Jynarque™ (tolvaptan) – New orphan drug approval

- On April 24, 2018, Otsuka announced the FDA approval of Jynarque (tolvaptan), to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

- ADPKD is a progressively debilitating and often painful genetic disorder in which fluid-filled cysts develop in the kidneys over time. These cysts enlarge the kidneys and impair their ability to function normally, leading to kidney failure in most patients. ADPKD is diagnosed in approximately 140,000 people in the U.S.

- Jynarque is a selective vasopressin V_2-receptor antagonist that is the first treatment approved to slow kidney function decline in patients at risk of ADPKD.

- Tolvaptan is also available as Samsca® tablets, for the treatment of clinically significant hypervolemic and euvolemic hyponatremia, including patients with heart failure and syndrome of inappropriate antidiuretic hormone.

- The efficacy of Jynarque was demonstrated in two studies: TEMPO 3:4 and REPRISE. TEMPO 3:4 enrolled 1,445 adults with earlier stages of disease for three years. The primary endpoint was the annual rate of change of total kidney volume (TKV). REPRISE enrolled 1,519 patients with later stages of the disease for one year. The primary endpoint was the treatment difference in the change of estimated glomerular filtration rate (eGFR) from pre-treatment baseline to post-treatment follow-up.

    — Over a 3-year period, the increase in TKV in the tolvaptan group was 2.8% per year (95% CI: 2.5 to 3.1), vs. 5.5% per year in the placebo group (95% CI: 5.1 to 6.0; $p < 0.001$).
    — In REPRISE, the change of eGFR from pretreatment baseline to post-treatment follow-up was −2.34 mL/min/1.73 m^2/year with tolvaptan vs. −3.61 mL/min/1.73 m^2/year with placebo. Tolvaptan resulted in a slower decline vs. placebo in eGFR at 1 year (difference: 1.27 mL/min/1.73 m^2/year; $p < 0.001$).

- Jynarque carries a boxed warning for risk of serious liver injury.

- Jynarque is contraindicated in patients with a history of signs or symptoms of significant liver impairment or injury that does not include uncomplicated polycystic liver disease; concomitant use of strong CYP 3A inhibitors; uncorrected abnormal blood sodium concentrations; unable to sense or respond to thirst; hypovolemia; hypersensitivity to tolvaptan or any of its components; uncorrected urinary outflow obstruction; and anuria.

- Warnings and precautions of Jynarque include Jynarque REMS program, hypernatremia, dehydration, and hypovolemia.

- The most common adverse reactions (> 10% and at least twice that of placebo) with Jynarque use were thirst, polyuria, nocturia, pollakiuria and polydipsia.

- The initial recommended dosage of Jynarque is 60 mg orally per day as 45 mg taken on waking and 15 mg taken 8 hours later. Titrate to 60 mg plus 30 mg then to 90 mg plus 30 mg per day if tolerated with at least weekly intervals between titrations.

    — Patients should be encouraged to drink enough water to avoid thirst or dehydration.

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- Jynarque will be sold in a 28-day treatment pack at a wholesale acquisition cost of $13,041.10. Jynarque will be available through a restricted distribution program.

- Otsuka's plans for launching Jynarque are pending. Jynarque will be available as 15 mg, 30 mg, 45 mg, 60 mg and 90 mg tablets.