

ANNEX

**CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF
THE MEDICINAL PRODUCT TO BE IMPLEMENTED BY THE MEMBER STATES**

The Member States must ensure that all conditions or restrictions with regard to the safe and effective use of the medicinal product described below are implemented in their national territory:

- Prior to launch of the product in the Member State, the national competent authority shall agree the content and format of the educational material with the Marketing Authorisation Holder
- The Marketing Authorisation Holder (MAH) should ensure that, at launch, all Healthcare Professionals who are expected to prescribe Daxas are provided with an Educational pack.

The educational pack should contain the following:

- Summary of Product Characteristics and Patient Information Leaflet for Daxas
- Educational material for the physician.
- Copies of the patient card to be given to patients before they receive Daxas

The educational material for the prescriber should include information on the following key elements:

- The specific indication approved. The fact that Daxas is not indicated for the treatment of COPD patients other than those covered by the approved indication, nor for use in patients with asthma or alpha 1 anti trypsin deficiency.
- The need to inform patients about the risks of Daxas and the precautions for safe use.
- The risk of weight decrease in underweight patients and the need to monitor the body weight at each visit and to stop the treatment in the event of an unexplained and clinically concerning weight decrease. Patients should be advised to weigh themselves at regular intervals and record the weight in the patient card.
- The risk of psychiatric disorders such as insomnia, anxiety, depression in patients receiving Daxas and the potential risk of suicide. Hence, the need to carefully assess the benefit risk balance of this treatment in patients with existing psychiatric symptoms or with history of depression and to inform patients to report any changes in behaviour, mood and any suicidal ideation. Daxas is not recommended in patients with a history of depression associated with suicidal ideation or behaviour.
- The potential risk of malignant tumours and the lack of experience in patients with past history of cancer. Daxas should not be initiated or should be stopped in patients with cancers (except basal cell carcinoma).
- That increased exposure might occur in certain populations and increase the risk of persistent intolerability:
 - Special populations who have increased PDE4 inhibition such as black non smoking females
 - Patients concomitantly treated with CYP1A2 inhibitors (such as fluvoxamine) or dual CYP3A4/1A2 inhibitors (such as enoxacin and cimetidine)
- The potential risk of infections: Daxas should not be initiated, or treatment should be stopped, in patients with severe acute infectious diseases. The limited experience in patients with latent infections such as tuberculosis, viral hepatitis or herpes infections.

- The lack of experience in patients with HIV infection or active hepatitis, with severe immunological diseases (e.g. multiple sclerosis, lupus erythematosus, multifocal leukoencephalopathy) or treated with immunosuppressive therapy (other than short-term systemic corticosteroids) and that Daxas should not be initiated or should be stopped in these patients.
- The potential cardiac risk: Daxas has not been studied in patients in congestive heart failure (NYHA grade 3 and 4); hence, it is not recommended in this population.
- The limited or missing information in patients with liver impairment. Daxas is contraindicated in patients with moderate or severe liver impairment (Child Pugh B or C). Clinical data are considered insufficient to recommend dose adjustment and caution should be observed in patients with mild liver impairment (child Pugh A).
- The lack of clinical data to support the combination with theophylline and that such combination is not recommended.

Patient Card

The patient card should contain the following key elements:

That they should tell their doctor if they have a history of any of the following conditions

- cancer
- insomnia, anxiety, depression, suicidal ideation or behaviour
- multiple sclerosis or SLE
- infection with tuberculosis, herpes, hepatitis, HIV

That patients should tell their doctor if they develop symptoms indicative of:

- insomnia, anxiety, depression, suicidal ideation or behaviour
- severe infection

That patients should tell their doctor if they are taking any other medicines.

That Daxas may cause weight loss and patients should weigh themselves regularly and record their weight on the patient card.

The patient card should include an area where patients can record their weight and the date they weighed themselves and they should be asked to bring the patient card with them at each visit.