CLINICAL UPDATE

Brand Name	Jynarque®
Generic Name	Tolvaptan
Drug Manufacturer	Otsuka Pharmaceutical Company, Ltd.

Clinical Update

TYPE OF CLINICAL UPDATE

Clinical Update - New strength

FDA APPROVAL DATE

N/A

LAUNCH DATE

FDB Date Added – 10/15/2020

REVIEW DESIGNATION

N/A

TYPE OF REVIEW

Standard

DISPENSING RESTRICTIONS

NA

Overview

INDICATION(S) FOR USE

Jynarque® is a selective vasopressin V2-receptor antagonist indicated to slow kidney function decline in adults at risk of rapidly progressing autosomal dominant polycystic kidney disease (ADPKD).

MECHANISMS OF ACTION

Tolvaptan is a selective vasopressin V2-receptor antagonist with an affinity for the V2-receptor that is 1.8 times that of native arginine vasopressin (AVP).

DOSAGE FORM(S) AND STRENGTH(S)

Tablets: 15 mg, 30 mg, 45 mg, 60 mg, and 90 mg

CLINICAL UPDATE

DOSE & ADMINISTRATION

Initial Dosage		Titration Step		Target Dosage	
1st Dose	45 mg	1st Dose	60 mg	1st Dose	90 mg
2nd Dose (8 hours later)	15 mg	2nd Dose (8 hours later)	30 mg	2nd Dose (8 hours later)	30 mg
Total Daily Dose	60 mg	**Total Daily Dose**	90 mg	**Total Daily Dose**	120 mg

EFFICACY

Since clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice. Jynarque® has been studied in over 3,000 patients with ADPKD. Long-term, placebo-controlled safety information of Jynarque® in ADPKD is principally derived from two trials where 1,413 subjects received tolvaptan and 1,098 received placebo for at least 12 months across both studies.

TEMPO 3:4 -NCT00428948: A Phase 3, Double-Blind, Placebo-Controlled, Randomized Trial in Early, Rapidly-Progressing ADPKD

The TEMPO 3:4 trial employed a two-arm, 2:1 randomization to tolvaptan or placebo, titrated to a maximally-tolerated total daily dose of 60 to 120 mg. A total of 961 subjects with rapidly progressing ADPKD were randomized to Jynarque®. Of these, 742 (77%) subjects who were treated with Jynarque® remained on treatment for at least 3 years. The average daily dose in these subjects was 96 mg daily. Adverse events that led to discontinuation were reported for 15.4% (148/961) of subjects in the Jynarque® group and 5.0% (24/483) of subjects in the placebo group. Aquaretic effects were the most common reasons for discontinuation of Jynarque®. These included pollakiuria, polyuria, or nocturia in 63 (6.6%) subjects treated with Jynarque® compared to 1 subject (0.2%) treated with placebo.

REPRISE-NCT02160145: A Phase 3, Randomized-Withdrawal, Placebo-Controlled, Double-Blind, Trial in Late Stage 2 to Early Stage 4 ADPKD

The REPRISE trial employed a 5-week single-blind titration and run-in period for Jynarque® prior to the randomized double-blind period. During the Jynarque® titration and run-in period, 126 (8.4%) of the 1,496 subjects discontinued the study, 52 (3.5%) were due to aquaretic effects and 10 (0.7%) were due to liver test findings. Because of this run-in design, the adverse reaction rates observed during the randomized period are not described.

Liver Injury: In the two double-blind, placebo-controlled trials, ALT elevations >3 times ULN were observed at an increased frequency with Jynarque® compared with placebo (4.9% [80/1637] versus 1.1% [13/1,166], respectively) within the first 18 months after initiating treatment and increases usually resolved within 1 to 4 months after discontinuing the drug.