

2. NONCLINICAL FINDINGS

- There were no signals in nonclinical studies to indicate that cilomilast would be associated with the convulsions, the severity of gastrointestinal effects, arrhythmias and drug interactions seen with currently available non-selective phosphodiesterase inhibitors.
- When pharmacologically predictable adverse effects were evaluated in animals, cilomilast was associated with a lower magnitude of effect than the first generation PDE4 inhibitor, rolipram.
- In toxicity studies in laboratory animals, gastrointestinal, cardiovascular, testicular, and neuroendocrine effects were observed. However, following thorough evaluation in the clinical development program there is no evidence to indicate that cilomilast is associated with toxicity at 15mg BID in humans.

Cilomilast has undergone an extensive nonclinical evaluation in multiple animal species including non-human primates. This has included primary pharmacology (see Section 1.2.1, safety pharmacology, absorption, distribution, metabolism and excretion studies, acute, repeat dose, reproductive and genetic toxicity studies, carcinogenicity studies, and special studies to investigate the vascular toxicity observed in rodents and the mammary lesions observed in mice in the carcinogenicity study.

In nonclinical studies to investigate secondary pharmacological actions, cilomilast showed no proconvulsant activity and did not markedly effect gastrointestinal function. Consistent with the pharmacological action of cilomilast and experience with nonselective PDE inhibitors and first generation PDE4 inhibitors, cilomilast demonstrated emetic and generalized psychotropic activity, and increased gastric acid secretion, but was markedly less potent than rolipram in inducing these effects. Signs indicative of mild behavioral depression were also evident at high doses in mice and rats. However, no clinically relevant central nervous system effects have been observed to date during Phase III clinical studies indicating that psychotropic activity and central nervous system depression are unlikely to occur in humans. No toxicologically important effects on cardiovascular function were observed in rats or monkeys and extensive clinical cardiovascular monitoring including frequent ECGs and holters performed during Phase III clinical trials has revealed no clinically relevant adverse cardiovascular effects to date (see Section 6.5.5). Finally, in vivo and in vitro results obtained in studies designed to determine the induction or inhibition of cytochrome P450 enzymes indicate that cilomilast is unlikely to have pharmacokinetic interaction potential with co-administered drugs.

In toxicity studies in laboratory animals, gastrointestinal, cardiovascular, testicular, and neuroendocrine effects were observed and were further evaluated in the nonclinical and/or clinical development programs. These are summarized below:

Gastrointestinal Effects: Emesis was observed in non-rodent species. Gastric erosion and squamous cell hyperplasia of the non-glandular stomach were evident in rodents indicating that cilomilast may have gastric irritant potential. However, the absence of

gastric lesions in monkeys at doses of 10mg/kg TID for 14 days or 10mg/kg/day for up to 1 year suggest that this finding is unlikely to be of clinical relevance. There was no evidence of any other pathological lesions in the rat gastrointestinal tract.

Cardiovascular Effects: Medial necrosis in small arteries of the stomach and thymus was observed in mice after repeated dosing at ≥ 200 mg/kg/day. In rats, repeated oral administration of cilomilast ≥ 40 mg/kg/day cilomilast for 10 days or 1 month was associated with medial necrosis of splanchnic arteries. The arterial medial necrosis was not associated with evidence of pathology in any organ system, including the gastrointestinal system. Arterial medial necrosis was not observed in rats following a 1 month drug-free recovery period indicating that this lesion may be reversible. No arterial toxicity was observed in rats given 20mg/kg/day for up to 6 months.

It is likely that arterial medial necrosis is a consequence of vasodilation and resulting hemodynamic changes since medial necrosis of rat splanchnic arteries has been observed with a number of vasodilating drugs [Kerns, 1989; Johansson, 1981; Collins, 1988; Westwood, 1990; Sandusky, 1987; Sandusky, 1989; Larson, 1996; Joseph, 1996; Joseph, 1997]. In addition, cilomilast caused vasorelaxation of rat mesenteric arterial rings in vitro at concentrations comparable to those seen at vasotoxic doses in vivo. In contrast, in the rabbit and monkey, species in which no effect on vascular toxicity were seen, little or no vasorelaxation was observed even at concentrations that were substantially greater than those achieved systemically.

Although the relevance of this finding to humans is unclear, the risk to humans is considered to be low based on the following:

- (1) Vascular lesions were not observed in monkeys given cilomilast for up to 1 year, or in rabbits after 1 month at estimated systemic exposures to unbound drug based on area under the curve (AUC) 7- and 66-fold greater, respectively, than that in humans following a clinical dose of 15mg twice daily.
- (2) At the no-effect dose in the rat (20mg/kg/day), estimated systemic exposure to unbound drug based on AUC was 7-fold that in humans following the proposed clinical dose and in the mouse was greater still.
- (3) Therapeutic index in rats and mice, based on the dose that inhibits tumor necrosis factor and the dose which induces vascular toxicity, is large (75 and 26, respectively), and considerably larger than the therapeutic index of 6 for theophylline in rats.
- (4) Non-selective PDE inhibitors, such as caffeine and theophylline, more selective type 4 (PDE4) inhibitors, such as rolipram and denbufylline, and dopaminergic agonists, such as dopamine and fenoldopam, all induce similar lesions within the rat splanchnic vascular bed, but are without associated safety issues in humans.

Focal myocardial necrosis was observed in a number of rats given very high, lethal doses (≥ 80 mg/kg/day) in the 10 day and 1 month toxicity studies. No such changes were evident in rats given 40mg/kg/day for 1 month, despite the mortality seen at this dose. Furthermore, myocardial necrosis was not evident in the 6 month rat study at the highest dose tested (20mg/kg/day). In this study, 20mg/kg/day resulted in systemic exposures of unbound drug approximately 9 times that achieved in humans. Cardiac lesions were not

observed in mice, rabbits or monkeys in studies of up to 3 months, 1 month and 1 year duration, respectively, despite much higher systemic exposures being achieved. Furthermore, only minor, transient effects on blood pressure and heart rate were evident in rats or monkeys continuously monitored through 24 hours after receiving a single oral dose of 20 or 80mg/kg and 1 or 10mg/kg, respectively. It was therefore considered likely that the cardiac changes observed in rats given 80mg/kg/day were agonal events secondary to multiple organ failure rather than the results of cardiotoxicity and were considered unlikely to be of clinical significance. To confirm this, extensive clinical cardiovascular monitoring including frequent ECGs and holters was performed during Phase III clinical trials and has revealed no clinically relevant adverse cardiovascular effects to date (see Section 6.5.5).

Testicular Effects: In the rat 1 month repeat dose and fertility studies, testicular degeneration was observed in 2/9 and 2/24 males at ≥ 40 mg/kg/day cilomilast. In a 1 month oral reproductive toxicity study in male rabbits, testicular findings were seen in 4/7, 4/6, 2/6 and 4/7 rabbits in the control, 3, 30 and 60mg/kg/day groups, respectively. In rabbits, the testicular findings were compatible in character with recognized spontaneous background findings in this breed [Morton, 1986]. Although in two out of 4 rabbits at 60mg/kg/day the lesion was more severe suggesting the possibility of an effect of treatment. In rats, the most likely explanation for the testicular degeneration is that it is a consequence of drug-induced hemodynamic alterations as it is associated with edema/arterial toxicity of the epididymides, accompanied by evidence of arterial damage in other organs, and has been observed in rats with other drugs at doses that cause arterial toxicity, including denbufylline and theophylline [Friedman, 1979].

Measurement of sperm motility in the rat fertility or rabbit reproductive studies showed no evidence of epididymal effects, and systemic exposure (AUC) to unbound drug at the no-effect dose for testicular degeneration (30mg/kg/day) was more than 13-fold greater in male rats and 18-fold greater in male rabbits than that observed in humans following the proposed clinical dose of 15mg twice daily. No testicular effects were evident in monkeys at doses of 10mg/kg TID for 14 days or 10mg/kg/day for up to 1 year, which resulted in estimated systemic exposures (AUC) to unbound drug 7 and 27 times greater, respectively, than that in humans. Furthermore, the results from a human semen assessment study indicate that effects similar to those in rats and rabbits are unlikely to occur in humans (see Section 3.7.3).

Neuroendocrine Effects: In a 2-year carcinogenicity study in mice, a weak tumorigenic effect was observed in the mammary glands of female mice at 100mg/kg/day associated with microscopic changes consistent with hyperprolactinemia. These observations together with the negative genotoxicity results suggest a non-genotoxic mechanism of tumor induction. Studies in mice showed no change in prolactin levels, but evidence of persistent diestrus was observed. The mammary gland lesions were therefore considered likely to be related to cilomilast-induced pseudopregnancy. No such findings were observed in rats and since there is no human analogy of pseudopregnancy, these tumors are considered of unlikely clinical relevance. Furthermore, there were no effects on prolactin levels in humans (see Section 3.7.4). Systemic exposure (AUC) to unbound drug at the no effect dose for the findings in mice (30mg/kg/day) was 18 times greater than that achieved in humans following administration of 15mg BID. Systemic exposure

(AUC) to unbound drug at the highest dose in the rat carcinogenicity study (20mg/kg/day) was 9 times greater than that achieved in humans following administration of 15mg BID.

Bilateral adrenocortical hypertrophy was observed in rats given cilomilast (≥ 5 mg/kg/day) for 1 month. This finding is a well recognized response of the rat to PDE4 inhibitors which has been clearly linked to stimulation of adrenal corticotropin hormone (ACTH) release in response to increased cyclic AMP concentration in the hypothalamus and anterior pituitary gland [Kumari, 1997]. Monitoring of plasma cortisol and ACTH concentrations during clinical studies following administration of cilomilast 15mg twice daily provided no evidence to suggest that cilomilast stimulates the hypothalamo-pituitary-adrenal axis in humans (see Section 3.7.4).

In conclusion, with the exception of emesis, the weight of evidence suggests that the effects described above are not of clinical relevance and there is no evidence from clinical experience to date to indicate that oral administration of cilomilast at 15mg BID induces these effects in humans.