4-[5-(3-CHLORO-PHENOXY)-OXAZOLO[5,4-D]PYRIMIDIN-2-YL]-2,6-DIMETHYL-PHENOXY}-ACETIC ACID FOR USE IN THE PREVENTION OR TREATMENT OF ACUTE KIDNEY INJURY

The present invention relates to {4-[5-(3-chloro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethyl-phenoxy}-acetic acid or a pharmaceutically acceptable salt thereof for use in the prevention or treatment of acute kidney injury (AKI), and a pharmaceutical composition thereof. The compound 4-[5-(3-chloro-phenoxy)-oxazolo[5,4-d]pyrimidin-2-yl]-2,6-dimethyl-phenoxy}-acetic acid or a pharmaceutically acceptable salt thereof and a preparative method thereof are described in the patent application WO2011/086079. This compound has affinity for $S1P_1$/EDG1 receptors.

Acute kidney injury (AKI), formerly known as “acute renal failure” is a frequent and potentially severe disorder that occurs in a variety of settings with clinical manifestations ranging from transient elevation in serum creatinine (SCr) to anuric definitive renal failure. AKI has been traditionally described as an abrupt (within 48 hours) decrease in kidney function as measured by increases in serum creatinine. The recent KDIGO (Kidney Disease Improving Global Outcomes) guidelines established consensus around the diagnostic criteria based on laboratory and clinical values listed below (Working group of ERBP (European Renal Best Practice), 2012, NDT 27: 4263-4272). AKI is defined and staged as any of the following:

- Increase in SCr by ≥0.3 mg/dL (≥26.5 µmol/L) within 48 hours; or
- Increase in SCr to ≥1.5 times baseline, which is known or presumed to have occurred within the prior 7 days; or
- Urine volume < 0.5 mL/kg/h for 6 hours.

AKI occurs in approximately 7% of all hospitalized patients (Nash et al., 2002, Am J Kidney Dis 39: 930-936) and up to 36-67% of critically ill patients, depending on the definition used. Severe AKI occurs in 4-25% of all Intensive Care Unit (ICU) admissions and about 5% of ICU patients with AKI require renal replacement therapy (Hoste et al. 2006, Crit Care 10: R73, Mehta et al., 2004, Kidney Int 66: 1613-1621; Uchino et al., 2005, Jama 294: 813-818; Uchino et al., 2006, Crit Care Med 34: 1913-1917; Ostermann et al., 2007, Crit Care Med 35: 1837-1843). The most common causes of AKI are sepsis, major surgery, hypovolemia and medications. Risk factors for development of AKI include old age (>75 yrs), chronic kidney disease (CKD, eGFR (estimated Glomerular Filtration Rate) < 60 mL/min/1.73m²), atherosclerotic peripheral vascular disease, cardiac failure, liver disease, diabetes mellitus and nephrotoxic medications.

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