Entresto® (sacubitril/valsartan) – New indication

- On October 2, 2019, Novartis announced the FDA approval of Entresto (sacubitril/valsartan), for the treatment of symptomatic heart failure (HF) with systemic left ventricular systolic dysfunction in pediatric patients aged one year and older. Entresto reduces N-terminal pro-B-type natriuretic peptide (NT-proBNP) and is expected to improve cardiovascular (CV) outcomes.

- Entresto is also approved to reduce the risk of CV death and hospitalization for HF in adult patients with chronic HF (NYHA Class II-IV) and reduced ejection fraction.

- HF is a chronic and progressive condition where the heart cannot pump enough blood to support the body's need for blood and oxygen. Children diagnosed with systolic HF face a poor prognosis. It has been estimated that half require a heart transplant before the age of five, and almost one-third die or require a transplant within one year.

- The approval of the new indication for Entresto was based on the PANORAMA-HF study enrolling 110 pediatric patients 1 to <18 years old with HF (NYHA/Ross Class II-IV) due to systemic left ventricular systolic dysfunction (LVEF ≤ 40%). Patients received Entresto or enalapril. The endpoint was the between-group difference in the change in plasma NT-proBNP from baseline to 12 weeks.

    - The reduction from baseline in NT-proBNP was 44% and 33% in the Entresto and enalapril groups, respectively.
    - While the between-group difference was not statistically significant, the reductions for Entresto and enalapril were similar to or larger than what was seen in adults.
    - Because Entresto improved outcomes and reduced NT-proBNP in adults in the PARADIGM-HF study, the effect on NT-proBNP was considered a reasonable basis to infer improved CV outcomes in pediatric patients.

- Entresto carries a boxed warning for fetal toxicity.

- The recommended dose of Entresto for pediatric patients aged one year and older is based on body weight and given orally twice daily. Adjust pediatric patient doses every 2 weeks, as tolerated by the patient as follows:

	Titration Step Dose (twice daily)		
	Starting	Second	Final
Pediatric patients less than 40 kg[†]	1.6 mg/kg	2.3 mg/kg	3.1 mg/kg
Pediatric patients at least 40 kg, less than 50 kg	24/26 mg	49/51 mg	72/78 mg[‡]
Pediatric patients at least 50 kg	49/51 mg	72/78 mg[‡]	97/103 mg

[†] Use of the oral suspension recommended in these patients. Recommended mg/kg doses are of the combined amount of both sacubitril and valsartan.
[‡] Doses of 72/78 mg can be achieved using three 24/26 mg tablets.

- Consult the Entresto drug label for adult dosing recommendations and for instructions on compounding the oral suspension using the 49/51 mg tablets.