26 February 2015
EMA/CHMP/115318/2015
Committee for Medicinal Products for Human Use (CHMP)

Summary of opinion[1] (initial authorisation)

Jinarc

tolvaptan

On 26 February 2015, the Committee for Medicinal Products for Human Use (CHMP) adopted a positive opinion, recommending the granting of a marketing authorisation for the medicinal product Jinarc, 15 mg, 30 mg, 45 mg, 60 mg and 90 mg tablets intended to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease. Jinarc was designated as an orphan medicinal product on 5 August 2013. The applicant for this medicinal product is Otsuka Pharmaceutical Europe Ltd. They may request a re-examination of any CHMP opinion, provided they notify the European Medicines Agency in writing of their intention within 15 days of receipt of the opinion.

The active substance of Jinarc is tolvaptan, a vasopressin antagonist decreasing cyst proliferation in ADPKD by reducing intracellular cAMP levels.

The benefits with Jinarc are its ability to slow the progression of cyst growth and renal insufficiency in adult patients with ADPKD with stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease. In the pivotal trial the rate of total kidney volume (TKV) increase over 3 years could be shown to be significantly less for tolvaptan-treated patients than for subjects receiving placebo: 2.80% per year vs 5.51% per year, respectively (ratio of geometric mean 0.974; 95% CI 0.969 to 0.980; $p < 0.0001$).

Events on worsening of kidney function (25% reduction in reciprocal serum creatinine during treatment) were 61.4% less likely for tolvaptan compared with placebo (hazard ratio, 0.39; 95% CI, 0.26 to 0.57; nominal $p < 0.0001$). Tolvaptan was also associated with a slowing of decline in kidney function by 32% compared with placebo (reciprocal of the serum creatinine level, −2.61 $[mg/mL]^{-1}$ per year vs. −3.81 $[mg/mL]^{-1}$ per year; $p<0.001$) showing relevant effects on renal function decline in secondary endpoints of the pivotal study.

[1] Summaries of positive opinion are published without prejudice to the Commission decision, which will normally be issued 67 days from adoption of the opinion.

30 Churchill Place ● Canary Wharf ● London E14 5EU ● United Kingdom
Telephone +44 (0)20 3660 6000 **Facsimile** +44 (0)20 3660 5555
Send a question via our website www.ema.europa.eu/contact

The most common side effects are deriving from its aquaretic effects. These included thirst, polyuria, nocturia, and pollakiuria occurring in approximately 55%, 38%, 29% and 23% of patients, respectively. Furthermore, tolvaptan has been associated with idiosyncratic elevations of blood alanine and aspartate aminotransferases (ALT and AST) with infrequent cases of concomitant elevations in total bilirubin (BT).

A pharmacovigilance plan for Jinarc will be implemented as part of the marketing authorisation.

The approved indication is: " Jinarc is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stage 1 to 3 at initiation of treatment with evidence of rapidly progressing disease (see Section 5.1)."

It is proposed that Jinarc must be initiated and monitored under the supervision of physicians with expertise in managing ADPKD and a full understanding of the risks of tolvaptan therapy including hepatic toxicity and monitoring requirements.

Detailed recommendations for the use of this product will be described in the summary of product characteristics (SmPC), which will be published in the European public assessment report (EPAR) and made available in all official European Union languages after the marketing authorisation has been granted by the European Commission.

The CHMP, on the basis of quality, safety and efficacy data submitted, considers there to be a favourable benefit-to-risk balance for Jinarc and therefore recommends the granting of the marketing authorisation.