| Pfizer | PF-03882845 – Mineralocorticoid Receptor Antagonist |
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| **Mechanism of Action** | Mineralocorticoid Receptor Antagonist<br>IUPHAR link for target: http://iuphar-db.org/DATABASE/ObjectDisplayForward?objectId=626<br>NCBI Gene data: http://www.ncbi.nlm.nih.gov/gene/4306<br>Previously in development for the treatment of diabetic nephropathy — terminated development for this indication for strategic reasons |
| **Overview** | PF-03882845 is a highly potent ($IC_{50}$ = 6.3-13.4 nM, 10% fetal bovine serum & $IC_{50}$ = 0.504–1.11 nM, absence of serum) selective orally bioavailable mineralocorticoid receptor antagonist. It is a non-steroidal pyrazoline, unlike steroidal compounds eplerenone and spironolactone. It does not significantly activate or inhibit human androgen receptor, estrogen receptor alpha, and glucocorticoid receptor. PF-03882845 has been shown to modestly inhibit the progesterone receptor (PR) yielding a 45-fold selectivity over PR in a cell-based functional assay. |
| **Safety/Tolerability** | In studies conducted in healthy subjects, oral doses of PF-03882845 as high as 215 mg as a single dose and repeated once-daily doses up to 110 mg for a duration of up to 12 days have been found to be safe and well tolerated. In addition, a dose of 5 mg once-daily for 14 days has been administered to 5 subjects with type 2 diabetes, macroalbuminuria and moderate renal function impairment and found to be safe and well tolerated. Based on the known attributes of the pharmacology and the observed clinical experience, the identified and potential risks with PF03882845 are summarized below.<br><br>Identified Risks (not dose-limiting effects)<br>• Gastrointestinal events (diarrhea, constipation, flatulence, abdominal discomfort)<br>• Testicular pain/discomfort in males<br>• Elevation in serum aldosterone and plasma renin activity<br><br>Potential Risks<br>• Hyperkalemia (≥6.0 mEq/L)<br>• Sex hormone–related adverse events (gynecomastia in males, vaginal hemorrhage in females)<br>• Hemoconcentration<br>• Decrease in blood pressure<br>• Signs and symptoms related to decrease in blood pressure such as dizziness, [pre-]syncope, orthostatic hypotension, hypotension |
| **Additional Information** | PF-03882845 was previously in development for the treatment of diabetic nephropathy — development for this indication was terminated for strategic reasons. An alternative indication of hypertension also was not pursued for strategic reasons.<br>Non-clinical toxicology studies have been conducted in rats and dogs for up to 3 months, supporting clinical studies up to 12 weeks in humans. |
| **Suitable for and Exclusions** | PF-03882845 is not suitable for pregnant women, subjects at risk for hyperkalemia, and patients already on angiotensin converting enzyme (ACE) and angiotensin receptor blocker (ARB) inhibitors or potassium-sparing diuretics.<br>Excluded Indications: Diabetic nephropathy and hypertension |
| **Clinical Trials** | http://www.clinicaltrials.gov/ct2/results?term=PF-03882845&Search=Search |
| **Additional Characteristics: CNS Penetrance/Pediatric Diseases** | PF-03882845 is not expected to be brain-penetrant. PF-03882845 is not suitable for evaluation in pediatric studies. |
| **Publications** | http://www.ncbi.nlm.nih.gov/pubmed/?term=PF-03882845 |