12 months) which is considered to be clinically significant. A post hoc analysis found that 28 people (64%) taking azithromycin had an improvement of 4 points on the SGRQ scale at 12 months, compared with 18 (46%) taking placebo (p value not reported).

The mean change in SGRQ total score at 6 and 12 months did not differ significantly between azithromycin and placebo in EMBRACE ([Wong C et al. 2012](#)).

Symptom scores

The BAT trial ([Altenburg J et al. 2013](#)) found that mean LRTI-VAS scores improved statistically significantly more in people taking azithromycin, compared with placebo (p=0.047). The difference between the groups was 1 point at 3 months and 4 points at 12 months. It is unclear whether this difference on the 50-point LRTI-VAS scale is clinically significant.

Symptoms scores were assessed in EMBRACE ([Wong C et al. 2012](#)), only as part of the assessment of health-related quality of life using the SGRQ. The symptom component of the SGRQ improved more in the azithromycin group compared with the placebo group at 6 months (−10.9 compared with −3.99; difference −6.70, 95% CI −13.37 to −0.04; p=0.049). However, the difference only just reached statistical significance at this time and no significant difference was seen at 12 months.

In EMBRACE, no significant differences were found between azithromycin and placebo in the 6-minute walking test at 6 or 12 months.
Other outcomes

In BAT (Altenburg J et al. 2013), changes in serum C-reactive protein levels and white blood cell counts did not differ significantly between the azithromycin and placebo groups. Also, analysis of sputum samples found that microbiological profiles did not differ significantly between the groups at baseline or 12 months.

In EMBRACE (Wong C et al. 2012), C-reactive protein levels and white blood cell counts were statistically significantly better in the azithromycin group compared with the placebo group at 6 months (p=0.006 and p=0.013 respectively). Blood tests were not performed at 12 months. At baseline, the microbiology profile for selected respiratory pathogens was similar between the azithromycin and placebo. There was no significant difference between the groups in the number of new respiratory pathogens cultured after 6 months of treatment.

Safety and tolerability

In BAT (Altenburg J et al. 2013), 42% of patients in each group experienced an adverse event. Adverse events were generally mild and occurred in the first weeks of treatment and subsequently subsided. One person in each group discontinued treatment due to a suspected adverse event. Diarrhoea and abdominal pain occurred more often in the azithromycin group, compared with the placebo group (20.9% compared with 2.5%, and 18.6% compared with 2.5% respectively). However, the trial was not powered to detect differences between the groups in adverse events.

In EMBRACE (Wong C et al. 2012), 83% of people taking azithromycin and 93% of people taking placebo experienced an adverse event. Overall, azithromycin was reported to be generally well tolerated. Adverse events were reported to be serious in 4 people taking azithromycin and 9 people taking placebo. One person in the azithromycin group was admitted for an exacerbation of bronchiectasis compared with 3 people in the placebo group. Gastrointestinal symptoms (nausea, vomiting, diarrhoea, epigastric discomfort and constipation) were reported significantly more often with azithromycin compared with placebo (p=0.005; see table 2 for details). Two patients in each group discontinued treatment because of gastrointestinal symptoms.

The summary of product characteristics for Zithromax capsules reports that, whilst azithromycin is generally well tolerated, diarrhoea, abdominal pain, nausea and flatulence occur very commonly with azithromycin treatment (incidence 1 in 10 or more). Common adverse effects (incidence between 1 in 100 and 1 in 10) include anorexia, dizziness, headache, paraesthesia, dysgeusia (abnormal taste), visual impairment, deafness, vomiting, dyspepsia, pruritus, rash, arthralgia, and fatigue. In common with other macrolides, azithromycin should be used with caution in people with
a predisposition to QT interval prolongation (including electrolyte disturbances and concomitant use of drugs that prolong the QT interval).

According to the British national formulary (September 2014), reversible hearing loss (sometimes with tinnitus) can occur after long-term therapy with azithromycin.

In BAT (Altenburg J et al. 2013), 88% of pathogens (53/60) tested for sensitivity in 20 people in the azithromycin group became macrolide-resistant, compared with 26% of pathogens (29/112) in 22 people in the placebo group (p<0.001). The authors note that emergence of resistant organisms was not mirrored by loss of efficacy in subsequent months.

In EMBRACE (Wong C et al. 2012), macrolide resistance testing was not routinely undertaken. However, 2 (4%) patients in the azithromycin group developed macrolide-resistant Streptococcus pneumoniae at 6 months.

**Evidence strengths and limitations**

The BAT (Altenburg J et al. 2013) and EMBRACE (Wong C et al. 2012) trials were both double-blind randomised, controlled trials, in which allocation appears to have been concealed and adherence to treatment was over 96%. Both trials were placebo-controlled but specialists involved in the production of this evidence summary have advised that there is no obvious active comparator. The numbers of patients included in the trials were small (n=89 and n=141 respectively) meaning that analysis of some outcomes may have been underpowered. The BAT paper states that the trial was not powered to assess safety of azithromycin compared with placebo.

Inclusion and exclusion criteria, baseline characteristics and the outcomes considered differed slightly between the trials, which complicates direct comparison of the results. Unlike the SGRQ, the symptom scale used in BAT, LRTI-VAS, has not yet been validated. In addition, it is unclear whether statistically significant changes seen on the LRTI-VAS scale were clinically significant.

The definitions of exacerbations differed slightly in BAT and EMBRACE, but both primary exacerbation outcomes were essentially exacerbations needing antibiotics, an appropriate outcome in people with bronchiectasis. In EMBRACE, although a statistically significant difference was seen between azithromycin and placebo in event-based exacerbations (requiring hospitalisation), no difference was seen in symptom-based exacerbations (worsening of symptoms compared to the previous week). The study authors state that this may have been because the definition of an exacerbation did not include cough (the most common symptom in bronchiectasis). In BAT, the number of exacerbations seen in the placebo group was lower during treatment than in
the year before study enrolment (median 2 compared with 5 respectively). The authors suggest that this may have been because patients were encouraged to contact their respiratory physician rather than having to contact their GP, or because sputum samples were obtained every 3 months facilitating culture-guided therapy, which may have prolonged the time until the next exacerbation.

In BAT, azithromycin 250 mg daily was used for 12 months, compared with azithromycin 500 mg 3 times weekly for 6 months (plus 6 months follow-up) in EMBRACE. These differences mean the optimal dose, frequency and treatment duration is unclear. When used according to the marketing authorisation, azithromycin is used for short courses, and there is relatively little data on its long-term safety. Rare adverse effects may not have been identified in the small numbers of patients studied over 6 to 12 months. In addition, the authors of EMBRACE note that more studies are needed to define the cardiovascular risks of azithromycin.

*P. aeruginosa* infection was present in only 10% of patients in BAT and 12% of patients in EMBRACE. It is unclear whether presence or absence of this microorganism affects the outcomes of long-term azithromycin treatment in non-cystic fibrosis bronchiectasis.

Unlike the EMBRACE trial, the BAT trial did not screen patients for mycobacterial infection at baseline or exclude patients with evidence of a nontuberculous mycobacterial infection. The authors of BAT note that clinical improvement in patients with nontuberculous mycobacterial infection might therefore be the result of the direct anti-mycobacterial action of macrolides. However, because standard treatment for nontuberculous mycobacterial infection in the participating hospitals included macrolide treatment, and recent use of macrolides was an exclusion criterion, these patients were not expected to be eligible for randomisation. In addition, sputum cultures obtained at baseline did not indicate nontuberculous mycobacterial infection. Nevertheless, there is concern that long-term use of azithromycin in individuals with occult or active nontuberculous mycobacteria infection could lead to resistance, which might complicate its treatment (US Cystic fibrosis pulmonary guidelines, 2013). The authors of EMBRACE recommend that patients with non-cystic fibrosis bronchiectasis who are selected for long-term azithromycin treatment should be screened for nontuberculous mycobacterial infection.

Also of concern is that macrolide-resistant pathogens were reported in both studies. The authors of BAT state that, because numerous alternative antibiotics are available to treat airway pathogens and azithromycin is not considered first-line in patients with exacerbations of non-cystic fibrosis bronchiectasis, macrolide resistance might not necessarily be an issue in this patient group. However, the clinical implications of macrolide resistance are unclear. An important risk of induction of macrolide resistance in individuals is the potential increase of macrolide-resistant microorganisms in the wider community. Wider macrolide resistance could be a potential cause of
treatment failure in patients with illnesses treated with macrolides first-line (for example, community-acquired pneumonia).

The BAT and EMBRACE trials included adults only from non-UK populations (the Netherlands and New Zealand) and the results may not be generalisable to children with bronchiectasis or to UK practice. A double-blind randomised controlled trial (Valery PC et al. 2013) has assessed long-term azithromycin in indigenous Australian, Maori and Pacific Island children in Australia and New Zealand (n=89) with non-cystic fibrosis bronchiectasis (82% confirmed and 18% clinically suspected). Participants were aged 1 to 8 years (mean age 4 years) and had experienced at least 1 exacerbation in the previous 12 months. They were randomised to receive azithromycin 30mg/kg (maximum 600 mg) or placebo once weekly for 12−24 months (mean 20.7 months). The study may have been underpowered, particularly for secondary outcomes, because only 89 children were enrolled, which is less than the required sample size of 102 children.

The study found that children taking azithromycin were statistically significantly less likely to have pulmonary exacerbations than those taking placebo (RR 0.50, 95% CI 0.35 to 0.71; p<0.0001). Carriage of azithromycin-resistant bacteria was statistically significantly higher in the azithromycin group than in the placebo group (46% compared with 11%; odds ratio 7.39, 95% CI 2.15 to 25.39; p=0.002). The most common adverse events were non-pulmonary infections (71 episodes in the azithromycin group and 132 in the placebo group) and bronchiectasis-related events (22 episodes in the azithromycin group and 48 in the placebo group: p values not reported). Azithromycin was generally well-tolerated.

The results of the study suggest that, compared with placebo, azithromycin reduces exacerbations in indigenous Australian, Maori and Pacific Island children with non-cystic fibrosis bronchiectasis. However, the results of the study may not be applicable to the children in the UK. No children or young people aged over 8 years were included in the study because, in the investigator's experience, children with bronchiectasis undergoing puberty have a different pattern of illness.

The trials show that long-term azithromycin reduces exacerbations compared with placebo, but the evidence for other outcomes is unclear. The improvement in exacerbations must be balanced against the risk of experiencing adverse events and the development of macrolide-resistance.
Context and estimated impact for the NHS

Cost effectiveness

No cost-effectiveness studies were identified that compared the use of off-label doses of azithromycin for non-cystic fibrosis bronchiectasis with other treatments or placebo.

Costs of 6 months' treatment with azithromycin in adults based on regimens used in the BAT (Altenburg J et al. 2013) and EMBRACE (Wong C et al. 2012) trials are shown in table 3.

Table 3 Costs of azithromycin treatment

<table>
<thead>
<tr>
<th>Drug</th>
<th>Cost (excluding VAT: Drug Tariff, October 2014)</th>
<th>Cost (excluding VAT) of 6 months' treatment</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>250 mg daily (BAT)</td>
<td>500 mg 3 times weekly (EMBRACE)</td>
</tr>
<tr>
<td>Azithromycin 500 mg tablets</td>
<td>£1.78 for 3 tablets</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Azithromycin 250 mg tablets</td>
<td>£1.97 for 4 tablets</td>
<td>£89.63</td>
</tr>
<tr>
<td>Azithromycin 250 mg capsules</td>
<td>£15.00 for 6 capsules</td>
<td>£455</td>
</tr>
<tr>
<td>Azithromycin 200 mg/5 ml suspension</td>
<td>£4.06 for 15 ml</td>
<td>£369.46&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>£6.10 for 22.5 ml</td>
<td>£372.10&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
<tr>
<td></td>
<td>£11.04 for 30 ml</td>
<td>£507.84&lt;sup&gt;a&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

<sup>a</sup> The costs of the suspension include wastage incurred due to the prescription of overage to allow full doses to be administered from a single bottle.

Current drug usage

No information on the use of azithromycin specifically for non-cystic fibrosis bronchiectasis was available at the time this evidence summary was prepared.

The NHS prescription cost analysis for England 2013 reports that 475,000 community prescriptions for azithromycin were dispensed in 2012, costing £10.3 million (net ingredient cost).
The indications for these prescriptions are not provided but it is likely that most will have been for licensed indications. In addition, these data do not include hospital prescriptions.

**Information for the public**

A plain English summary is available on the NICE website. This sets out the main points from the evidence summary in non-technical language and may be especially helpful for people with non-cystic bronchiectasis who are thinking about trying long-term azithromycin.

**Relevance to NICE guidance programmes**

This use of azithromycin for non-cystic fibrosis bronchiectasis is not appropriate for referral for a NICE technology appraisal and is not currently planned into any other work programme.

A NICE medicines and prescribing guideline on Antimicrobial stewardship (expected March 2015) and a NICE public health guideline on Antimicrobial resistance – changing risk-related behaviours (expected March 2016) are currently being produced.

**References**

Altenburg J, de Graaff CS, Stienstra Y 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


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Pfizer Limited (2014) Zithromax capsules summary of product characteristics [online; accessed 9 October 2014]


Development of this evidence summary

The integrated process statement sets out the process NICE uses to select topics for the evidence summaries for unlicensed/off-label medicines and how the summaries are developed, quality assured and approved for publication.

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Declarations of interest

No relevant interests declared.
About this evidence summary

‘Evidence summaries: unlicensed or off-label medicines’ summarise the published evidence for selected unlicensed or off-label medicines that are considered to be of significance to the NHS, where there are no clinically appropriate licensed alternatives. The summaries provide information for clinicians and patients to inform their decision-making and support the construction and updating of local formularies.

The summaries support decision-making on the use of an unlicensed or off-label medicine for an individual patient, where there are good clinical reasons for its use, usually when there is no licensed medicine for the condition requiring treatment, or the licensed medicine is not appropriate for that individual.

The strengths and weaknesses of the relevant evidence are critically reviewed within this summary, but this summary is not NICE guidance.

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