Coventry & Warwickshire Area Prescribing Committee

Drug Positioning Statement	DPS008
Roflumilast (Daxas®)▼	April 2019

VERDICT

The Coventry & Warwickshire APC recommend that roflumilast can be considered, as an add-on to bronchodilator therapy, for treating severe chronic obstructive pulmonary disease in adults with chronic bronchitis, only if:

- the disease is severe, defined as a FEV1 after a bronchodilator of less than 50% of predicted normal,

And

- **either** 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
- **or** the person has had 2 or more exacerbations in the previous 12 months despite double inhaled therapy with a long-acting muscarinic antagonist and a long-acting beta-2 agonist and they have a blood eosinophil level of <100/microlitre., when roflumilast is to be preferred to the addition of an inhaled corticosteroid.

Treatment should initiated by the specialist and follow on prescribing can take place in primary care once the Specialist Initiated Drug Checklist has been received by the GP.

Specialist Drugs Status: Specialist Initiation (SI) with completed Specialist Initiated Drugs Checklist

SUMMARY NOTES

Indication: Roflumilast is indicated as an add on to bronchodilator treatment for maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (Forced Expiratory Volume in 1 second (FEV_1) post-bronchodilator less than 50% predicted) associated with chronic bronchitis in adult patients with a history of frequent exacerbations.

Pharmacological action: Roflumilast is a Phosphodiesterase-4 (PDE4) inhibitor, a non-steroid, anti-inflammatory agent designed to target both the systemic and pulmonary inflammation associated with COPD. The mechanism of action is the inhibition of PDE4, a major cyclic adenosine monophosphate (cAMP)-metabolizing enzyme found in structural and inflammatory cells important to the pathogenesis of COPD.

Presentation: Daxas® 500 microgram film-coated tablets

Dose: The recommended maintenance dose is one tablet of 500 micrograms roflumilast once daily after 28 days of the starting dose of 250 microgram once daily

Cost Comparison: 30 days supply[2]

Roflumilast 500 microgram daily	£37.71
Azithromycin 250 mg – 500 mg	£3.08 – 6.70 tablets / capsules three times per week

DRUG PROFILE

Clinical Effectiveness

The evidence came from REACT, a multicentre double-blind RCT of 1935 patients with severe COPD, chronic bronchitis and 2 or more exacerbations in the previous year. It compared roflumilast plus inhaled combination therapy (a long-acting beta-2 agonist (LABA)plus inhaled corticosteroids (ICS), with or without a long-acting muscarinic antagonist (LAMA)) with placebo plus inhaled combination therapy. The evidence was pooled with 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[1].

Safety

Adverse effects: PDE4 inhibitors have more adverse effects than inhaled medications for COPD. The most frequent are diarrhoea, nausea, reduced appetite, weight loss, abdominal pain, sleep disturbance, and headache. Adverse effects have led to increased withdrawal rates from clinical trials. Adverse effects seem to occur early during treatment, are reversible, and diminish over time with continued treatment. In controlled studies an average unexplained weight loss of 2 kg has been seen and weight monitoring during treatment is advised [1,3,4]. in addition to avoiding roflumilast treatment in underweight patients. Roflumilast should also be used with caution in patients with depression[1].

DRUG PROFILE cont'd

Elderly, renal impairment: no dosage adjustment
Hepatic impairment: Caution with mild hepatic impairment, contra-indicated with moderate to severe hepatic impairment[1].

Pregnancy: Not recommended
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[1].

Cautions: 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, the intake of roflumilast should be stopped and body weight should be further followed-up. 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[1].
Treatment with roflumilast should not be initiated or existing treatment with roflumilast should be stopped in patients with severe immunological diseases (e.g. HIV infection, 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). Experience in patients with latent infections such as tuberculosis, viral hepatitis, herpes viral infection and herpes zoster is limited[1].

Patients with congestive heart failure (NYHA grades 3 and 4) have not been studied and therefore treatment of these patients is not recommended[1]

Psychiatric disorders: 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.

Roflumilast is 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 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[1].

Persistent intolerability: 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[1]

Interactions: see SPC; of note: concomitant treatment with theophylline is not recommended.

CURRENT PLACE IN THERAPY

National Institute for Clinical Excellence (NICE[3])
NICE recommends roflumilast, as an add-on to bronchodilator therapy, for treating severe chronic obstructive pulmonary disease in adults with chronic bronchitis, only if:

- the disease is severe, defined as a FEV_1 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.

Global Initiative for Chronic Obstructive Lung Disease (GOLD[4])
GOLD recommend roflumilast for the following: For patients on LABA/LAMA with exacerbations if blood eosinophils <100cells /microlitre (where there is a low beneficial ICS response).

For patients treated with LABA/LAMA/ICS who still have exacerbations and FEV1 <50% predicted and chronic bronchitis, particularly if they have experience on hospitalisation for an exacerbation in the previous year.

Scottish Medicines Consortium (SMC[5]) Not recommended for use

Summary

- Roflumilast is a once daily oral medication with no direct bronchodilator activity[1].
- Roflumilast reduces moderate and severe exacerbations treated with systemic corticosteroids in patients with chronic bronchitis, severe to very severe COPD, and a history of exacerbations[4].
- There has been no study directly comparing roflumilast with an inhaled corticosteroid[4].
- NICE states that treatment with roflumilast should be started by a specialist in respiratory medicine and states pre-set criteria for initiation[3].
- Additional monitoring for weight loss is needed[1].

References

1. SPC Roflumilast (Daxas®). Last updated 23rd April 2018.Available from www.medicines.org.uk
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3. NICE TAG 461. Roflumilast for treating chronic COPD. TA461. July 2017. https://www.nice.org.uk/guidance/ta461/chapter/4-Committee-discussion
4. Global Strategy for Prevention, Diagnosis, Management of COPD. 2019 Report. Available at https://goldcopd.org/wp-content/uploads/2018/11/GOLD-2019-v1.7-FINAL-14Nov2018-WMS.pdf
5. SMC. Daxas®. 635/10. September 2017. Available at https://www.scottishmedicines.org.uk/medicines-advice/roflumilast-daxas-resubmission-63510/