**BRIEF SUMMARY OF THE TRANSPARENCY COMMITTEE OPINION**

**JINARC** (tolvaptan), vasopressin antagonist

**Minor improvement in the treatment of autosomal dominant polycystic kidney disease in adults.**

**Main points**

- JINARC has been granted a Marketing Authorisation to slow the progression of the development of cysts and renal failure in autosomal dominant polycystic kidney disease (ADPKD) in adults with stage 1 to 3 chronic kidney disease (CKD) at treatment initiation, with signs of rapid disease progression.
- It reduces the total kidney volume but does not prevent the growth of cysts or cause their decrease. When the treatment is stopped, growth of the renal cysts resumes. Chronic treatment with tolvaptan is thus required even if the safety of an elevated cumulative dose is unknown.
- Its use should be limited only to adults with confirmed (Pei-modified Ravine criteria, family history or genetic testing), progressive ADPKD at risk of unfavourable progression of renal function.
- There are still uncertainties regarding the long-term hepatic safety and the consequences of combination with medicinal products that block the renin-angiotensin system.

**Therapeutic use**

Treatment of patients with polycystic kidney disease is based on the prevention of disease complications and protection of renal function:

- management of renal and extrarenal symptoms and complications,
- reduction of cardiovascular risks, essentially based on control of blood pressure (ACE inhibitors, ARBs, as first-line, beta-blockers and diuretics; normalisation of blood pressure also exerting a nephroprotective effect), diet and lifestyle changes, etc.

No treatment to slow the progression of ADPKD is currently available. Upon reaching end-stage renal failure, dialysis or transplantation is offered.

**Role of the medicinal product in the therapeutic strategy**

JINARC should be limited only to patients with a GFR > 30 ml/min/1.73 m² and a significant nephromegaly associated with a risk of loss of renal function (a size-adjusted kidney volume > 600 ml/m in MRI; ≥ 630 ml/m in ultrasound or a kidney length > 16.7 cm in MRI; > 16.8 cm in ultrasound) and signs of rapid disease progression such as the presence of clinical manifestations (kidney pain, or intracystic infection or bleeding, macroscopic haematuria) or a significant decrease in GFR of at least 5 ml/min/year (assessed by the MDRD or CKD-EPI formulas or by creatinine clearance).

**Clinical data**

- A clinical trial, performed in 1445 patients with ADPKD monitored for 3 years showed the efficacy of tolvaptan vs placebo. The primary efficacy endpoint was rate of total kidney volume change (%). After 3 years of treatment, the total kidney volume increased significantly less in the tolvaptan group than in the placebo group: 2.78% (5.66) versus 5.61% (5.33), difference -2.708% [-3.269; -2.147], p<0.0001. Similarly, a reduction in occurrence of first event related to clinical progression of ADPKD (combined secondary criterion) was observed: HR 0.87 [0.78; 0.97]; p=0.01. The clinical progression of ADPKD assessed by the composite endpoint was linked to changes in renal function and kidney pain.

- The most commonly reported adverse effects are thirst, polyuria, nocturia and urinary frequency. Tolvaptan has also been associated with increases in blood levels of alanine aminotransferase and aspartate aminotransferase (ALT and AST), with rare cases of concomitant increase in total bilirubin.
To limit the risk of significant or irreversible liver damage, a blood test of liver transaminases is required before starting treatment with JINARC, then monthly for 18 months and every 3 months thereafter. The most common adverse effects are related to fluid loss. It is therefore essential that patients are able to drink enough to compensate for the polyuria induced by the medicinal product. The fluid status of patients taking tolvaptan should be monitored to prevent dehydration.

Special prescribing conditions

- Medicine for initial six-monthly hospital prescription
- Initial prescription and renewal by nephrology specialists only
- Medicine requiring special monitoring during treatment

Benefit of the medicinal product

- The actual benefit* of JINARC is moderate, only in adult patients with verified (Pei-modified Ravine criteria, family history or genetic testing), progressive ADPKD, i.e.:
  - a GFR > 30 ml/min/1.73 m²
  and
  - a significant nephromegaly associated with a risk of loss of renal function, i.e.:
    - a size-adjusted kidney volume > 600 ml/m² in MRI; ≥ 630 ml/m² in ultrasound,
    or
    - a kidney length > 16.7 cm in MRI; > 16.8 cm in ultrasound.
  and
  - signs of rapid disease progression, such as:
    - the presence of clinical manifestations (renal pain or bleeding or intracystic infection, macroscopic haematuria)
    or
    - a significant decrease in GFR of at least 5 ml/min/year (assessed by the MDRD or CKD-EPI formulas or by creatinine clearance).

- JINARC provides clinical added value** (CAV level IV, minor) in the aforementioned patients.
- Recommends inclusion on the list of reimbursable products for supply by pharmacists and for hospital use.

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* The actual benefit (AB) of a proprietary medicinal product describes its benefit primarily in terms of its clinical efficacy and the seriousness of the condition being treated. The HAS Transparency Committee assesses the AB, which can be substantial, moderate, low or insufficient for reimbursement for hospital use.

** The clinical added value (CAV) describes the improvement in treatment provided by a medicinal product compared with existing treatments. The HAS Transparency Committee assesses the degree of CAV on a scale from I (major) to IV (minor). A level V CAV means "no clinical added value".

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