interactions between ambrisentan and cyclosporine A and tacrolimus as a further basis for the role of ambrisentan in preventing calcineurin-inhibitor nephrotoxicity.

In a further article by Zhang et al (in European review for medical & pharmacological science, 2014, 18, pp. 2575-2583) results obtained with the co-administration of tacrolimus and ambrisentan in rats show that ambrisentan can counter the renal toxicity of tacrolimus, at least partially. The dose of ambrisentan used in this study was 0.5 mg/kg/day, which is allometrically equivalent to 35 mg per day in humans.

SUMMARY

In one aspect, the present invention refers to the use of ambrisentan in the manufacture of a medicament for treating Hepatorenal Syndrome, wherein the medicament is to be administered to a treated subject such that the plasma levels of ambrisentan are maintained below about 100 ng/ml.

In another aspect, the present invention refers to the use of ambrisentan in the manufacture of a medicament for treating Refractory Ascites, wherein the medicament is to be administered to a treated subject such that the plasma levels of ambrisentan are maintained below about 100 ng/ml.

In yet another aspect, the present invention refers to the use of ambrisentan in the manufacture of a medicament for treating Dilutional Hyponatremia, wherein the medicament is to be administered to a treated subject such that the plasma levels of ambrisentan are maintained below about 100 ng/ml.

In yet another aspect, the present invention refers to the use of ambrisentan in the manufacture of a medicament for treating Cardiorenal Syndrome, wherein the medicament is to be administered to a treated subject such that the plasma levels of ambrisentan are maintained below about 100 ng/ml.

The inventors have found that certain types of acute renal failure can be prevented and treated by administering selective ETR-A antagonists in amounts that block the endothelin

receptor subtype A (ETR-A) and its activity in the kidney while not significantly blocking the endothelin receptor subtype B (ETR-B) in the kidney.

The inventors have further found that selective ETR-A antagonists interact with and antagonize the ETR-B when administered at doses approved for the treatment of other conditions such as pulmonary arterial hypertension. In this regard, several ETR antagonists are approved for oral administration to treat pulmonary arterial hypertension, such as ambrisentan and other compounds discussed below. Some of these, including ambrisentan, are considered selective ETR-A antagonists. However, their systemic administration in approved dosage forms, notwithstanding their selectivity for ETR-A, results in plasma levels that are substantially too high to be purely ETR-A selective and therefore ineffective in preventing and treating acute renal failure associated with renal vasoconstriction.

In particular, the formulations and methods of the present disclosure are intended to treat, or prevent conditions leading to acute renal failure due to vasoconstriction including Hepatorenal Disorders such as Hepatorenal Syndrome, Refractory Ascites and Dilutional Hyponatremia; treat or prevent complications from renal transplantation such as Delayed Graft Function and Calcineurin-Inhibitor Nephrotoxicity; treat or prevent complications of radiological

CLAIMS

1. Use of ambrisentan in the manufacture of a medicament for treating Hepatorenal Syndrome, wherein the medicament is to be administered to a treated subject such that the plasma levels of ambrisentan are maintained below about 100 ng/ml.

2. Use of ambrisentan in the manufacture of a medicament for treating Refractory Ascites, wherein the medicament is to be administered to a treated subject such that the plasma levels of ambrisentan are maintained below about 100 ng/ml.

3. Use of ambrisentan in the manufacture of a medicament for treating Dilutional Hyponatremia, wherein the medicament is to be administered to a treated subject such that the plasma levels of ambrisentan are maintained below about 100 ng/ml.

4. Use of ambrisentan in the manufacture of a medicament for treating Cardiorenal Syndrome, wherein the medicament is to be administered to a treated subject such that the plasma levels of ambrisentan are maintained below about 100 ng/ml.