## Lutathera® (lutetium Lu 177 dotatate) – New orphan drug approval

- On January 26, 2018, the FDA announced the approval of Advanced Accelerator Applications' Lutathera (lutetium Lu 177 dotatate), for the treatment of somatostatin receptor-positive gastroenteropancreatic neuroendocrine tumors (GEP-NETs), including foregut, midgut and hindgut neuroendocrine tumors in adults.

- NETs are rare tumors originating in the neuroendocrine cells of numerous organs, including the gastrointestinal tract, pancreas and lung.

    — Some patients develop symptoms arising from the excessive production of hormones by NET cells, while others remain clinically silent for years.
    — Patients with well- and moderately-differentiated tumors and distant metastases have a 5-year survival probability of 35%.
    — Approximately 1 out of 27,000 people are diagnosed with GEP-NETs per year.

- Lutathera is the first available peptide receptor radionuclide therapy, a form of targeted treatment comprising a targeting molecule that carries a radioactive component. The targeting molecule binds to a specific receptor on tumor cells, and is then internalized into the target cells, where the radioactive component destroys the tumor cells from within.

- The efficacy of Lutathera was demonstrated in an open-label, active-controlled study of 229 patients with inoperable midgut NETs called NETTER-1. Patients were randomized to Lutathera plus best standard of care (Sandostatin® LAR Depot [octreotide] 30 mg after each Lutathera dose and every four weeks after completion of Lutathera treatment) or 60 mg of octreotide LAR every four weeks alone. The major efficacy outcome was progression free survival (PFS).

    — Median PFS was not reached in the Lutathera arm vs. 8.5 months for the 60 mg octreotide LAR arm (HR = 0.21 [95% CI: 0.13, 0.32]; $p < 0.0001$).
    — Moreover, in a second study involving 1,214 patients, complete or partial tumor shrinkage was reported in 16% of a subset of 360 patients with GEP-NETs. Of the responders, the median duration of response was 35 months (95% CI: 17, 38). Less than 1% of patients were complete responders.

- Warnings and precautions of Lutathera include risk from radiation exposure, myelosuppression, secondary myelodysplastic syndrome and leukemia, renal toxicity, hepatotoxicity, neuroendocrine hormonal crisis, embryo-fetal toxicity, and risk of infertility.

- The most common grade 3 – 4 adverse reactions (≥ 4% with a higher incidence in the Lutathera arm) with Lutathera use were lymphopenia, increased gamma-glutamyl transferase, vomiting, nausea, increased aspartate transaminase, increased alanine transaminase, hyperglycemia and hypokalemia.

- The recommended dosage of Lutathera is 7.4 GBq (200 mCi) given intravenously every 8 weeks for a total of 4 doses.

    — Lutathera should be used by or under the control of physicians who are qualified by specific training and experience in the safe use and handling of radiopharmaceuticals, and whose experience and training have been approved by the appropriate governmental agency authorized to license the use of radiopharmaceuticals.

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  - Lutathera should be handled with appropriate safety measures to minimize radiation exposure. Waterproof gloves and effective radiation shielding should be used when handling Lutathera.
  - Consult Lutathera's drug label for additional information, including recommendations for pre- and concomitant medications.

- Advanced Accelerator Applications' launch plans for Lutathera are pending. Lutathera will be available as a 370 MBq/mL (10 mCi/mL) injection in a single-dose vial.