Sacubitril/Valsartan (Entresto)

Manufacturer: Novartis, East Hanover, New Jersey
Date of Approval: July 7, 2015

Indication: Sacubitril/valsartan is indicated to reduce the risk of cardiovascular death and hospitalization for heart failure in patients with chronic heart failure (New York Heart Association Class II–IV) and reduced ejection fraction.

Drug Class: This combination product comprises sacubitril, a neprilysin inhibitor, and valsartan, an angiotensin II receptor blocker.

Uniqueness of Drug: Sacubitril inhibits neprilysin (neutral endopeptidase, NEP), an enzyme responsible for the breakdown of natriuretic peptides that can help to counteract many of the physiological and structural changes associated with heart failure. Valsartan blocks the vasoconstrictor and aldosterone-secreting effects of angiotensin II.

Warnings and Precautions:

Fetal toxicity. Sacubitril/valsartan can cause fetal harm when administered to a pregnant woman. When pregnancy is detected, consider alternative drug treatments and discontinue this treatment. However, if there is no appropriate alternative to therapy and if the drug is considered lifesaving for the mother, advise a pregnant woman of the potential risk to the fetus.

Angioedema. Sacubitril/valsartan should not be used in patients with a known history of angioedema related to previous therapy with an angiotensin-converting enzyme (ACE) inhibitor or angiotensin receptor blocker (ARB).

Hypotension. Correct volume or salt depletion prior to treatment administration or start at a lower dose. If hypotension occurs, consider dose adjustment of diuretics, concomitant antihypertensive drugs, and treatment of other causes of hypotension (e.g., hypovolemia). If hypotension persists despite such measures, reduce the dosage or temporarily discontinue treatment. Permanent discontinuation of therapy is usually not required.

Impaired renal function. Closely monitor serum creatinine, and down-titrate or interrupt treatment in patients who develop a clinically significant decrease in renal function.

Hyperkalemia. Monitor serum potassium periodically and treat appropriately, especially in patients with risk factors for hyperkalemia such as severe renal impairment, diabetes, hypoadosteronism, or a high-potassium diet. Dosage reduction or interruption may be required.

Dosage and Administration: The recommended starting dose of sacubitril/valsartan is 49/51 mg orally twice daily. The dose should be doubled after two to four weeks to the target maintenance dose of 97/103 mg twice daily, as tolerated by the patient.

Commentary: Heart failure (HF) is a leading cause of death and disability among U.S. adults, affecting approximately 5.1 million people. Food and Drug Administration (FDA) approval of Entresto is a monumental milestone for the treatment of HF because it is the first drug that reduces the strain on the failing heart. The drug was given a fast-track designation and approved through the FDA’s priority review program several weeks ahead of the anticipated action date.

Sources: www.fda.gov, www.novartis.com, Entresto prescribing information

Brexipiprazole (Rexulti)

Manufacturer: Otsuka Pharmaceutical Company Ltd., Tokyo, Japan
Date of Approval: July 10, 2015

Indications: Brexipiprazole is indicated for:

- Adjunctive treatment of major depressive disorder (MDD)
- Treatment of schizophrenia

Drug Class: Brexipiprazole is a second-generation antipsychotic.

Uniqueness of Drug: The drug’s mechanism of action in the treatment of MDD or schizophrenia is unknown. However, the efficacy of brexipiprazole may be mediated through a combination of partial agonist activity at serotonin 5HT1A and dopamine D2 receptors, and antagonist activity at serotonin 5HT2A receptors.

Warnings and Precautions:

Increased mortality in elderly patients with dementia-related psychosis. Elderly patients with dementia-related psychosis treated with antipsychotic drugs are at an increased risk of death. Brexipiprazole is not approved for the treatment of patients with dementia-related psychosis.

Suicidal thoughts and behaviors in children, adolescents, and young adults. Monitor all treated patients for clinical worsening and emergence of suicidal thoughts and behaviors, especially during the initial few months of drug therapy and at times of dosage changes. Counsel family members or caregivers of patients to monitor for changes in behavior and to alert the health care provider. Consider changing the therapeutic regimen, including possibly discontinuing treatment, in patients whose depression is persistently worse or who are experiencing emergent suicidal thoughts or behaviors.

Cerebrovascular adverse reactions, including stroke, in elderly patients with dementia-related psychosis. Brexipiprazole is not approved for the treatment of patients with dementia-related psychosis.

Neuroleptic malignant syndrome (NMS). If a patient requires antipsychotic drug treatment after recovery from NMS, the potential reintroduction of drug therapy should be considered carefully. The patient should be monitored closely, since recurrences of NMS have been reported.

Tardive dyskinesia. If signs and symptoms of tardive dyskinesia appear in a patient, drug discontinuation should be considered.

Metabolic changes. Second-generation antipsychotic drugs have been associated with metabolic changes that include hyperglycemia/diabetes mellitus, dyslipidemia, and weight gain.

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**Massachusetts Lumacaftor/Ivacaftor (Orkambi)**

**Indication:** Lumacaftor/ivacaftor is indicated for the treatment of cystic fibrosis (CF) in patients 12 years of age and older who are homozygous for the F508del mutation in the CFTR gene.

**Drug Class:** Orkambi is a combination of lumacaftor and ivacaftor, a CFTR potentiator.

**Uniqueness of Drug:** Lumacaftor improves the conformational stability of F508del-CFTR, resulting in increased processing and trafficking of mature protein to the cell surface. Ivacaftor facilitates increased chloride transport by potentiating the channel-open probability (or gating) of the CFTR protein at the cell surface.

**Warning and Precautions:**

**Use in patients with advanced liver disease.** Use with caution in patients with advanced liver disease and only if the benefits are expected to outweigh the risks. If the drug is used in these patients, they should be closely monitored after the initiation of treatment and the dose should be reduced.

**Liver-related events.** It is recommended that alanine aminotransferase (ALT), aspartate aminotransferase (AST), and bilirubin be assessed prior to initiation, every three months during the first year of treatment, and annually thereafter. For patients with a history of ALT, AST, or bilirubin elevations, more frequent monitoring should be considered. Patients who develop increased ALT, AST, or bilirubin should be closely monitored until the abnormalities resolve.

**Respiratory events.** Additional monitoring of patients with percent predicted forced expiratory volume in one second (ppFEV1) of less than 40 is recommended during initiation of therapy.

**Drug interactions.** Lumacaftor is a strong inducer of CYP3A. Administration may decrease systemic exposure of medicinal products that are substrates of CYP3A and in turn decrease their therapeutic effect. Coadministration with sensitive CYP3A substrates or CYP3A substrates with a narrow therapeutic index is not recommended.

**Cataracts.** Baseline and follow-up ophthalmological examinations are recommended in pediatric patients initiating treatment.

**Dosage and Administration:** Adults and pediatric patients 12 years of age and older should take two tablets (each containing lumacaftor 200 mg/ivacaftor 125 mg) orally every 12 hours.

**Commentary:** Cystic fibrosis is a genetic disorder resulting in thick mucus buildup in various parts of the body that leads to life-threatening complications. Orkambi received breakthrough and orphan drug designations and was approved through the priority review program.

**Sources:** www.fda.gov and Orkambi prescribing information