

## ITRACONAZOLE for allergic bronchopulmonary aspergillosis

**The Pan Mersey Area Prescribing Committee recommends the prescribing of ITRACONAZOLE for allergic bronchopulmonary aspergillosis.**

### **AMBER patient retained by specialist**

Itraconazole is licensed for the treatment of systemic mycoses including aspergillosis. It is active against *A fumigatus*.

Allergic Bronchopulmonary Aspergillosis (ABPA) manifests as poorly controlled asthma, and other symptoms are haemoptysis, fever, malaise, and expectoration of mucous plugs<sup>1</sup>. If untreated, it can lead to permanent lung damage through the development of bronchiectasis. Hypersensitivity to *Aspergillus* is reflected by elevated *Aspergillus* – specific IgE levels or by a positive aspergillus skin test. Although ABPA is not an invasive fungal infection, eradication of the fungus may modify the disease caused by the hypersensitivity reaction to the fungus in the bronchi.

Although inhaled fungal conidia are normally removed from the airways, defective clearance in patients with asthma and cystic fibrosis allows conidia to germinate and produce hyphae. These hyphae induce the production of inflammatory cytokines which are responsible for the development of symptoms<sup>1</sup>.

Management of ABPA is straightforward and patients do not need to be referred to tertiary services. Itraconazole is considered an adjunctive but not primary therapy. When a patient has ABPA and is taking oral corticosteroid therapy on an ongoing basis, itraconazole may be considered as a corticosteroid-sparing agent<sup>2</sup>. Patients will receive the first prescription for itraconazole from the respiratory clinic and will be followed up in routine clinic appointments. If IgG anti-aspergillus markers return to normal levels, therapy will be discontinued although some patients with bronchiectasis will require long term therapy. Long lasting remissions are seen in around 50% of patients. Many patients will require recurrent courses of therapy<sup>3</sup>.

The licensed dose for aspergillosis is 200mg itraconazole (2x100mg capsules) up to twice a day. Duration of treatment is usually 2-6 months and should be adjusted depending on clinical efficacy.

**NB Itraconazole has a Red designation for the treatment of chronic and invasive aspergillosis which is managed by the National Aspergillosis Centre in Wythenshawe Hospital. Antifungal treatment is commissioned by NHS England for these indications.**

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

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### Effectiveness

A systematic review evaluated the efficacy and safety of antifungal therapy for ABPA<sup>4</sup>. Thirty-eight studies – four randomized controlled trials and 34 observational studies – met the eligibility criteria. An improvement in symptoms, frequency of exacerbations and lung function was reported in most of the studies and was more common with oral azoles. Antifungals also had a positive impact on biomarkers and radiological pulmonary infiltrates, but adverse effects were also common. The quality of the evidence supporting these results was low or very low due to a shortage of controlled studies, heterogeneity between studies and potential bias. Antifungal interventions in ABPA improved patient and disease outcomes in both asthma and cystic fibrosis. However, the recommendation for their use is weak and clinicians should therefore weigh up desirable and undesirable effects on a case-by-case basis.

### Cost

Cost for one year's supply based on 2 capsules daily is £147.95<sup>5</sup>.  
Approximately 2% of patients with asthma and 1-15% of patients with cystic fibrosis develop ABPA<sup>3</sup>.  
This translates to 162 asthma patients per 100,000 population and 2 cystic fibrosis patients per 100,000 population. Not all patients will be treated with courses of itraconazole – for many patients, corticosteroids are the mainstay of therapy.

### Safety

Contraindicated in pregnancy and in patients prescribed some CYP3A4-metabolised substrates. Caution should be used in prescribing itraconazole capsules to patients with hypersensitivity to other azoles.  
Itraconazole should not be used in patients with congestive heart failure or with a history of congestive heart failure unless the benefit clearly outweighs the risk.  
It is recommended that patients with impaired hepatic function be carefully monitored when taking itraconazole.  
In patients taking medication to reduce gastric acidity, itraconazole should be administered with an acidic beverage such as non-diet cola  
Use with caution in the elderly and in renal impairment. Headache, abdominal pain and nausea are common side effects.  
See SPC for all contraindications, cautions and side effects.

### Patient factors

All patients should be followed up in the respiratory clinic to determine efficacy and recommended duration of therapy.

### Prescribing information

The licensed dose for aspergillosis is 200mg itraconazole (2x100mg capsules) up to twice daily. Duration of treatment is usually 2-6 months, but may be long-term, and should be adjusted depending on clinical efficacy. GPs will not be asked to take over prescribing until the patient is stable and the dose has been optimised.

### Implementation notes

Patients should be followed up in the respiratory clinic to determine response to treatment and duration of therapy.

### References

1. Kosmidis C, Denning DW. The clinical spectrum of pulmonary aspergillosis. Thorax Published Online First 29 October 2014. <https://thorax.bmj.com/content/thoraxjnl/early/2014/10/29/thoraxjnl-2014-206291.full.pdf>
2. Allergic bronchopulmonary aspergillosis. BMJ Best Practice 29 May 2018. <https://bestpractice.bmj.com/topics/en-gb/836>
3. Orphanet monograph for ABPA. [https://www.orpha.net/consor/cgi-bin/OC\\_Exp.php?lng=en&Expert=1164](https://www.orpha.net/consor/cgi-bin/OC_Exp.php?lng=en&Expert=1164)
4. Moreira S et al. Antifungal treatment in allergic bronchopulmonary aspergillosis with and without cystic fibrosis: a systematic review. Clin Exp Allergy 2014 (Oct); 44(10): 1210-27. <https://onlinelibrary.wiley.com/doi/abs/10.1111/cea.12333>
5. Electronic [Drug Tariff](#). Accessed 26.02.2019.