SHARED CARE GUIDELINE FOR ROFLUMILAST FOR TREATING CHRONIC OBSTRUCTIVE PULMONARY DISEASE (COPD)

INDICATION

Roflumilast has a marketing authorisation in the UK for maintenance treatment of severe COPD (forced expiratory volume in the first second [FEV₁] post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations as add-on to bronchodilator treatment.

Roflumilast is an oral selective phosphodiesterase 4 (PDE4) inhibitor which has anti-inflammatory activity designed to target both the systemic and pulmonary inflammation associated with COPD. It is a maintenance treatment and has no direct bronchodilator activity.

**NICE TA 461** supports the use of roflumilast as follows:

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.

The Global Initiative for Chronic Obstructive Lung Disease (GOLD) published an updated 2017 version of their Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease. In patients who continue to have exacerbations despite triple therapy (ICS/LABA/LAMA), GOLD recommends three options:

- Consideration of the addition of roflumilast in patients with FEV₁ <50% predicted, chronic bronchitis, and a hospitalisation for an exacerbation in the previous year.

- Consideration of the addition of a macrolide, with best available evidence supporting the use of azithromycin. (The guidance cautions that consideration should also be given to the development of resistant organisms when deciding if this is an appropriate treatment choice)

- Discontinuation of ICS. GOLD states that this recommendation is supported by evidence of a lack of efficacy, increased risk of adverse effects, and evidence demonstrating no harm associated with withdrawal of ICS.

**Formulary status in Dorset**

Within Dorset roflumilast will be considered as a therapeutic add-on option initiated by specialists in respiratory medicine for treating severe COPD (defined as FEV₁ after a bronchodilator of less than 50% of predicted normal) in adults with chronic bronchitis who have had 2 or more exacerbations in the previous 12 months (1 of which involving hospitalisation) despite 12 months optimized therapy with triple inhaled therapy of a long-acting muscarinic antagonist, a long-acting beta-2 agonist and an inhaled corticosteroid.
AREAS OF RESPONSIBILITY FOR SHARED CARE

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

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

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

REFERRAL AND INITIATION

Patients under routine follow-up in secondary care, hospitalised with an exacerbation or referred for further input to the management of their condition will be considered for the initiation of roflumilast by the specialist in accordance with the criteria on page 1.

Specialist Responsibilities

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<td>Confirm diagnosis and review patient medical history including consideration as to whether roflumilast is an option to optimise pharmacological management of the condition.</td>
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| 2 | Before roflumilast is initiated, undertake baseline monitoring of the patient:  
  • Weight  
  • Depression screening system  |
| 3 | Review patient’s medication history to check for contra-indications or interactions with roflumilast (see special cautions section below). |
| 4 | Provide initial prescription for at least one month’s supply. Where appropriate, the GP can be asked in writing to take over the future prescribing of repeat treatment within this guidance. The length of ongoing prescribing by the hospital should be determined by the GP’s response. |
| 5 | Provide patient/carer with verbal and written information about the risks and precautions for safe use of roflumilast. |
| 6 | Provide the GP with baseline assessment results and a copy of the shared care guideline. |
| 7 | Review of the patient’s treatment in outpatient appointments. Changes to therapy because of these reviews (or at any other time) should be reported to the GP promptly. |
| 8 | Notifying the patient’s GP if treatment is to be discontinued and the reason for this. |
| 9 | Ensuring that clear arrangements are in place for GP to obtain back up, advice and support. |
| 10 | This medicinal product is subject to additional monitoring under the MHRA black triangle scheme ▼. The specialist should report known or suspected adverse events to the MHRA via the Yellow Card scheme and share this information with the GP. |
### General Practitioner Responsibilities

1. Referral of the patient to the specialist where necessary.
2. Responding to the request from the specialist to take on prescribing as soon as is practicable.
3. Continue to prescribe the roflumilast, under the guidance of specialist, ensuring prescriptions include a review date to check for ongoing benefit.
4. Monitor, with comparison to baseline results where necessary, for weight loss or changes to behavior or mood or any suicidal ideation.
5. Where review of the patient indicates that there has been a reduction in exacerbations by the addition of roflumilast maintain prescribing.
6. To check for possible drug interactions when newly prescribing or stopping concurrent medication. See Interactions section below.
7. Refer queries to the specialist service, e.g. regarding treatment/side effects (e.g. suicidal ideation, weight loss – after discontinuing therapy if necessary), and concerns about compliance with treatment.
8. This medicinal product is subject to additional monitoring under the MHRA black triangle scheme. The GP should report known or suspected adverse events to the MHRA via the Yellow Card scheme and share this information with the specialist.
9. Stopping treatment on instruction of the specialist service or where no evidence of reduction in exacerbations or hospital admissions is evident.

### Patient’s role (or that of carer)

1. Report to GP or specialist significant loss of body weight or any changes in behaviour or mood. Seek help urgently if the patient (or carer) notices any suicidal thoughts.
2. Attend appropriate consultant and GP appointments.
4. Use written and other information on the medication to ensure compliance with treatment.
5. If the patient is seen by another service, clinic or hospital, they should advise the healthcare professionals offering treatment about their treatment, particularly if new medicines are administered or prescribed.

### SUPPORTING INFORMATION

### Dosage and Administration

The recommended dose is 500 micrograms (one tablet) roflumilast once daily.

Roflumilast may need to be taken for several weeks to achieve its effect.

### Contraindications

- Patients with moderate or severe hepatic impairment classified as Child-Pugh B or C must not take roflumilast.
- Hypersensitivity to the active substance or to any of the excipients listed in the summary of product characteristics.
- Patients with congestive heart failure (NYHA grades 3 and 4) have not been studied and therefore treatment of these patients is not recommended.
• Due to lack of relevant experience, treatment with roflumilast should not be initiated or existing treatment with roflumilast should be stopped in patients with severe immunological diseases (e.g. HIV, multiple sclerosis, lupus erythematosus, progressive multifocal leukoencephalopathy), severe acute infectious diseases, cancers (except basal cell carcinoma), or patients being treated with immunosuppressive medicinal products (i.e.: methotrexate, azathioprine, infliximab, etanercept, or oral corticosteroids to be taken long-term; except short-term systemic corticosteroids).

• Roflumilast is not recommended in patients with a history of depression associated with suicidal ideation or behaviour.

• Roflumilast tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, the Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.

• Roflumilast treatment is not recommended in patients receiving strong cytochrome P450 enzyme inducers (e.g. phenobarbital, carbamazepine, phenytoin).

• 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.

• Roflumilast is not recommended during pregnancy or breastfeeding.

Special cautions

• 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.

• Roflumilast has been associated with a decrease in body weight, therefore it should be carefully monitored during treatment, see section on monitoring below.

• Experience in patients with latent infections such as tuberculosis, viral hepatitis, herpes viral infection and herpes zoster is limited.

• Roflumilast is associated with an increased risk of psychiatric disorders such as insomnia, anxiety, nervousness and depression. Rare instances of suicidal ideation and behaviour, including suicide, have been observed in patients with or without history of depression, usually within the first weeks of treatment. The risks and benefits of starting or continuing treatment with roflumilast should be carefully assessed if patients report previous or existing psychiatric symptoms or if concomitant treatment with other medicinal products likely to cause psychiatric events is intended.

• Patients and caregivers should be instructed to notify the prescriber of any changes in behaviour or mood and of any suicidal ideation. If patients suffered from new or worsening psychiatric symptoms, or suicidal ideation or suicidal attempt is identified, it is recommended to discontinue treatment with roflumilast.

• 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.

Monitoring

• Body weight of underweight patients should be checked at each visit. Patients should be advised to check their body weight on a regular basis. In the event of an unexplained and clinically concerning weight decrease, roflumilast should be stopped and body weight should be further followed-up.
Side effects

- Common (more than 1/100, but less than 1/10) or very common (more than 1/10): abdominal pain; decreased appetite; diarrhoea; headache; insomnia; nausea; weight loss.

- While these adverse effects mainly occur within the first weeks of therapy and mostly resolve on continued treatment, roflumilast treatment should be reassessed in case of persistent intolerability.

Drug interactions

- A combination of roflumilast with CYP1A2/3A4 and CYP1A2/2C19/3A4 inhibitors (enoxacin, cimetidine and fluvoxamine respectively), might lead to an increase of exposure and persistent intolerability. In this case, roflumilast treatment should be reassessed.

- 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.

The lists of potential side effects and potential drug interactions included within this document are not exhaustive. The manufacturer’s summary of product characteristics (SPC) and the most current edition of the British National Formulary should be consulted for full information on contraindications, warnings, side-effects and drug interactions.

Drug costs:
Daxas® ▼ 500 microgram tablets x 30 = £37.71 (Drug Tariff March 2018).
Annual treatment cost: £490.23

References
Daxas® 500mcg tablet summary of characteristics (accessed 29/3/2018).
NICE TA 461: Roflumilast for treating chronic obstructive pulmonary disease
BNF online (accessed 13/10/2017)

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