Oxford University Hospitals NHS
NHS Trust

NHS
Oxfordshire
Clinical Commissioning Group

Roflumilast (Daxas) Therapy in the Treatment of Chronic Obstructive Pulmonary Disease

AMB C

Amber Continuation Guideline

This guideline provides prescribing and monitoring guidance for roflumilast (Daxas®) therapy in the treatment of chronic obstructive pulmonary disease (COPD). It should be read in conjunction with the Summary of Product Characteristics (SPC) available on www.medicines.org.uk/emc and the BNF.

Specialist responsibilities prior to transfer of prescribing

- Complete pre-treatment assessment in accordance with 'pre-treatment assessment' section.
- Initiate treatment and prescribe first three months of treatment prior to transfer of prescribing to GP.
- Ensure the patients understand the nature and complications of drug therapy and their role in reporting adverse effects promptly.
- Provide copy of patient information leaflet and drug monitoring card where appropriate.
- Be available to give advice to GP and patient during treatment.

GP responsibilities summary

- Prescribe medication as recommended below, once transfer of prescribing is complete.
- Ensure all monitoring is completed in accordance with 'on-going monitoring' section.
- Monitor patient for adverse effects, contraindications and precautions as listed below.
- Take subsequent recommended actions as outlined below, including referral back to specialist if appropriate.

Patient responsibilities summary

- Agree to treatment and monitoring after making an informed decision.
- Request verbal or written information as needed.
- Ensure roflumilast is taken as prescribed – notifying GP or specialist of any adverse effects or concerns about medication
- Ensure attendance for relevant monitoring as indicated by prescriber and record weight regularly on drug monitoring card and bring to all appointments
- Attend GP and outpatient appointments as necessary and discuss any information needs or concerns as relevant.

Background for Use

Roflumilast is an orally administered long-acting selective phosphodiesterase-4 enzyme inhibitor. It targets cells and mediators believed to be important in COPD.
In July 2017, the National Institute of Clinical Excellence technological appraisal guidance (NICE TA 461) was passed for 'Roflumilast for Treating Chronic Obstructive Pulmonary Disease'[1]. TA 461 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 bronchonchodilator 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-gonist and an inhaled corticosteroid.*

It is also recommended that treatment is initiated by a specialist in respiratory medicine.

Roflumilast should also be started when the patient is stable, such as when they have an out-patient appointment.

Supporting Information

- National Institute of Clinical Excellence technological appraisal guidance (TA 461) published 26 July 2017. Available at https://www.nice.org.uk/guidance/TA461 Accessed 16/09/2017
- Summaries of Product Characteristics (SPC) for Daxas 500 microgram Film-Coated Tablets. Available at: http://www.medicines.org.uk/EMC/medicine/23416/SPC/DAXAS+500+micrograms+film-coated+tablets/ Accessed 16/09/2017

Contraindications and Precautions[2]

Contraindication	Action
Patients with moderate or severe hepatic impairment classified as Child-Pugh B or C	Do not use.
Hypersensitivity to roflumilast or to any of the excipients in the tablet.	Do not use.
Special clinical conditions	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) - 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). - Patients with latent infections such as tuberculosis, viral hepatitis, herpes viral infection and herpes zoster. - Patients with congestive heart failure (NYHA grades 3 and 4).
Psychiatric disorders	Roflumilast is not recommended in patients with a history of depression associated with suicidal ideation or behaviour.
Women of childbearing potential	Roflumilast is not recommended in women of childbearing potential not using contraception.
Pregnancy	Do not use.
Breast-feeding	Do not use.
Precautions	**Action**
Patients with mild hepatic impairment classified as Child-Pugh A	Use with caution as no data available to suggest dosing at lower doses.
Weight reduction / Decreased appetite	Common (≥1/100 to <1/10) side effect – patients are asked to record their weight every two weeks on their 'Daxas Treatment Card for Patients' together with any comments such as decreased appetite, nausea and / or vomiting. The patients should bring their card to each visit with their respiratory Consultant or GP, and in the event of an unexplained and clinically concerning weight reduction, treatment will be stopped.
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. 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.
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.
Body weight less than 60 kg	Treatment with roflumilast may lead to a higher risk of sleep disorders (mainly insomnia) in patients with a baseline body weight of less than 60 kg.

Dosage[2]

Indication	Dose
Maintenance treatment of severe chronic obstructive pulmonary disease (COPD) (FEV_1 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.	The recommended dose is 500 micrograms (one tablet) roflumilast once daily. The tablet should be swallowed with water and taken at the same time every day. It can be taken with or without food.

Time to Response

Roflumilast may need to be taken for several weeks to achieve its effect and has been studied in clinical studies for up to one year[2].

The summary of product characteristics[2] (SPC) notes that roflumilast is subject to additional monitoring and that a higher incidence of weight decrease, decreased appetite, headache and depression was observed in the COPD studies in patients receiving ICS / LABA / LAMA and randomised to roflumilast in comparison with placebo.

The SPC notes an increased risk of psychiatric disorders and that (rarely) 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. All patients should be informed about the risks of roflumilast and the precautions for safe use and should be given a 'Daxas Treatment Card for Patients'[2,3]

The GP takes over prescribing responsibilities after 3 months treatment from the Hospital.

Pre-Treatment Assessment

The following pre-treatment assessment should be carried out prior to initiation roflumilast:

- Patients weight
- Lung functions tests – FEV1 and FVC
- Full Liver function tests (AST / ALT / Bilirubin / Gamma – GT)
- Child-Pugh assessment of hepatic function
- Psychiatric history

- Medicines adherence checks
- Inhaler technique checks

The patient will be counselled about the possible side effects that may occur when taking roflumilast and given a 'Daxas Treatment Card for Patients'[3]. This includes information regarding mood changes that should be recorded and reported to the Consultant / GP and a section for the patient to record their weight very two weeks. Further copies of this card are available via the SPC for roflumilast[3] under the 'risk materials' section.

The GP will also receive a copy of the 'Daxas in your Practice – Information for Prescribers' leaflet when a patient starts roflumilast, so that they are aware that their patient has started treatment. Further supplies of this leaflet are available via the SPC for roflumilast[4] under the 'risk materials' section.

Ongoing Monitoring

The following monitoring should be carried out every 6 months whilst patients continue taking roflumilast:

- Patients weight*
- Lung functions tests – FEV1 and FVC
- Full Liver function tests (AST / ALT / Bilirubin / Gamma – GT)
- Child-Pugh assessment of hepatic function**
- Recent psychiatric history
- Inhaler technique checks

*The patient should take their 'Daxas Treatment Card for Patients'[3] to all GP appointments so that 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. Further copies of this card are available via the SPC for roflumilast[3].
**Only necessary in patients with cirrhosis of the liver. Scoring criteria is below:

Parameter	**Score**		
	1	**2**	**3**
Ascites	None	Mild	Moderate or Severe
Encephalopathy (grade)	None	1-2	3-4
Bilirubin (micromole/L) **OR** Bilirubin in Primary Biliary Cirrhosis (micromole/L)	<35 <70	35-50 70-170	>50 >170
Albumin (g/L)	>35	28-35	<28
INR	<1.7	1.8-2.3	>2.3

Child-Pugh grade	**Child-Pugh Score**
A	5-6
B	7-9
C	10-15

Actions to be taken

Side Effects	Action
Suicidal ideation and behaviour (These symptoms have most commonly been reported to occur during the first 3 months of treatment whilst patient is under the Consultants care)	Stop roflumilast treatment
New symptoms of insomnia, anxiety, nervousness and depression	Stop roflumilast treatment
Weight loss	If unexplained and clinically concerning weight decrease, the intake of roflumilast should be stopped and body weight should be further followed-up.
Raised AST and / or gamma-GT	Stop roflumilast treatment and follow-up LFT's after 2 weeks to ensure liver function is back to baseline.
Hepatic impairment becomes moderate or severe hepatic (classified as Child-Pugh B or C)	Stop roflumilast treatment
Treatment is required with immunosuppressive medicinal products (i.e.: methotrexate, azathioprine, infliximab, etanercept, or long term oral corticosteroids)	Stop roflumilast treatment
Muscle spasms, myalgia, with / without blood creatine phosphokinase (CPK) increase	Stop roflumilast treatment
Nausea, vomiting and abdominal pain	These are common side effects that usually occur at start of treatment and resolve with continuation of treatment. If the patient complains of these side effects once treatment has transferred to primary care, hold treatment for a couple of weeks and re-challenge . If the side effects re-occur, stop treatment.

Notable Drug Interactions (Refer to BNF and SPC)

Roflumilast is mainly metabolized via the liver via CYP1A2 and CYP3A4. Therefore the following interactions should be noted:

1. Avoid interactions with **strong CYP1A2 inhibitors** which include:

Ciprofloxacin and fluvoxamine

2. Avoid interactions with **strong and moderate CYP3A4** inhibitors which include:

Clarithromycin, ciprofloxacin, clindamycin, erythromycin, fluvoxamine, Itraconazole, ketoconazole, posaconazole, voriconazole.

3. Avoid interactions with **strong CYP3A4 inducers** which include:

Carbamazepine, enzalutamide, phenobarbital, phenytoin, rifampicin and St, John's wort

4. **Methylyxanthines** (aminophylline and theophylline) are CYP1A2 substrates and compete with roflumilast for CYP1A2. Therefore patients should **NOT** be on methylxanthines when they are prescribed roflumilast.

Note: This is not an exhaustive list of interactions, therefore refer to the latest BNF for the latest list of drug interactions.

Back-up Information and Advice

Name, job title, department	Contact Details (phone/email)
Dr Maxine Hardinge Consultant in Respiratory Medicine Lead for COPD service Oxford Centre for Respiratory Medicine Oxford University Hospitals	Maxine.hardinge@ouh.nhs.uk
Dr Mona Bafadhel Consultant in Respiratory Medicine Oxford Centre for Respiratory Medicine Oxford University Hospitals	Mona.bafadhel@ouh.nhs.uk
Rachel Russell-Sharp Secretary for Dr Maxine Hardinge and Dr Mona Bafadhel Oxford Centre for Respiratory Medicine Oxford University Hospitals	01865 225234
Sarah Poole Lead Respiratory Pharmacist Oxford University Hospitals	01865 741841 – bleep 4500 Sarah.poole@ouh.nhs.uk

References

1 National Institute of Clinical Excellence technological appraisal guidance (TA 461) published 26 July 2017. Available at https://www.nice.org.uk/guidance/TA461 Accessed 17/09/2017

2. Summaries of Product Characteristics (SPC) for Daxas 500 microgram Film-Coated Tablets. Available at: http://www.medicines.org.uk/EMC/medicine/23416/SPC/DAXAS+500+micrograms+film-coated+tablets/ Accessed 17/09/2017

3. 'Daxas Treatment Card for Patients' - Summaries of Product Characteristics (SPC) for Daxas 500 microgram Film-Coated Tablets. Available at: www.medicines.org.uk/emc/RMM.816.pdf Accessed 17/09/2017

4 'Daxas in your Practice – Information for Prescribers' leaflet - Summaries of Product Characteristics (SPC) for Daxas 500 microgram Film-Coated Tablets. Available at: www.medicines.org.uk/emc/RMM.817.pdf Accessed 17/09/2017