Cystic fibrosis: long-term azithromycin

Evidence summary
Published: 25 November 2014
nice.org.uk/guidance/esuom37

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), BNF for children (BNFc) or the MHRA or NICE websites for up-to-date information.

Summary

A Cochrane review (10 studies, n=959) assessed the use of long-term azithromycin for cystic fibrosis. Six studies (n=836) had a low risk of bias. Various dosing regimens were used, the most common being 250–500 mg 3 times weekly. In 4 studies (n=549), treatment with azithromycin statistically significantly improved forced expired volume in 1 second (FEV₁; the primary outcome) over 6 months compared with placebo. Azithromycin doubled the rate of being free of exacerbations over 6 months compared with placebo; however, the data were heterogeneous and should be interpreted with caution. The need for oral antibiotics was statistically significantly reduced with azithromycin, but there were limited data on the need for intravenous antibiotics and other secondary outcomes. Adverse events were uncommon and not obviously associated with azithromycin. There is little published evidence to determine the safety of azithromycin when used for over 6 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 cystic fibrosis.
### Effectiveness

In the [Cochrane review](https://link.to/cochrane.review), compared with placebo, azithromycin statistically significantly:

- improved FEV₁ (the primary outcome) over 6 months compared with placebo (4 studies, n=549; mean difference 3.97% of predicted, 95% confidence interval [CI] 1.74 to 6.19).

- improved the rate of being free from exacerbations over 6 months (4 studies, n=609; odds ratio [OR] 1.96, 95% CI 1.15 to 3.33). However, the data were heterogeneous and should be interpreted with caution.

- reduced the need for oral antibiotics (3 studies, n=527; OR 0.28, 95% CI 0.19 to 0.42). However, there were limited data on the need for intravenous antibiotics and other secondary outcomes.

### Safety

- In the [Cochrane review](https://link.to/cochrane.review), adverse events were uncommon and not obviously associated with azithromycin. Over 2–12 months, no serious adverse events were reported and study withdrawals were rare.

- The [summary of product characteristics for Zithromax capsules](https://link.to/zithromax) 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).

- 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 (particularly *Staphylococcus aureus*) during long-term azithromycin treatment.
### Patient factors

- In the RCTs in the Cochrane review, no clear effect was found on patient-reported quality of life with azithromycin.
- No children aged under 6 years were included in the studies in the Cochrane review.
- Azithromycin is taken orally. Some people may prefer oral to inhaled antibiotic treatment.
- The most common dosing frequency used in studies in the Cochrane review was 250–500 mg 3 times weekly; the optimum dosing regimen is unclear.

### 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.

Based on guidance from the Cystic Fibrosis Trust, depending on the formulation used, the cost (excluding VAT) of 6 months’ treatment with azithromycin ranges from:

- £46.28 to £430.56 in adults (500 mg 3 times weekly)
- £38.41 to £220.80 in children and young people weighing 15–40 kg (250 mg 3 times weekly).

### Introduction and current guidance

The lungs of people with cystic fibrosis can become infected by bacteria (most commonly *Pseudomonas aeruginosa*). Recurrent, intermittent infection of the airways occurs and, if bacterial infection is not controlled, chronic infection can develop, which may accelerate declining lung function, respiratory failure and death. The length and quality of life for people with cystic fibrosis is thought to be strongly influenced by the success or failure to eradicate *P. aeruginosa* in early childhood and by subsequent antibiotic treatment of respiratory infective exacerbations.

The guideline on antibiotic treatment for cystic fibrosis from the Cystic Fibrosis Trust (2009) advises that a 6 month trial of oral azithromycin should be considered in people with cystic fibrosis who are deteriorating on conventional therapy, irrespective of their infection status. However, not all patients will benefit from this therapy.
This evidence summary considers the evidence to support the off-label use of long-term azithromycin for treating people with cystic fibrosis. For the purpose of this evidence summary, long-term is defined as 6 months or more, as recommended by the Cystic Fibrosis Trust guideline.

A NICE clinical guideline on diagnosis and management of cystic fibrosis is in development. The expected date of publication is February 2017.

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

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). Use of azithromycin for cystic fibrosis is off-label.

Although they are active against some other pathogens seen in people with cystic fibrosis, macrolides such as azithromycin have no direct bactericidal activity against *P. aeruginosa*. The Cystic Fibrosis Trust Guideline on antibiotic treatment for cystic fibrosis notes that the mode of action of macrolides in cystic fibrosis is unknown. Possible mechanisms may involve an anti-inflammatory action, and interference with the protective biofilm of *P. aeruginosa* and the adherence of *P. aeruginosa* to epithelial cells.

If a 6 month trial of azithromycin is considered necessary, the Cystic Fibrosis Trust guideline recommends that the dose is generally 250–500 mg 3 times weekly, depending on the person's weight.

Consideration should be given to official guidance regarding the appropriate use of antibacterial agents. NICE is developing guidelines on antimicrobial stewardship (expected May 2015) and antimicrobial resistance – changing risk-related behaviours (expected March 2016).

Full text of Product overview.
Evidence review

This evidence review is based on a Cochrane review that examined the use of macrolide antibiotics for treating cystic fibrosis (Southern KW et al. 2012).

- The Cochrane review (8 randomised controlled trials and 2 crossover studies: n=17 to 260) included 959 adults and children with confirmed cystic fibrosis. Eight of the included studies compared azithromycin with placebo; 1 compared high- and low-dose azithromycin; and 1 compared once weekly and once daily dosing regimens. Four of the studies (n=544) comparing azithromycin with placebo used a 250–500 mg 3 times weekly dosage. Treatment duration ranged from 2–12 months.

- Meta-analysis of 4 studies (n=549) found that azithromycin statistically significantly improved FEV₁ (the primary outcome) over 6 months compared with placebo (mean difference 3.97% of predicted, 95% CI 1.74 to 6.19). The authors state that this is likely to be of clinical significance in people with cystic fibrosis. Beyond 6 months, the benefits of azithromycin treatment on FEV₁ are less clear because they are based on 1 small study only (n=82).

- At 6 months, people treated with azithromycin were about twice as likely to be free of exacerbations as people treated with placebo (4 studies, n=609; OR 1.96, 95% CI 1.15 to 3.33). However, the data were heterogeneous and should be interpreted with caution.

- In 3 studies (n=527), treatment with azithromycin was associated with a statistically significant reduction in the need for oral antibiotics (OR 0.28, 95% CI 0.19 to 0.42). However, the data were limited for intravenous antibiotics. See the evidence review section of this evidence summary for more information.

- People taking azithromycin gained statistically significantly more weight than those taking placebo (2 studies, n=445; mean difference 0.62 kg, 95% CI 0.26 kg to 0.98 kg).

- No clear effect was seen with azithromycin treatment on patient-reported quality of life.

- Meta-analysis of 2 studies (n=445) found no statistically significant difference between the groups in rates of admission to hospital.

- There is little information on the long-term safety of azithromycin treatment for cystic fibrosis. No serious adverse events were reported in the studies included in the Cochrane review with azithromycin use for 2–12 months. In studies comparing azithromycin with placebo, study withdrawals were reportedly rare and not obviously associated with azithromycin.
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 10 and 1 in 100) include anorexia, vomiting, dyspepsia, dizziness, headache, paraesthesia, dysgeusia (abnormal taste), visual impairment, deafness, 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). Reversible hearing loss can occur with long-term therapy with azithromycin (British national formulary, September 2014).

No children aged under 6 years were included in the studies in the Cochrane review. Various dosing regimens were used, the most common being 250–500 mg 3 times weekly. In the key meta-analyses discussed in this evidence summary (including lung function, pulmonary exacerbations, need for antibiotics and hospitalisation), more than 90% of participants used this dosing regimen. There is little published evidence to determine the efficacy and safety of azithromycin when used for cystic fibrosis in other dosing regimens or for more than 6 months.

Concerns have been raised over the emergence of macrolide resistance (particularly Staphylococcus aureus) during long-term azithromycin treatment. The US Cystic fibrosis pulmonary guidelines (2013) state that long-term use of azithromycin in individuals with occult or active nontuberculous mycobacteria infection could lead to resistance, which might complicate its treatment. Therefore, the guideline suggests that patients should be screened for nontuberculous mycobacteria before azithromycin is initiated, and reassessed periodically at 6- to 12-month intervals. Azithromycin monotherapy should not be used in patients infected with nontuberculous mycobacteria.

Context and estimated impact for the NHS

Depending on the formulation used, costs (excluding VAT) of 6 months' treatment with azithromycin based on regimens included in the Cystic Fibrosis Trust Guideline on antibiotic treatment for cystic fibrosis are as follows:

- Adult (500 mg 3 times weekly): £46.28 to £390.00 for tablets or capsules and £316.68 to £430.56 for suspension.

- Child or young person weighing 15–40 kg (250 mg 3 times weekly): £38.41 for tablets, £195.00 for capsules and £158.34 to £220.80 for suspension (Drug Tariff, October 2014).
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 or parents of children with cystic fibrosis who are considering starting 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

Cystic fibrosis is an inherited condition characterised by abnormal transport of chloride and sodium across the epithelium in all exocrine tissues. This leads to thick viscous secretions in the lungs, pancreas, liver, intestine, and reproductive tract, and an increase in the salt content in sweat gland secretions. It affects over 8500 children and young adults in the UK and has an incidence of 1 in 2500 live births. Although cystic fibrosis is a progressive condition that limits life expectancy, it has an improving prognosis. More than half of people with cystic fibrosis in the UK are older than 16 years of age (NICE technology appraisal 276 final scope: Cystic fibrosis (pseudomonas lung infection) colistimethate powder and tobramycin powder).

The lungs of people with cystic fibrosis can become infected by bacteria (most commonly Pseudomonas aeruginosa), which thrive in the altered mucus that collects in the small airways. Recurrent, intermittent infection of the airways occurs and, if bacterial infection is not controlled,
ch \[\text{chronic infection can develop. In chronic infection, bacterial micro-environments known as biofilms are formed that are difficult for immune cells and antibiotics to penetrate. Bacterial infection is rarely eradicated once chronic infection has developed (NICE technology appraisal 276 final scope: Cystic fibrosis (pseudomonas lung infection) colistimethate powder and tobramycin powder).}\]

The commonest cause of death in people with cystic fibrosis is respiratory failure resulting from chronic pulmonary infection. The length and quality of life for people with cystic fibrosis is thought to be strongly influenced by the success or failure to eradicate \(P. \text{aeruginosa}\) in early childhood and by subsequent antibiotic treatment of respiratory infective exacerbations (NICE technology appraisal 276 final scope: Cystic fibrosis (pseudomonas lung infection) colistimethate powder and tobramycin powder).

The guideline on antibiotic treatment for cystic fibrosis from the Cystic Fibrosis Trust (2009) advises that:

- when \(P. \text{aeruginosa}\) is found in the respiratory secretions of a person with cystic fibrosis who was previously free of \(P. \text{aeruginosa}\) or who has never had the organism, they should receive an appropriate eradication regimen (such as ciprofloxacin and nebulised colistin) in a timely fashion.

- all people with cystic fibrosis and chronic pulmonary infection with \(P. \text{aeruginosa}\) should have long-term nebulised anti-pseudomonal therapy, unless it is contra-indicated.

- a 6 month trial of oral azithromycin should be considered for people who are deteriorating on conventional therapy, irrespective of their infection status. However, not all patients will benefit from this therapy.

- pulmonary exacerbations should be treated promptly with oral or intravenous antibiotics. Intravenous treatment must be used if the patient's condition does not improve with oral treatment.

A NICE clinical guideline on diagnosis and management of cystic fibrosis is in development. The expected date of publication is February 2017. NICE has issued technology appraisal guidance on colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis and mannitol dry powder for inhalation for treating cystic fibrosis. A NICE evidence summary on the use of long-term azithromycin for non-cystic fibrosis bronchiectasis is also available.
This evidence summary considers the evidence to support the off-label use of long-term azithromycin for treating people with cystic fibrosis. For the purpose of this evidence summary, long-term is defined as 6 months or more, as recommended by the Cystic Fibrosis Trust guideline.

**Product overview**

**Drug action**

Azithromycin is a macrolide antibiotic. Although they are active against some other pathogens seen in people with cystic fibrosis, macrolides have no direct bactericidal activity against *P. aeruginosa*. The Cystic Fibrosis Trust Guideline on antibiotic treatment for cystic fibrosis notes that the mode of action of macrolides in cystic fibrosis is unknown. Possible mechanisms may involve an anti-inflammatory action, and interference with the protective biofilm of *P. aeruginosa* and the adherence of *P. aeruginosa* to epithelial cells.

**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 in 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 cystic fibrosis is off-label. If a 6 month trial of azithromycin is considered necessary, the Cystic Fibrosis Trust Guideline on antibiotic treatment for cystic fibrosis recommends the following doses are used 3 times weekly:

- 10 mg/kg for children weighing less than 15 kg
- 250 mg in children and young people weighing 15–40 kg
- 500 mg in children and young people weighing over 40 kg and adults.
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 May 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 review is based on a Cochrane review that examined the use of macrolide antibiotics for treating cystic fibrosis. Other studies identified by searches performed for the evidence summary were excluded because they were not double-blind randomised controlled trials including patient oriented outcomes, or they had other limitations. A further study has been completed but not yet published (NCT00411736) and another is still ongoing (NCT01270074).

**Cochrane review on macrolide antibiotics for cystic fibrosis**
(Southern KW et al. 2012)

- **Design:** This systematic review and meta-analysis of 10 studies (8 randomised controlled trials [RCT] and 2 crossover studies) investigated whether short- or long-term use of a macrolide antibiotic improved clinical status in people with cystic fibrosis, compared with placebo or another class of antibiotic, another macrolide, or the same macrolide at a different dose.

- **Population:** The 10 studies (n=17 to 260) included 959 people with confirmed cystic fibrosis. Four studies enrolled children and young people aged over 6 years, 1 enrolled adults, and the remaining 5 enrolled adults and children. Presence and absence of *P. aeruginosa*
airway infection were each an entry criterion in 2 studies. Other studies enrolled people with and without this infection. See table 1 for details.

- **Intervention and comparison:** 8 of the included studies compared azithromycin with placebo; 1 compared high- and low-dose azithromycin; and 1 compared once weekly and once daily dosing regimens. Various dosing regimens were used in the 8 studies comparing azithromycin with placebo, primarily 250–500 mg 3 times weekly (4 RCTs, n=544). Treatment duration ranged from 2–12 months. See table 1 for details.

- **Outcomes:** The primary outcome in all of the studies was change in forced expired volume in 1 second (FEV$_1$) over the course of the study. Other outcomes included pulmonary exacerbations, need for antibiotics and adverse events.

### Table 1 Summary of studies included in the Cochrane review

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Participants</th>
<th>Intervention</th>
<th>Dosing regimen</th>
<th>Duration</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clement 2006</td>
<td>Parallel RCT</td>
<td>82 people 6–21 years</td>
<td>Azithromycin versus placebo</td>
<td>250 mg or 500 mg 3 times/week depending on weight</td>
<td>12 months</td>
</tr>
<tr>
<td>Equi 2002</td>
<td>Crossover RCT</td>
<td>41 people 8–18 years</td>
<td>Azithromycin versus placebo</td>
<td>250 mg or 500 mg daily depending on weight</td>
<td>6 months each arm (2 month washout)</td>
</tr>
<tr>
<td>Kabra 2010</td>
<td>Parallel RCT</td>
<td>47 people 5–18 years</td>
<td>Low-versus high-dose azithromycin</td>
<td>5 mg/kg versus 15 mg/kg</td>
<td>6 months</td>
</tr>
<tr>
<td>McCormack 2007</td>
<td>Parallel RCT</td>
<td>208 people 6–58 years</td>
<td>Weekly versus daily azithromycin</td>
<td>250 mg daily versus 1200 mg weekly</td>
<td>6 months</td>
</tr>
<tr>
<td>O’Connor 2009</td>
<td>Crossover RCT</td>
<td>17 people 6–20 years</td>
<td>Azithromycin versus placebo</td>
<td>250 mg or 500 mg 3 times/week depending on weight</td>
<td>4 months each arm (2 month washout)</td>
</tr>
<tr>
<td>Rotschild 2005</td>
<td>Parallel RCT</td>
<td>18 people 5–36 years</td>
<td>Azithromycin versus placebo</td>
<td>250 mg twice weekly</td>
<td>3 months</td>
</tr>
</tbody>
</table>
### Clinical effectiveness

**Cochrane review on macrolide antibiotics for cystic fibrosis**  
(Southern KW et al. 2012)

#### Lung function (FEV₁: primary outcome)

Meta-analysis of 4 studies (Clement A et al. 2006, Equi A et al. 2002, Saiman L et al. 2003 and Saiman L et al. 2010; n=549) found that azithromycin statistically significantly improved FEV₁ over 6 months compared with placebo (mean difference 3.97% of predicted, 95% confidence interval [CI] 1.74 to 6.19). All of the studies included in the systematic review assessed FEV₁ at different time points. The results before 6 months show a trend consistent with this finding, although statistical significance was only seen at 1 month. Beyond 6 months, the benefits of azithromycin treatment on FEV₁ are less clear because they are based on 1 small study only (Clement A et al. 2006; n=82).

#### Pulmonary exacerbations

Exacerbations were recorded in different ways in the studies. Using data from 5 studies, the number of people free of exacerbations at various time points was calculated. Meta-analysis of
4 studies (Clement A et al. 2006, Equi A et al. 2002, Saiman L et al. 2003 and Saiman L et al. 2010; n=609), showed that, at 6 months, people treated with azithromycin were about twice as likely to be free of exacerbations as people treated with placebo (odds ratio [OR] 1.96, 95% CI 1.15 to 3.33). This is consistent with data from other time points.

**Need for antibiotic treatment**

In 3 studies (Equi A et al. 2002, Saiman L et al. 2003 and Saiman L et al. 2010; n=527), treatment with azithromycin was associated with a statistically significant reduction in the need for oral antibiotic treatment, compared with placebo (OR 0.28, 95% CI 0.19 to 0.42). However, the data were less conclusive for intravenous antibiotics. In the same 3 studies, azithromycin did not statistically significantly reduce the need for intravenous antibiotics. However, 2 other studies (Clement A et al. 2006 and Wolter J et al. 2002) reported statistically significantly fewer courses and days on intravenous antibiotics with azithromycin compared with placebo.

**Other secondary outcomes**

In a meta-analysis of 2 studies (Saiman L et al. 2003 and Saiman L et al. 2010; n=445), there was no statistically significant difference between the groups in rates of admission to hospital. In the same 2 studies, people taking azithromycin gained statistically significantly more weight than those taking placebo (mean difference 0.62 kg, 95% CI 0.26 kg to 0.98 kg). Across all studies, no clear effect was seen with azithromycin treatment on patient-reported quality of life.

In 4 studies (Clement A et al. 2006, Saiman L et al. 2003, Saiman L et al. 2010 and Steinkamp G et al. 2007; n=353), treatment with azithromycin was associated with a statistically significantly reduced acquisition of *Staphylococcus aureus* on respiratory culture compared with placebo (n=353; OR 0.25, 95% CI 0.12 to 0.51). However, the antibiotic did not eradicate this pathogen significantly more than placebo in the 2 studies that looked at this outcome (Clement A et al. 2006 and Saiman L et al. 2003).

Three studies (Clement A et al. 2006, Saiman L et al. 2003, Saiman L et al. 2010) reported acquisition of *P. aeruginosa*, but the number of events was very small and insufficient to assess efficacy.

**Safety and tolerability**

There is little information on the long-term safety of azithromycin treatment for cystic fibrosis. However, no serious adverse events were reported over 2–12 months in the studies included in the
Cochrane review. In studies comparing azithromycin with placebo, study withdrawals were rare and not obviously associated with azithromycin.

In 1 study included in the Cochrane review (McCormack J et al. 2007), which compared azithromycin 250mg daily and azithromycin 1200 mg weekly, statistically significantly more patients taking the weekly dose experienced gastrointestinal adverse events (27/105 compared with 9/103; OR 3.62, 95% CI 1.61 to 8.14) over 6 months. Similarly, more patients in the weekly treatment group discontinued treatment than in the daily treatment group (12/105 compared with 5/103; OR 2.53, 95% CI 0.86 to 7.46).

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 10 and 1 in 100) include anorexia, vomiting, dyspepsia, dizziness, headache, paraesthesia, dysgeusia (abnormal taste), visual impairment, deafness, 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 with long-term therapy with azithromycin.

Concerns over the emergence of macrolide resistance (particularly S. aureus) during long-term azithromycin treatment were raised in the most recent study included in the Cochrane review (Saiman L et al. 2010, n=260), and the authors of the Cochrane review note that other epidemiological studies have reported the emergence of macrolide resistance in clinics prescribing azithromycin for all their patients. They suggest that, if the mechanism of action of azithromycin relates to its anti-staphylococcal activity, there may be antibiotics with better potency and a narrower spectrum of action against S. aureus that are more appropriate to use.

The US Cystic fibrosis pulmonary guidelines state that long-term use of azithromycin in individuals with occult or active nontuberculous mycobacteria infection could lead to resistance, which might complicate its treatment. Therefore, the guideline suggests that patients should be screened for nontuberculous mycobacteria before azithromycin is initiated, and reassessed periodically at 6- to 12-month intervals. Azithromycin monotherapy should not be used in patients infected with nontuberculous mycobacteria.
Evidence strengths and limitations

Six of the 10 studies included in the Cochrane review were considered to be at low risk of bias. These enrolled the majority of patients (836 of the total 959 participants). In 4 of these studies (Equi A et al. 2002, McCormack J et al. 2007, Saiman L et al. 2003 and Saiman L et al. 2010), randomisation, allocation concealment and blinding were sufficient, and outcome data were complete and fully reported. In the other 2 of the 6 studies (Clement A et al. 2006 and Wolter J et al. 2002), there were only minor concerns over reporting and baseline characteristics. The authors report that data from the 4 studies that had methodological concerns did not have any significant effect on the overall conclusions of the meta-analysis, although numbers were too small to perform a sensitivity analysis.

Two of the studies used a crossover design, which may not be appropriate for an intervention that could have a significant impact on longer-term disease progression. However, both studies had 2-month washout periods and there did not appear to be any carryover effects. Only data from the first arm of 1 study was included in the meta-analyses; data from the other study was not included because of concerns about bias.

No children aged under 6 years were enrolled in the studies in the Cochrane review. Various dosing regimens were used, the most common being 250–500 mg 3 times weekly. In the key meta-analyses discussed in this evidence summary (including lung function, pulmonary exacerbations, need for antibiotics and hospitalisation), more than 90% of participants used this dosing regimen. There is little data on the efficacy and safety of azithromycin when used in cystic fibrosis for over 6 months.

In the Cochrane review, compared with placebo, the improvement seen with azithromycin in the primary disease orientated outcome, change in predicted FEV$_1$, was around 4%. The authors state that this is likely to be of clinical significance in people with cystic fibrosis. They also note that, although azithromycin doubled the rate of freedom from exacerbations at 6 months compared with placebo, data were heterogeneous and should be interpreted with caution. Greater weight gain was reported in patients taking azithromycin; however, this was only 0.62 kg compared with placebo.

In the Cochrane review, most studies included patients with and without *P. aeruginosa* infection and it is unclear whether presence or absence of this microorganism affects the outcomes of treatment. Based on analysis of 6 of the 10 studies included in the Cochrane review, the committee that developed the US *Cystic fibrosis pulmonary guidelines* make slightly different recommendations for the use of azithromycin depending on whether *P. aeruginosa* infection is present or not:
For individuals with cystic fibrosis aged 6 years or over with *P. aeruginosa* persistently present in cultures of the airways, the Cystic Fibrosis Foundation recommends the long-term use of azithromycin to improve lung function and reduce exacerbations.

For individuals with cystic fibrosis aged 6 years of age or over without *P. aeruginosa* persistently present in cultures of the airways, the Cystic Fibrosis Foundation recommends the long-term use of azithromycin should be considered to reduce exacerbations.

**Context and estimated impact for the NHS**

**Cost effectiveness**

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

Other anti-inflammatory drugs that have been used in cystic fibrosis include inhaled and oral corticosteroids, ibuprofen and leukotriene receptor antagonists (US *Cystic fibrosis pulmonary guidelines*, 2013).

Costs of 6 months' treatment with azithromycin based on regimens included in the Cystic Fibrosis Trust *Guideline on antibiotic treatment for cystic fibrosis* are shown in table 2.

**Table 2 Costs of azithromycin treatment**

<table>
<thead>
<tr>
<th></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>Adult: 500 mg 3 times weekly</td>
<td>Child or young person weighing 15−40 kg: 250 mg 3 times weekly</td>
</tr>
<tr>
<td>Azithromycin 500 mg tablets</td>
<td>£1.71 for 3 tablets</td>
<td>£46.28</td>
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<tr>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Azithromycin 250 mg tablets</td>
<td>£1.83 for 4 tablets</td>
<td>£76.83</td>
</tr>
<tr>
<td></td>
<td></td>
<td>£38.41</td>
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<tr>
<td>Azithromycin 250 mg capsules</td>
<td>£14.98 for 6 capsules</td>
<td>£390.00</td>
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<td>£195.00</td>
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</tbody>
</table>
Azithromycin 200 mg/5 ml suspension

<table>
<thead>
<tr>
<th>Volume</th>
<th>NHS Prescription Cost</th>
<th>Manufacturer Price</th>
<th>Wholesale Price</th>
</tr>
</thead>
<tbody>
<tr>
<td>15 ml</td>
<td>£4.06</td>
<td>£316.68</td>
<td>£158.34</td>
</tr>
<tr>
<td>22.5 ml</td>
<td>£6.10</td>
<td>£475.80</td>
<td>£158.60</td>
</tr>
<tr>
<td>30 ml</td>
<td>£11.04</td>
<td>£430.56</td>
<td>£220.80</td>
</tr>
</tbody>
</table>

\(^a\) 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 cystic fibrosis 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 around £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 cystic fibrosis who are thinking about trying long-term azithromycin.

Relevance to NICE guidance programmes

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

NICE has issued guidance on:

- Colistimethate sodium and tobramycin dry powders for inhalation for treating pseudomonas lung infection in cystic fibrosis (2013) NICE technology appraisal guidance 276.
- Mannitol dry powder for inhalation for treating cystic fibrosis (2012) NICE technology appraisal guidance 266.

A NICE clinical guideline on diagnosis and management of cystic fibrosis is in development. The expected date of publication is February 2017.
A NICE medicines and prescribing guideline on antimicrobial stewardship (expected May 2015) and a NICE public health guideline on antimicrobial resistance – changing risk-related behaviours (expected March 2016) are also being produced.

References

British national formulary (September 2014) [online; accessed 6 October 2014]


National Health Service (2014) Electronic drug tariff [online; accessed 10 October 2014]

National Institute for Health and Clinical Excellence (2011) Cystic fibrosis (pseudomonas lung infection) colistimethate powder and tobramycin powder. NICE technology appraisal final scope [online; accessed 09 September 2014]

Pfizer Limited (2014) Zithromax 250 capsules summary of product characteristics [online; accessed 16 September 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.

Expert advisers

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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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ISBN 978-1-4731-0839-4