Medicines Management Programme

Managed Access Protocol – Tolvaptan (Jinarc®▼) for the treatment of autosomal dominant polycystic kidney disease

Approved by:	Prof. Michael Barry, Clinical Lead, MMP.
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▼ This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions.

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List of Abbreviations

ADPKD	Autosomal dominant polycystic kidney disease
ALT	Alanine transaminase
AST	Aspartate aminotransferase
BT	Bilirubin-total
CKD	Chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
eGFR	Estimated glomerular filtration rate
GFR	Glomerular filtration rate
HSE	Health Service Executive
HTH	High Tech Hub
INR	International normalised ratio
MAP	Managed access protocol
MDRD	Modification of Diet in Renal Disease
mGFR	Measured glomerular filtration rate
MMP	Medicines Management Programme
PCRS	Primary Care Reimbursement Service
REPRISE	Replicating Evidence of Preserved Renal Function: an Investigation of Tolvaptan Safety and Efficacy in ADPKD
SmPC	Summary of Product Characteristics
TEMPO	Tolvaptan Efficacy and Safety in Management of Autosomal Dominant Polycystic Kidney Disease and Its Outcomes
ULN	Upper limit of normal

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1. Tolvaptan (Jinarc®)

1.1 Licensed indication

Tolvaptan (Jinarc®▼[i]) is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with chronic kidney disease (CKD) stage 1 to 4 at initiation of treatment with evidence of rapidly progressing disease. [ii]

1.2 Reimbursement

On 1 July 2019, tolvaptan (Jinarc®) was added to the High Tech Arrangement. Reimbursement is confined to the following subgroup of the licensed population:

- Treatment of ADPKD patients with CKD stage 2 or 3 at initiation of treatment with evidence of rapidly progressing disease.

Prescribers are required to apply for reimbursement approval on an individual patient basis. The *Application for individual reimbursement approval of Tolvaptan (Jinarc®)* should be completed and sent by secure email to the Medicines Management Programme (MMP) at mmp@hse.ie.

If a patient is recommended for reimbursement by the MMP, the High Tech prescription for tolvaptan (Jinarc®) should be generated on the High Tech Hub (HTH). High Tech prescriptions which are not hub generated for tolvaptan (Jinarc®) will not be eligible for reimbursement by the Health Service Executive (HSE) Primary Care Reimbursement Service (PCRS).

If a patient is recommended for reimbursement of tolvaptan (Jinarc®), reimbursement will be supported for the licensed dosage regimen.

1.2.1 Presentations

Tolvaptan (Jinarc®) is available as 15 mg, 30 mg, 45 mg, 60 mg and 90 mg tablets on the High Tech Arrangement in the following presentations:

- Jinarc® 15 mg Tablets (7 Tablets)
- Jinarc® 30 mg Tablets (7 Tablets)
- Jinarc® [45 mg x 28 & 15 mg x 28] Tablets (56 Tablets)
- Jinarc® [60 mg x 28 & 30 mg x 28] Tablets (56 Tablets)
- Jinarc® [90 mg x 28 & 30 mg x 28] Tablets (56 Tablets)

[i] ▼This medicinal product is subject to additional monitoring

[ii] Please refer to the Summary of Product Characteristics for Jinarc® for full prescribing information

1.2.2 Licensed dosage regimen

Tolvaptan (Jinarc®) should be administered twice daily in split-dose regimens of 45 mg + 15 mg, 60 mg + 30 mg or 90 mg + 30 mg. The morning dose is to be taken at least 30 minutes before breakfast and the second daily dose eight hours later, with or without food. According to these split-dose regimens the total daily doses are 60 mg, 90 mg, or 120 mg.[iii] Reimbursement will be supported up to the maximum daily dose of 120 mg.

1.3 Reimbursement price

The reimbursement prices of the presentations of tolvaptan (Jinarc®) available on the High Tech Arrangement as of 1 November 2022 are outlined in Table 1 below.

Table 1: Reimbursement prices of various strengths and presentations of tolvaptan (Jinarc®)

Strength (pack size)	Reimbursement code	Reimbursement price
Jinarc® Tablets 15 mg (7)	88943	€389.34
Jinarc® Tablets 30 mg (7)	88944	€398.23
Jinarc® [45 mg x 28 & 15 mg x 28] Tablets (56)	88940	€1,467.00
Jinarc® [60 mg x 28 & 30 mg x 28] Tablets (56)	88941	€1,472.60
Jinarc® [90 mg x 28 & 30 mg x 28] Tablets (56)	88942	€1,478.19

A commercial-in-confidence arrangement is in place with the marketing authorisation holder to reduce the net acquisition cost of Jinarc® to the HSE.

2. Reimbursement criteria - Initiation

This section outlines the criteria that must be satisfied in order for a patient to be recommended for reimbursement of tolvaptan (Jinarc®) for the treatment of ADPKD under the High Tech Arrangement.

2.1 Prescribers

The prescribing of tolvaptan (Jinarc®) under the High Tech Arrangement will be confined to consultant nephrologists who have been approved by the HSE and have agreed to the terms of this managed access protocol (MAP). Applications for reimbursement approval will only be considered from these prescribers.

[iii] Please refer to the Summary of Product Characteristics for Jinarc® for full prescribing information

2.2 Patient clinical history

In line with the TEMPO 3:4 and REPRISE trials, the information contained within the Summary of Product Characteristics (SmPC) and the 2021 European consensus statement update[iv] on the use of tolvaptan for ADPKD, the reimbursement criteria for initiation of tolvaptan (Jinarc®) are:

- Aged 18 - 55 years at time of application,
- Diagnosis of ADPKD,
- CKD stage 2 or 3, **and**
- Evidence of rapidly progressing disease.

2.2.1 Patient age

As per the SmPC, limited data on the safety and effectiveness of tolvaptan (Jinarc®) in ADPKD patients aged over 55 years are available. Applications for reimbursement approval will only be considered for individuals aged 18 - 55 years at time of application.

2.2.2 Confirmed diagnosis of autosomal dominant polycystic kidney disease

For reimbursement approval, clinicians will be required to confirm the diagnosis of ADPKD at the time of application.

A diagnosis of ADPKD can be established:

- **in patients with a family history**: age-related modified Pei-Ravine imaging (Table 2) **or**
- **in patients without a family history**: more than 10 cysts per kidney (using any imaging method) and exclusion of other forms of cystic kidney disease.

Table 2: Unified ultrasound age-related modified Pei-Ravine imaging criteria

Age (years)	Diagnostic criteria
15 - 29	≥ 3 cysts (total)
30 - 39	≥ 3 cysts (total)
40 - 59	≥ 2 cysts (each kidney)

These criteria are only valid in patients with a positive family history and are specific for ultrasound imaging only.

Note reimbursement will only be supported for patients aged 18 - 55 years at time of application.

[iv] Müller RU, Messchendorp AL, Birn H et al. An update on the use of tolvaptan for autosomal dominant polycystic kidney disease: consensus statement on behalf of the ERA Working Group on Inherited Kidney Disorders, the European Rare Kidney Disease Reference Network and Polycystic Kidney Disease International. *Nephrol Dial Transplant* 2022; 37(5): 825-839.

2.2.3 Chronic kidney disease stage 2/3

Similar to other chronic kidney diseases, ADPKD is typically staged by renal function status. The estimated glomerular filtration rate (eGFR) measurements corresponding to each stage are shown in Table 3 below. Reimbursement will only be supported for ADPKD patients with CKD stage 2 or 3 at initiation of treatment (i.e. eGFR 30 - 89 ml/min/1.73 m^2).

Table 3: Classification of chronic kidney disease by estimated glomerular filtration rate (eGFR)

Stage	Description	eGFR (ml/min/1.73 m^2)
1	Kidney damage with normal or increased eGFR	≥ 90
2	Kidney damage with mild decrease in eGFR	60 - 89
3a	Moderate decrease in eGFR	45 - 59
3b	Moderate decrease in eGFR	30 - 44
4	Severe decrease in eGFR	15 - 29
5	Kidney Failure	< 15 or dialysis

In the application for reimbursement approval, glomerular filtration rate (GFR) should be estimated by either the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation or the Modification of Diet in Renal Disease (MDRD) study equation.

The following patient measurements must be provided in the application for reimbursement approval:

- Weight
- Height
- Serum creatinine
- Estimated GFR ($eGFR_{MDRD}$ or $eGFR_{CKD\text{-}EPI}$)

The following patient measurement can be provided in the application for reimbursement approval:

- Measured GFR (mGFR) i.e. 24-hour urine clearance or by isotope method

When reviewing applications, the MMP may request this measurement as additional information to support the staging of CKD.

All measurements should be taken in the **six week period prior to date of application**.

2.2.4 Evidence of rapidly progressing disease

Evidence to support rapid progression of ADPKD must be included in the application for reimbursement approval. A historical fast eGFR decline, with no other confounding cause than ADPKD is a marker of rapid disease progression.

Rapid disease progression in ADPKD can be defined as a sustained decline in eGFR of ≥ 3 ml/min/1.73m^2 per year over a period of four years or greater.

- At least five measurements over a period of at least four years must be provided.
- The date of the first and last eGFR measurement must be at least four years apart.
- Measurements must be provided for at least three individual years during this period.
- The date of the most recent measurement must be within the six week period prior to date of application.

Clinicians are required to provide copies of lab reports to confirm eGFR measurements.

3. Prescribing of tolvaptan (Jinarc®)

Please refer to the SmPC for tolvaptan (Jinarc®) for full prescribing information including monitoring and patient counselling requirements. Prescriptions must be generated through the HTH and only approved prescribers will have access to prescribe tolvaptan (Jinarc®).

The following confirmations are required when prescribing tolvaptan (Jinarc®) on the HTH:

- Confirmation that tolvaptan (Jinarc®) is being prescribed for a MMP approved patient in accordance with the MAP established in line with the terms of reimbursement approval given by the HSE
- Confirmation that the prescriber will assist the HSE/MMP in their conduct of audits* through provision of information as requested, to provide assurance that the product is being prescribed in line with HSE reimbursement approval and the MAP
- Confirmation that the patient is aware that the application for reimbursement approval is being made on their behalf and that audits may occur during which their personal data will be reviewed.

**** Follow-up data may be requested by the HSE/MMP for audit purposes and provision of same is a condition of ongoing reimbursement.***

4. Contraindications

In line with the SmPC, if any of the following contraindications apply to the patient, reimbursement of tolvaptan (Jinarc®) will not be considered:

- Elevated liver enzymes and/or signs or symptoms of liver injury prior to initiation of treatment that meet the requirements for permanent discontinuation of tolvaptan (see Table 4 below and SmPC)
- Anuria
- Volume depletion
- Hypernatraemia
- Patients who cannot perceive or respond to thirst
- Pregnancy and breast-feeding
- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1 of the SmPC or to benzazepine or benzazepine derivatives.

Table 4: Recommended guidelines for permanent discontinuation of tolvaptan (Jinarc®) in patients with hepatic injury

ALT or AST	> 8-times ULN
ALT or AST	> 5-times ULN for more than 2 weeks
ALT or AST	> 3-times ULN and (BT > 2-times ULN or INR > 1.5)
ALT or AST	> 3-times ULN with persistent symptoms of hepatic injury*

ALT: Alanine transaminase; AST: Aspartate aminotransferase; BT; Bilirubin-total; INR: International normalised ratio; ULN: Upper limit of normal

*Symptoms which may indicate hepatic injury include fatigue, anorexia, nausea, right upper abdominal discomfort, vomiting, fever, rash, pruritus, dark urine or jaundice

5. Reimbursement - Discontinuation

5.1 Chronic kidney disease stage 5

The SmPC states that patients should cease tolvaptan (Jinarc®) treatment if renal insufficiency progresses to CKD stage 5, therefore reimbursement will no longer be supported if a patient progresses to stage 5.

5.2 Chronic kidney disease stage 4

Although reimbursement is not supported for patients with CKD stage 4 on initiation, approved patients who progress to stage 4 will receive ongoing reimbursement support.