Mechanism of Action

Glucokinase (GK; hexokinase 4) activator

Overview

AZD1656 is a potent, selective (>100-fold versus hexokinase 1 and 2 and a pharmacology screening panel) activator of human and rat glucokinase in vitro; EC<sub>50</sub> = 0.057 and 0.072 μM, respectively, for the recombinant enzymes, which translates into cellular systems (EC<sub>50</sub> = 1.39 and 0.47 μM in human and rat hepatocytes, respectively). AZD1656 reduces plasma glucose levels in a dose-dependent fashion, with a rapid onset of action, in normo-glycaemic insulin resistant rats and diabetic mice, when dosed acutely and when dosed once daily for up to 28 days.

Safety/Tolerability

AZD1656 has been studied in single doses of up to 180 mg and multiple doses to 150 mg BID for 8 days in healthy volunteers as well as alone and in combination with other blood glucose control agents in diabetic patients at 200 mg daily for up to 6 months’ duration. In both healthy volunteers and diabetic patients, no significant clinical effects other than glucose lowering were noted.

Preclinical studies of up to 12 months’ duration have been performed. These revealed a potent glucose-lowering effect, and thereby, the results of chronic toxicology studies in healthy animals were confounded by severe hypoglycaemia at higher doses and sequelae such as Wallerian-type nerve degeneration and skeletal muscle fibre degeneration. Additional changes, also considered secondary to hypoglycaemia, were seen in the liver (loss of hepatocellular glycogen).

Additional Information

In a Phase 2 study in Japanese type 2 diabetic subjects, AZD1656, given BID at high (40–200 mg/day), medium (20–140 mg/day), and low (10–80 mg/day) doses over a 4-month period, has been found to lower HbA1c and fasting plasma blood (FPG) glucose levels with a 50-mg dose producing compound levels of ~2 × EC<sub>50</sub> in plasma. However, this effect was transient, trending towards pre-dose levels between weeks 8 and 16, and there was no statistically significant change in either HbA1c or FPG from baseline at 4 months.

Suitable for and Exclusions

Preclinical reprotoxicology data are available and have not identified any specific risks. Women of child-bearing potential using highly effective contraception can be included.

Proposed indications should be evaluated against the risk of hypoglycaemia in non-diabetic subjects.

Clinical Trials


Additional Characteristics: CNS Penetration

AZD1656 has low CNS penetration and thus is probably not suitable for a CNS indication. With evidence of effect tolerance, may be best suited to acute (< 1 week) applications.

Publications