

## 9. APPROPRIATE USE OF ARIFLO IN THE MANAGEMENT OF COPD

### 9.1. Proposed Label: Indications, dosage and administration

The indication statement for **ARIFLO** is different from other medications that are currently approved for the treatment of patients with COPD. The wording in the proposed label is supported by the results of the clinical program. **ARIFLO** maintained lung function over 6 months of treatment, while patients treated with placebo experienced loss of lung function over the study period. The difference in lung function between the treatment groups was statistically significant.

**ARIFLO** is intended to be used regularly as maintenance therapy for the treatment of COPD, and should not be used to treat acute symptoms.

The proposed indication, dosage, and administration for **ARIFLO** (cilomilast) Tablets are as follows:

#### Proposed Indication

***ARIFLO** is indicated for the maintenance of lung function ( $FEV_1$ ) in patients with chronic obstructive pulmonary disease (COPD) who are poorly responsive to albuterol (increase in  $FEV_1$  of  $\leq 15\%$  or  $\leq 200$  mL). The efficacy of **ARIFLO** has not been established in clinical trials beyond 24 weeks.*

#### Proposed Dosage and Administration

*The recommended dose of **ARIFLO** is 15 mg twice daily. It is recommended that **ARIFLO** be taken with food. No dosage adjustments are required for elderly subjects or for smokers. Therapy with **ARIFLO** should be continued during acute exacerbations of COPD. Inhaled albuterol should be used for relief of acute breathlessness.*

***Patients With Hepatic Impairment:** **ARIFLO** is contraindicated in patients with severe (Child-Pugh Grade C) hepatic impairment. **ARIFLO** should be used with caution in patients with moderate (Child-Pugh Grade B) hepatic impairment because these subjects may have higher exposures to unbound cilomilast. Since there are no data on patients with mild hepatic impairment, caution is also warranted in these patients.*

***Patients With Renal Impairment:** **ARIFLO** should be used with caution in patients with severe renal impairment (creatinine clearance  $< 30$  mL/min) because these subjects may have higher exposures to unbound cilomilast.*

#### 9.1.1. Clinical implications of the administration of more than one 15mg tablet BID

If there is an increase in symptoms, or if a dose is missed, patients with COPD may take more than the prescribed dose of **ARIFLO**. Although **ARIFLO** labeling will

specifically warn against using more than one tablet twice daily, it is acknowledged that some patients may, contrary to recommended use, double the dose of when they perceive a deterioration in their condition. Patients who received more than 30mg of **ARIFLO** had an increase in adverse events including headache, nausea, vomiting, diarrhea and abdominal pain. Patients who receive a higher than recommended dose of **ARIFLO** to treat worsening symptoms may experience an increased incidence of pharmacologically predictable adverse events associated with PDE inhibitors.

### 9.1.2. Labeling

The Indications and Dosage and Administration sections of the label have been discussed above. The indication statement describes the population of Patients with COPD for whom the drug benefits have been demonstrated to exceed the possible risks.

- The proposed CONTRAINDICATIONS section describes the patients for whom the potential risks of **ARIFLO** outweigh the benefits. These include patients with severe hepatic impairment (defined as Child-Pugh Grade C) and those who are hypersensitive to cilomilast or any of its ingredients.
- The proposed WARNINGS section of the labeling advises caution if **ARIFLO** is used in patients with moderate hepatic impairment since these patients are susceptible to elevated exposure to high levels of unbound cilomilast. Also in this section, prescribers are warned that due to its mechanism of action, cilomilast should not be used as a treatment for acute bronchospasm.
- The proposed PRECAUTIONS section of the labeling advises prescribers about the management of potential GI adverse events. Because pre-clinical studies revealed medial necrosis in the splanchnic arteries in mice and rats, clinical trials included assessments for fecal occult blood and diagnostic follow up in cases involving gastrointestinal events of special interest e.g. unexplained bleeding per rectum. Although the available data from clinical trials does not support a conclusion that **ARIFLO** is associated with serious gastrointestinal adverse events, prescribers are advised to medically evaluate patients that present with serious gastrointestinal complaints or bloody/ black stools.

## 9.2. SUMMARY

The results from this clinical program support the following indication and recommendations for dosage and administration:

- **ARIFLO** is indicated for the maintenance of lung function (FEV<sub>1</sub>) in patients with chronic obstructive pulmonary disease (COPD) who are poorly responsive to albuterol (increase in FEV<sub>1</sub> of  $\leq 15\%$  or  $\leq 200$  mL). The efficacy of **ARIFLO** has not been established in clinical trials beyond 24 weeks.
- The recommended dose of **ARIFLO** is 15mg twice daily. It is recommended that **ARIFLO** be taken with food. No dosage adjustments are required for elderly subjects or for smokers. Therapy with **ARIFLO** should be continued during acute

exacerbations of COPD. Inhaled albuterol should be used for relief of acute breathlessness.