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For Immediate Release

Company name	Otsuka Holdings Co., Ltd.
Representative	Tatsuo Higuchi President and Representative Director, CEO
Code number	4578 First Section , Tokyo Stock Exchange
Inquiries	Yuji Kogure Director, Investors Relations Department

FDA ACCEPTS OTSUKA'S RESUBMISSION TO SUPPORT A REGULATORY REVIEW OF TOLVAPTAN IN THE TREATMENT OF ADPKD

- Tolvaptan has been studied in patients with Autosomal Dominant Polycystic Kidney Disease (ADPKD) in a clinical trial program which included more than 3,165 trial participants exposed to at least one dose of tolvaptan across 18 trials[*1]
- ADPKD is a progressive disease leading to kidney failure, diagnosed in 100,000 to 150,000 people in the U.S.[*2]
- April 2018 is the anticipated completion timing of the FDA's review (based on Prescription Drug User Fee Act [PDUFA] timeline)

Otsuka Pharmaceutical Co., Ltd. (Otsuka) announces that the U.S. Food and Drug Administration (FDA) has accepted Otsuka's resubmission to support a regulatory review of Otsuka's New Drug Application (NDA) for tolvaptan in the treatment of adults with Autosomal Dominant Polycystic Kidney Disease (ADPKD).

Otsuka's resubmission is a response to the Complete Response Letter (CRL) that FDA issued in August 2013. The FDA considers the resubmission to be filed as of October 24, 2017, with a PDUFA action date of April 24, 2018.

The NDA for the proposed indication for tolvaptan in adults with ADPKD is supported by an extensive clinical trial program.

About Tolvaptan

Tolvaptan is a selective vasopressin V_2-receptor antagonist. By selectively blocking vasopressin at the V_2-receptor, tolvaptan has been shown in preclinical trials to decrease cyst-cell proliferation and fluid secretion, ultimately reducing cyst growth.[*3]

In an initial phase 3 trial, tolvaptan demonstrated a reduction in kidney growth and a slower decline in kidney function, measured as the decline in estimated GFR (glomerular filtration rate), compared with placebo in patients with relatively preserved kidney function.[*4] In a subsequent phase 3 trial that included patients at later stages of ADPKD, a slower decline in estimated GFR for patients taking tolvaptan was again observed compared with patients taking placebo.[*5] Through monthly blood monitoring, this subsequent trial confirmed originally observed frequency of liver abnormalities. With early enough detection, confirmation and discontinuation, progression to more serious liver injury was avoided in this trial.

Tolvaptan is approved for the treatment of adult patients with ADPKD in Japan, the EU, Canada, South Korea, Switzerland, Hong Kong and Australia (see local prescribing information for specific indications in each country). No treatment for ADPKD is currently approved for use in the U.S. Tolvaptan is an investigational agent currently under review by the FDA.

Reference

*1 From a November 4, 2017 investor presentation hosted by Otsuka. See slide number four, accessible via the following link: https://www.otsuka.com/en/ir/library/presentation.html

*2 Descriptive epidemiology of ADPKD in the United States: Final study report. National ambulatory medical care survey (NAMCS), Centers for Disease Control National Center for Health Statistics. 2012-2014.

*3 Reif, GA, Yamaguchi, T et al. Tolvaptan inhibits ERK-dependent cell proliferation, Cl – secretion, and in vitro cyst growth of human ADPKD cells stimulated by vasopressin. Am J Physiol Renal Physiol; 2011; 301:F1005-F1013

*4 Torres V, Chapman A et al. Tolvaptan in patients with autosomal dominant polycystic kidney disease. N Engl J Med; 2012; 367:2407-2418.

*5 Torres V, Chapman A et al. Tolvaptan in later-stage autosomal dominant polycystic kidney disease. N Engl J Med; 2017; DOI: 10.1056