Roflumilast (Daxas®) for COPD treatment (AMBER)

Background

NICE TA461 (July 2017) recommends Roflumilast, as an add-on to bronchodilator therapy, is recommended as an option for treating severe chronic obstructive pulmonary disease in adults with chronic bronchitis, only if:

- **The disease is severe, defined as a forced expiratory volume in 1 second (FEV1) after a bronchodilator of less than 50% of predicted normal, AND**
- **The person has had 2 or more exacerbations in the previous 12 months despite triple inhaled therapy with a long-acting muscarinic antagonist, a long-acting beta-2 agonist and an inhaled corticosteroid.**
- **Treatment with roflumilast should be started by a specialist in respiratory medicine.**

Referral Information

Our local respiratory specialists have suggested that COPD patients should only be referred to secondary care for consideration of roflumilast if they meet the above NICE criteria plus have all the following characteristics:

a) Have a chronic bronchitic phenotype (i.e. chronic productive cough)

b) Have good inhaler technique and compliance with their triple inhaled therapy

c) Have completed pulmonary rehabilitation within the last 3 years

d) Are not underweight (i.e. BMI >20)

Patients should be aware that roflumilast is not always well tolerated, typically due to gastrointestinal side effects. They should also be aware that, following assessment in secondary care, they may not be offered roflumilast if this is not felt to be an appropriate choice for them.

Effectiveness[1]

Roflumilast is an orally administered long-acting selective phosphodiesterase-4 enzyme inhibitor. It targets cells and mediators believed to be important in chronic obstructive pulmonary disease (COPD).

Evidence came from REACT, a large, multicentre double-blind RCT of patients with severe COPD, chronic bronchitis and 2 or more exacerbations in last 12 months, comparing roflumilast plus inhaled combination therapy with placebo plus inhaled combination therapy and RE2SPOND, a large multicentre double-blind trial of patients with severe COPD, chronic bronchitis and 2 or more exacerbations and/or hospitalisations in previous 12 months. It was concluded that the company's pooled analyses provided sufficient evidence of the clinical efficacy of roflumilast compared with placebo in the subgroup of patients with severe COPD having exacerbations despite triple inhaled therapy.

Safety[1,2]

Most common adverse reactions include diarrhoea, weight loss, nausea, abdominal pain and headache.
Roflumilast is generally well-tolerated but weight loss and gastrointestinal adverse effects can lead to discontinuation of treatment in some people.
Roflumilast is subject to additional monitoring for weight loss and the weight of underweight patients should be checked at each GP appointment.
While adverse reactions like diarrhoea, nausea, abdominal pain and headache mainly occur within the first weeks of therapy and mostly resolve on continued treatment, roflumilast treatment should be reassessed in case of persistent intolerability.

Safety continued[1,2]

Roflumilast is associated with an increased risk of psychiatric disorders such as insomnia, anxiety, nervousness & depression. In clinical studies and post-marketing experience, rare instances of suicidal ideation and behaviour, including suicide, were reported. Roflumilast is therefore not recommended in patients with a history of depression associated with suicidal ideation or behaviour. Patients and caregivers should be instructed to notify the prescriber of any suicidal ideation.
For full details of adverse reactions and contraindications, see the SPC.

Body weight <60 kg:

Treatment with roflumilast may lead to a higher risk of sleep disorders (mainly insomnia) in patients with a baseline body weight of <60 kg, due to a higher total PDE4 inhibitory activity found in these patients.

Information for health professionals from the manufacturer can be found here: http://www.medicines.org.uk/emc/RMM.817.pdf

Patient Factors[2]

Hepatic Impairment - Roflumilast should be used with caution in patients with mild hepatic impairment (Child-Pugh A) and contra-indicated in patients with moderate or severe hepatic impairment (Child-Pugh B or C).

Not recommended during pregnancy or breastfeeding.

Women of childbearing age should be advised to use an effective method of contraception during treatment. Roflumilast is not recommended in women of childbearing potential not using contraception.

Prescribing information[2]

The recommended dose is 250 micrograms (1 tablet) of roflumilast once daily for the first 28 days. Then increase to maintenance dose of 500mcg once daily. The tablet should be swallowed with water and taken at the same time every day. The tablet can be taken with or without food. Roflumilast may need to be taken for several weeks to achieve its effect.
All patients should be informed about the risks of roflumilast and the precautions for safe use and should be given a patient card before starting roflumilast. This resource for patients can be found here: https://www.medicines.org.uk/emc/rmm/816/Document

Interactions of note[2] (See SPC for full details[2])

- The use of strong cytochrome P450 enzyme inducers (e.g. phenobarbital, carbamazepine, phenytoin) may reduce the therapeutic efficacy of roflumilast. Thus, roflumilast treatment is not recommended in patients receiving strong cytochrome P450 enzyme inducers.
- There are no clinical data to support the concomitant treatment with theophylline for maintenance therapy. Therefore, the concomitant treatment with theophylline is not recommended.

Stopping criteria

No specific stopping criteria are suggested in the NICE TA for roflumilast or in the license. Pragmatically, when these patients are reviewed, if there has been no change in the number of exacerbations or hospital admissions they have in a year, it might be worth considering whether it is worth continuing.

Cost

Roflumilast costs £37.71 for 30 tablets. Annual cost: £459

References

1. NICE TA461 Roflumilast for treating chronic obstructive pulmonary disease 26th July2017 https://www.nice.org.uk/guidance/ta461

2. DAXAS 500 micrograms film-coated tablets SPC http://www.medicines.org.uk/emc/medicine/23416