

## **SUMMARY OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS FINDINGS**

Ariflo® tablets contain cilomilast, an orally active, synthetic, selective phosphodiesterase-4 (PDE4) inhibitor proposed for the maintenance of lung function (FEV<sub>1</sub>) in patients with chronic obstructive pulmonary disease (COPD) who are poorly responsive to albuterol.

Ariflo has been evaluated in 77 Phase I, II and III clinical studies by GlaxoSmithKline. The efficacy and safety of Ariflo in COPD patients was primarily assessed in seven double-blind, placebo-controlled, multicenter studies. The sponsor assessed the clinical pharmacology of Ariflo immediate release tablets in 37 studies. Some of these studies included: pharmacokinetic studies in healthy volunteers (14), pharmacokinetic studies in special populations (5), drug-drug interaction studies (9), studies in COPD Patients (7, three of which were used in population PK analysis and one exposure-response study). Additionally, the sponsor included the assay method validation and dissolution information. The majority of these studies were reviewed (29). The remaining studies were not reviewed because they did not provide additional information. Ariflo will be available in 15 mg immediate release tablets at the proposed dose of 15 mg twice daily. The oral doses studied in the clinical pharmacology studies include single doses of 2, 4, 5, 7, 10, 15 and 20 mg and multiple doses of 2, 4, 5, 7, 10, 15, 20, 25 and 30 mg .

### **Pharmacokinetics in Healthy Volunteers**

#### **Single Dose**

Cilomilast pharmacokinetics were linear (dose-proportional) in the range of 2 to 20 mg. Cilomilast plasma clearance was about 1.5-2 L/h, indicating that cilomilast is a low extraction ratio drug. The volume of distribution (10-17 L) and half-life (7-8 h) were approximately the same following oral or intravenous administration. C<sub>max</sub> occurred at 1.5-2 hr. The pharmacokinetics of cilomilast were not affected by the time of administration.

#### **Repeat Dose**

Cilomilast pharmacokinetics were dose-proportional in the range of 2 to 30 mg and the half-life was about 6-8 hrs. Steady-state was reached within 2 to 3 days of repeated twice daily dosing. Steady-state plasma concentrations were predictable from single dose data; the accumulation ratio ranged between 1.32-1.53 across doses of 2-15 mg. T<sub>max</sub> was similar to that after single dose administration. The mean C<sub>max</sub> and AUC<sub>t</sub> of the major metabolite were 13- and 11-fold lower, respectively than those observed for the parent drug following multiple oral administration of 15 mg . The half-life was similar (7.2 hrs) to that for cilomilast.

#### **Bioavailability**

The average absolute bioavailability of cilomilast in the fasted state was 103%. Administration after a high-fat breakfast did not affect AUC, but delayed T<sub>max</sub> by 2 hours and reduced C<sub>max</sub> by 38%. The antacid preparation 'Maalox' did not affect cilomilast bioavailability.

#### **Absorption**

Cilomilast is absorbed fairly rapidly. T<sub>max</sub> ranged from 1.5-2 hrs.

#### **Distribution**

After intravenous administration, the steady-state volume of distribution (V<sub>ss</sub>) ranged from 10 to 17 L, which is similar to the extracellular water volume, indicating that Ariflo is not extensively distributed into the tissues. After oral administration, a one-compartment population pharmacokinetic model (mean V<sub>ss</sub>/F = 12.9 L) adequately described the cilomilast steady-state plasma concentration versus time data from COPD patients receiving 15 mg twice daily in Phase 3 clinical trials. Cilomilast is highly bound to plasma proteins (> 99 %).

## **Metabolism and Elimination**

Cilomilast is extensively metabolized via hydroxylation mainly by CYP 2C8 to the most abundant metabolite SB-217493. The enzymes responsible for two other major pathways (decyclopentylation and glucuronidation) have not been identified. Following oral administration, cilomilast was the principal circulating moiety, accounting for at least 70% of total systemic exposure of drug-related material in plasma. Minor metabolites were also observed and none individually accounted for more than 10% of plasma radioactivity even as late as 24 hours post-dose. More than 90% of the radiolabeled dose was eliminated in urine. Unchanged cilomilast in urine and feces accounted for a mean of approximately 1% of the administered dose, indicating that its predominant route of elimination in man is by metabolism, followed by renal excretion of the metabolic products. SB-217493 was the major metabolite found in urine and feces accounting for about 43 % of the administered dose; no other metabolites individually accounted for more than 13% of the administered dose. The pharmacological activity of the metabolite SB-217493 is less than one-tenth that of cilomilast, and its plasma concentrations (AUCt) at steady-state are about 10-fold lower.

## **Pharmacokinetics in COPD Patients**

The predicted (from population PK analysis) C<sub>max</sub> and AUC ranged from 0.596 to 1.140 mcg/mL (mean=0.986 mcg/mL) and 4.76 to 34.48 mcg\*hr/mL (mean=11.58 mcg\*hr/mL, SD=3.42), respectively in COPD patients receiving cilomilast 15 mg twice daily. The AUC values were comparable with the corresponding parameters derived from non-compartmental analysis in pharmacokinetic studies in healthy volunteers. However, C<sub>max</sub> values appeared to be lower in COPD patients [healthy subjects (mean C<sub>max</sub>= 1.58 mcg/mL); mean AUC<sub>0-12</sub> = 12.88 mcg\*hr/mL)].

## **Pharmacokinetics in Special Populations**

### **Age, Gender, Weight, Smoking Status, Race**

The population pharmacokinetics analysis of data from COPD patients revealed that body weight was the only demographic factor which significantly influenced cilomilast disposition. Neither age, gender, creatinine clearance nor smoking were found to significantly affect CL/F or V<sub>ss</sub>/F. The effect of race on the PK of cilomilast was not clear due to the small number of subjects of different races included (1.7% Black, 0.76 oriental, 1.05% other). The population predicted estimates of cilomilast CL/F and V<sub>ss</sub>/F at the median body weight observed in these patients (75 kg) were 1.33 L/h and 12.9 L, respectively.

In a single dose pharmacokinetic study, the mean AUC<sub>inf</sub> and C<sub>max</sub> of cilomilast were reduced by 10% and 20%, respectively in smokers compared with non-smokers. There was no difference in T<sub>max</sub> and elimination half-life between smokers and non-smokers. The half-life was increased by 0.64 hrs in smokers compared to non-smokers.

In a single dose pharmacokinetic study, the mean AUC<sub>inf</sub> and C<sub>max</sub> of cilomilast were increased by 23% and 13%, respectively, in the elderly (>65 years) compared to young adults. T<sub>max</sub> values were 2 and 3 hrs in the elderly and young, respectively. The extent of plasma protein binding of cilomilast was 99.6% and 99.5% for young and elderly subjects, respectively.

## **Renal Impairment**

The effect of renal impairment (RI) on the pharmacokinetics of cilomilast (and its principal metabolite SB-217493) was examined after repeated 15 mg twice daily dosing to patients with mild, moderate, and severe RI, in each case compared to healthy volunteers. The total average AUC<sub>0-12</sub>, total C<sub>max</sub>, unbound C<sub>max</sub> and total C<sub>min</sub> for cilomilast in subjects with mild, moderate or severe RI were not significantly different than those observed in normal volunteers. The unbound AUC<sub>0-12hr</sub> in mild, moderate and severe RI subjects increased by 26%, 34%, and 60%, respectively. The half-life and fraction unbound in plasma gradually increased with decreasing renal function. The half-life increased by

up to 4.8 hrs and the fraction unbound increased by up to 35%.  $Ae_{0-12}$  and renal clearance gradually decreased with decreasing renal function.  $Ae$  decreased by up to 2.3-fold and renal clearance decreased by up to 2.6-fold.

The metabolite's total average  $C_{max}$ ,  $AUC_{0-12}$ , and  $C_{min}$  in RI subjects increased gradually by up to 2.3-, 2.9, and 3.6-fold, respectively. The half-life increased gradually by up to 5.4 hrs. The average unbound  $C_{max}$ , unbound  $AUC_{0-12}$ , and fraction unbound in RI subjects increased by up to 2-fold, 2.74-fold and 5%, respectively.  $A_{2(0-12)}$  and renal clearance decreased gradually with decreasing renal function.  $Ae_{0-12}$  decreased by up to 4.6-fold and renal clearance decreased by up to 13.2-fold.

### **Hepatic Impairment**

The effect of hepatic impairment (HI) on the pharmacokinetics of a single 10 mg oral dose of cilomilast was examined in 10 subjects with moderate to severe HI (Child-Pugh category B (6) and in category C (4)), in each case compared to healthy volunteers. The total average  $AUC_{inf}$ , total  $C_{max}$ , and total clearance/F for cilomilast in subjects with Child-Pugh B and C HI were not significantly different.  $AUC_{0-12}$  increased 8% and  $C_{max}$  decreased 15% in Child-Pugh C subjects. The unbound  $AUC_{inf}$  in subjects with Child-Pugh B and C HI were increased by 2.2- and 4.7-fold, respectively. The unbound  $C_{max}$  in subjects with Child-Pugh B and C HI were increased by 1.9- and 4.3-fold, respectively. The unbound CL/F in subjects with Child-Pugh B and C HI were decreased by 1.7- and 4.4 -fold, respectively. The half-life did not change significantly. Half-life increased by 0.86 hrs in Child-Pugh C subjects. Cilomilast was not evaluated in Child-Pugh Class A subjects.

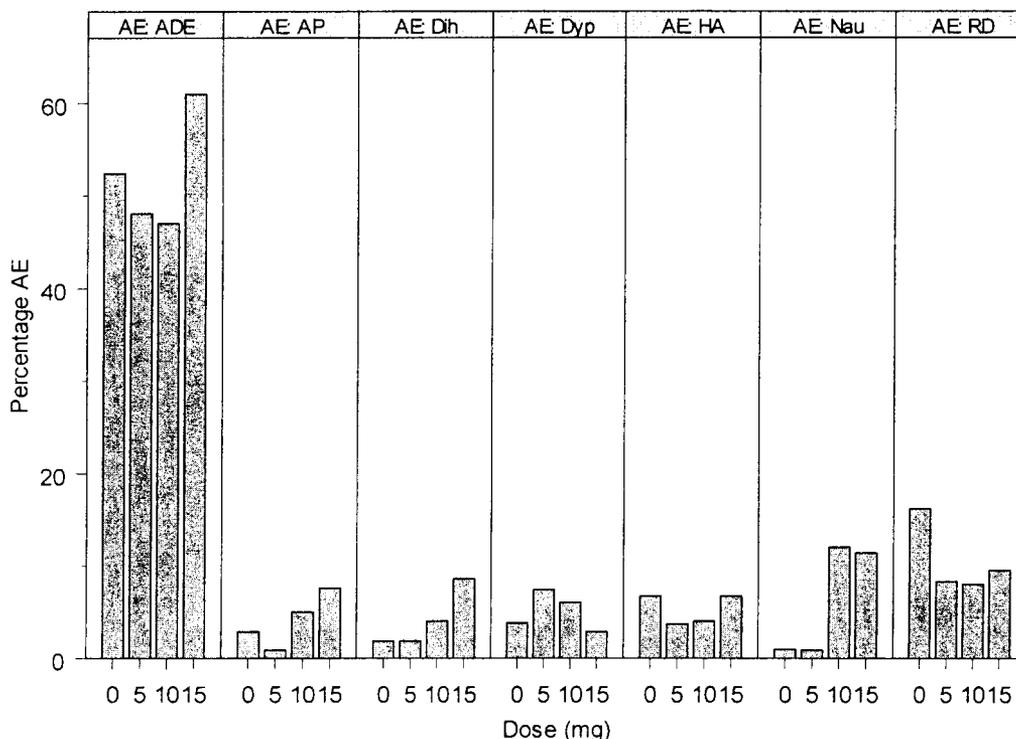
### **Drug/Drug Interactions**

In-vitro metabolism studies using human microsomes indicated that cilomilast is mainly metabolized by CYP 2C8 and does not affect the activity of the major CYP P450 enzymes such as CYP1A2, CYP2A6, 2C8, CYP2C9/8, CYP2C19, CYP2D6, CYP2E1, CYP3A and CYP4A. Taxol 6 $\alpha$ -hydroxylase and tolbutamide 4-hydroxylase activities were inhibited to the largest extent, averaging 34% and 22% inhibition, respectively. Therefore, no major effects of cilomilast should be expected on the PK of other drugs. The sponsor conducted drug-drug interactions with the following drugs: digoxin, erythromycin, warfarin, oral prednisolone, theophylline, inhaled albuterol and antacid. No significant interactions were observed with these drugs; however, coadministration of cilomilast with erythromycin was associated with an increased incidence of gastrointestinal adverse events. The effect of 2C8 inhibitors on the PK of cilomilast has not been evaluated.

### **Concentration-Response Relationships**

The concentration-response relationship of cilomilast was evaluated in a placebo-controlled, parallel group study of multiple administration of oral cilomilast (5, 10 and 15mg twice daily) for 6 weeks to patients with COPD. No dose order -response relationship was reported for cilomilast at these doses because the 10 mg dose showed lower effect than the 5 mg dose. The primary efficacy endpoint (change from baseline in  $FEV_1$ ) was statistically different from placebo at all visits only at the dose of 15 mg. However, further analysis of the data showed that the 10 mg dose group had a higher  $FEV_1$  baseline compared to the 5- and 15 mg dose group. Therefore, the significance in the change from baseline in  $FEV_1$  after the 10 mg dose compare to placebo is unknown. Trough plasma concentrations of cilomilast were proportional to dose at all visits. However, no clear exposure (predose cilomilast plasma concentrations) -response ( $FEV_1$  or PEFr) was observed at 5, 10, or 15 mg for 6 weeks. This statement should be interpreted with caution since a large degree of variability was observed in the plasma concentrations (CV>60%), which may had precluded an existing correlation. A higher incidence of side effects (such as nausea, abdominal pain, diarrhea) was observed with increasing doses of cilomilast (Figure 1). Although plasma concentrations increased proportionally to dose, no clear correlation between trough plasma concentrations of cilomilast and adverse events (AEs) was observed, most likely due to the variability of the data. Patients experiencing gastrointestinal adverse events had trough plasma

concentrations as low as 35 ng/mL and as high as 1583 ng/mL. Cilomilast concentrations have not been reported at the times when the AEs were manifested.



**Figure 1.** Adverse experiences occurring in more than 5% of patients in any treatment group (% of patients). ADE:any adverse side effect; Nau=nausea; RD=respiratory disorder; Dih= diarrhea; AP=abdominal pain; HA=headache; Dyp=dyspnoea.

In a multiple dose study conducted in male volunteers cilomilast did not significantly prolong QT at doses up to 30 mg. No clear relationship between cilomilast plasma concentrations and QTc change from baseline was observed.

### Dissolution

The dissolution method is discriminating and was developed based on earlier recommendations from the FDA. The dissolution test is performed using USP Apparatus 2 (Paddle) operating at 50 rpm. The media is 900 mL of deaerated potassium phosphate buffer, pH 6.0 at 37°C. Sampling times of 5, 10, 15, 30, 45 and 60 minutes were used for this comparative dissolution. The acceptance criterion is  $Q=$  at 30 minutes. The in vitro dissolution characteristics of the clinical batches and to-be-marketed batches meet the acceptance criteria for similarity ( $f_2 > 50$ ). Dissolution profiles from the bio-batches support the dissolution specification of  $Q=$  at 30 minutes.