NHS South West Yorkshire Partnership NHS Foundation Trust

NHS Barnsley Hospital NHS Foundation Trust

NHS Barnsley Clinical Commissioning Group

DAXAS® (Roflumilast)

Introduction

Indication/Licensing information

As Per NICE TA 461, 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 (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.

Place in therapy

Within BHNFT 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.

Pharmacology

Roflumilast is a phosphodiesterase type-4 inhibitor with anti-inflammatory properties.
Roflumilast is a PDE4 inhibitor, a non-steroid, anti-inflammatory active substance 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. Roflumilast targets the PDE4A, 4B and 4D splicing variants with similar potency in the nanomolar range. The affinity to the PDE4C splicing variants is 5 to 10-fold lower. This mechanism of action and the selectivity also apply to roflumilast N-oxide, which is the major active metabolite of roflumilast.

Dosage and administration

Initially 250 micrograms once daily for 28 days, then maintenance 500 micrograms once daily.

This starting dose is intended to reduce adverse events and patient discontinuation when initiating therapy, but it is a sub-therapeutic dose. Therefore, the 250 micrograms dose should be used only as a starting dose.

After 28 days of treatment with the 250 micrograms starting dose, patients must be up-titrated to one tablet of 500 micrograms roflumilast, to be taken once daily.

Daxas 500 micrograms may need to be taken for several weeks to achieve its full effect. Daxas 500 micrograms has been studied in clinical trials for up to one year, and is intended for maintenance treatment. This should be trialed for at least six month and then the specialist should assess the benefit to the patient. If there is no benefit or if the patient is not tolerating then this can be discontinued.

Special populations

Elderly

No dose adjustment is necessary.

Renal impairment

No dose adjustment is necessary.

Hepatic impairment

The clinical data with Daxas in patients with mild hepatic impairment classified as Child-Pugh A are insufficient to recommend a dose adjustment and therefore Daxas should be used with caution in these patients.

Patients with moderate or severe hepatic impairment classified as Child-Pugh B or C must not take Daxas.

Women of child-bearing potential should use effective contraception.

Responsibilities of the specialist initiating treatment

Summary

- To assess the suitability of the patient for treatment.
- To discuss the benefits and side effects of treatment with the patient/carer and the need for long term monitoring if applicable.
- To perform baseline tests and if appropriate routine tests until the patient is stable.
- To prescribe for the first 12 weeks of treatment
- To ask the GP whether they are willing to participate in shared care.
- To provide the GP with a summary of information relating to the individual patient to support the GP in undertaking shared care (See Shared care request form in Appendix A).
- To advise the GP of any dosage adjustments required, monitoring required, when to refer back, and when and how to stop treatment (if appropriate).
- To advise the GP when the patient will next be reviewed by the specialist.
- To monitor the patient for adverse events and report to the GP and where appropriate Commission on Human Medicines/MHRA (Yellow card scheme).
- To provide the GP with contact details in case of queries.

After six month, the specialist should assess the exacerbation rate and body weight before making the decision to continue Roflumilast or not.

Responsibilities of other prescribers

Acceptance of Responsibility by the Primary Care Clinician

It is optional for GPs to participate in taking on responsibility for shared care for the patient. GPs will take on shared care only if they are willing and able.

Summary

- To reply to the request for shared care as soon as possible.
- To prescribe and adjust the dose as recommended by the specialist.
- To ensure there are no interactions with any other medications initiated in primary care.
- To continue monitoring as agreed with secondary care (guideline should include details of monitoring requirements and what to do when each of the defined parameters alters).
- To refer back to the specialist where appropriate. For example:
  - Patient or general practitioner is **not** comfortable to continue with the existing regime due to either change in condition or drug side effects.
  - Advice in respect of concordance.
  - Special situations, (e.g. Pregnancy)
- Discontinue the drug as directed by the specialist if required
- To identify adverse events if the patient presents with any signs and liaise with the hospital specialist where necessary. To report adverse events to the specialist and where appropriate the Commission on Human Medicines/MHRA (Yellow card scheme).

Clinical Particulars

BNF therapeutic class	Phosphodiesterase type-4 inhibitors
Cautions and Contraindications	**Cautions:** • History of psychiatric illness (discontinue if new or worsening psychiatric symptoms occur). • Latent infection (such as tuberculosis, viral hepatitis, herpes infection). • 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. **Contra-indications:** • Cancer (except basal cell carcinoma). • Pregnancy/breast feeding • Concomitant treatment with immunosuppressive drugs (except short-term systemic corticosteroids). • **History of depression associated with suicidal ideation or behaviour**. • Moderate to severe cardiac failure. • Severe acute infectious disease. • Severe immunological disease.
Adverse Drug Reactions	**Common (more than 1/100, but less than 1/10) or very common (more than 1/10)** • Appetite decreased. • Diarrhoea. • Gastrointestinal discomfort. • Headache. • Insomnia.

	• Nausea. • Weight decreased. Whilst these adverse effects occur within the first weeks of therapy and mostly resolve on continued treatment, roflumilast treatment should be reassessed in case of persistent intolerability.
Monitoring	Monitor body-weight. <u>Weight decrease</u> Body weight of underweight patients should be checked at each visit (yearly). 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.
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 should be reassessed. roflumilast treatment is not recommended in patients receiving strong cytochrome P450 enzyme inducers (phenobarbital, carbamazepine, phenytoin) as this may reduce therapeutic efficacy of roflumilast. The above is not an exhaustive list. Please see the manufacturers summary of product characteristics (SPC) and the most current edition of the British National Formulary for full information in terms of the side effects, contra-indications, warnings and drug interactions.

Communication

Specialist to GP
The specialist will inform the GP when they have initiated Roflumilast. When the patient is near completing the satisfactory initiation period, the specialist will write to the GP to request they take over prescribing and where possible give an indication as to the expected length of treatment. The Specialist will also send a Shared care request form to support the GP in undertaking shared care. (Appendix A)

GP to specialist
If the GP has concerns over the prescribing of Roflumilast, they will contact the specialist as soon as possible.

Contact names and details

Contact Details	**Telephone number**	**Email**
Dr Hazim Mahdi	01226 730000	h.mahdi@nhs.net
Dr Muhammad Malik	01226 730000	mj.malik@nhs.net
Dr Akhtar Akhtar	01226 730000	akhtar.akhtar@nhs.net
Dr Amir Khalil	01226 730000	amirkhalil@nhs.net
Dr Salim Meghjee	01226 730000	s.meghjee@nhs.net
Dr Muhammad Hussain	01226 730000	muhammad.hussain51@nhs.net

Shared Care Protocol –remains open to review in light of any new evidence
***Amber** = To be initiated and titrated to a stable dose in secondary care with follow up prescribing and monitoring by primary care.*

Development Process

This guidance has been produced by Lauren Clarke – Senior Pharmacist - Interface following an AMBER classification status of Roflumilast by the Barnsley Area Prescribing Committee. This guideline has been subject to consultation and endorsement by the Area Prescribing Committee on 10th March 2021.

Appendix A – Shared Care request form (Amber)

- Specialist to complete when requesting GP to enter a shared care arrangement.
- GP to return signed copy of form.
- Both parties should retain a signed copy of the form in the patient's record.

From (**Specialist**): _____ **To** (**GP**): _____

Patient details

Name: _____ ID Number: _____

Address: _____ DOB: _____

Diagnosed condition: _____

Amber Drug details

Drug name: _____ Dose and frequency: _____

Date of initiation: _____ Length of treatment: _____

The patient will be reviewed by the Consultant on: _____

The patient should be reviewed by the GP by: _____

Monitoring

The following monitoring should be undertaken by the GP:

Parameter	Date next test due	Frequency

Communication

Consultant
Telephone number: _____ Fax number:_____

Email address: _____

Specialist Nurse
Telephone number: _____ Fax number: _____

Email address: _____

Confirmation of acceptance of shared care

Specialist (Doctor/Nurse) name: _____

Specialist (Doctor/Nurse) signature: _____ Date: _____

I, Dr ……., can confirm I :

☐ accept the request to participate in shared care for the patient named above.

☐ reject the request to participate in shared care for the patient named above. The reason for this being ……..

GP signature: _____ Date: _____

To save resources you have been sent appendix A of the shared care document.

The full document (DAXAS® (Roflumilast) Shared Care Guideline, date approved March 2021) can be accessed on the Barnsley BEST website at the following link:
http://best.barnsleyccg.nhs.uk/clinical-support/medicines/shared-care-guidelines/
Or via the Barnsley Area Formulary www.barnsleyformulary.nhs.uk