Tolvaptan (Jinarc®) for the treatment of chronic kidney disease

Summary of recommendations by *Zorginstituut Nederland* (National Health Care Institute, the Netherlands) dated 2 April 2019

Zorginstituut Nederland carried out an assessment of the medicinal product tolvaptan (Jinarc®), whereby they came to the following conclusion.

In a letter dated 12 February 2019 (CIBG-19-07666), The Ministry of Health, Welfare and Sport asked *Zorginstituut Nederland* to alter the specific conditions for the product tolvaptan (Jinarc®), which is indicated for autosomal dominant polycystic kidney disease (ADPKD). This was prompted by the publication of new study results and, consequently, revised guidelines on the effectiveness and safety of tolvaptan, particularly in patients with a more severely impaired renal function. As the request relates to a change in an existing indication for tolvaptan, we replied by means of a letter.

Current situation
Based on an earlier assessment by *Zorginstituut Nederland*, tolvaptan (Jinarc®) was placed on List 1B of the Medicine Reimbursement System (GVS).[1] We concluded that tolvaptan has a therapeutic added value compared to best supportive care for ADPKD patients with chronic kidney disease (CKD) stages 1 to 3. For the effectiveness of tolvaptan in patients with CKD stage 3b, the evidence was scant. As a result, reimbursement is currently possible based on the following condition:

Only for an insured person aged 18 years and older with autosomal dominant polycystic kidney disease (ADPKD) with chronic kidney disease (CKD) in stages 1 to 3a at the start of the treatment, with evidence of rapidly progressing disease, and in line with the guidelines as approved by the relevant professional groups in the Netherlands.

According to the guidelines of the Dutch Federation of Nephrologists (NFN), patients under the age of 50 years with a glomerular filtration rate (GRF) >30 ml/min (CKD stages 1 to 3) are eligible for treatment with tolvaptan.[2]

Extension in specific conditions for CKD stage 3b
Tolvaptan (Jinarc®) accessed the market in 2015 for the indication ADPKD with CKD stages 1 to 3 (i.e. including CKD stage 3b) under the following condition: a supplementary study would be carried out in patients in later CKD stages at the start of the treatment.[3] This study (REPRISE) has now been completed. Based on this study, the indication for tolvaptan was extended with CKD stage 4 by the EMA in 2018[4]:

[1] *Zorginstituut Nederland*. Tolvaptan (Jinarc) in cases of autosomal dominant polycystic kidney disease. 2016. https://www.zorginstituutnederland.nl/publicaties/adviezen/2016/12/05/gvs-advies-tolvaptan-jinarc-bij-cyste-ontwikkeling-en-nierinsufficientie-bij-adpkd-herbeoordeling

[2] Dutch Federation of Nephrologists. Tolvaptan in cases of ADPKD: comments on the ERA-EDTA position statement, update 2018. https://www.nefro.nl/richtlijnen/tolvaptan-bij-adpkd

[3] CHMP. Summary of opinion tolvaptan (Jinarc®). 2015. https://www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-jinarc_en.pdf

[4] CHMP. Summary of opinion (post-authorization) tolvaptan (Jinarc®). 2018. https://www.ema.europa.eu/en/documents/smop/chmp-post-authorisation-summary-positive-opinion-

Jinarc is indicated to slow the progression of cyst development and renal insufficiency of autosomal dominant polycystic kidney disease (ADPKD) in adults with CKD stages 1 to 4 treatment with evidence of rapidly progressing disease.

In response to the results of the REPRISE study, the manufacturer has applied for an extension in the specific conditions for tolvaptan (Jinarc®) by including CKD stage 3b. In the recently revised guidelines, the NFN also states that treatment with tolvaptan can be considered in patients with ADPKD with CKD stage 3b.[2] However, the health benefits may be limited in this stage since few years remain until end stage renal disease is reached (CKD stage 5). The NFN therefore advises to start treatment with tolvaptan in patients with CKD stage 3b in consultation with the centres of expertise. The manufacturer has no intention to claim reimbursement for subgroup CKD stage 4, mainly because, according to the NFN guidelines, these patients are not eligible for starting treatment with tolvaptan.

Conclusion regarding therapeutic value
The results of the REPRISE study are described in the appendix that is sent to the Minister along with this letter. Based on the data in the appendix, we conclude that, in line with our previous assessment of patients with CKD stages 1 to 3, in comparison with best supportive care, tolvaptan has a therapeutic added value in patients with CKD stage 3b with evidence of rapidly progressing disease.

Conclusion on budget impact analysis
The budget impact analysis examined the additional costs related to the extension of the specific conditions with patients in CKD stage 3b. Assuming 120 to 149 adult ADPKD patients with rapid progression in CKD stage 3b, who could potentially be eligible for treatment with tolvaptan and a 45% market penetration, we expect that, three years after extending the specific condition, an extra 54 to 67 patients with CKD type 3b will be treated with tolvaptan. The costs of treatment with tolvaptan amount to €19,100 per patient per year. This will result in total additional costs of extending the specific condition (to include CKD type 3b) between €1,031,400.00 and €1,279,700.00 per year. If treatment is given according to the recommendations in the published guidelines (i.e. age <50 years), the budget impact could be lower.

Advice of *Zorginstituut Nederland*
Tolvaptan (Jinarc®) has already been included on List 1B with specific conditions for ADPKD. Based on the above considerations, we advise the Minister to alter the List 2 conditions for tolvaptan by including patients with CKD stage 3b. Altering this specific condition will be accompanied by additional costs.

Proposed conditions for tolvaptan
Only for an insured person aged 18 years and older with autosomal dominant polycystic kidney disease (ADPKD) with chronic kidney disease (CKD) in stages 1 to 3 when initiating treatment, with evidence of rapidly progressing disease, and in line with the guidelines as approved by the relevant professional groups in the Netherlands.

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The original text of this excerpt from advice of Zorginstituut Nederland was in

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Dutch. Although great care was taken in translating the text from Dutch to English, the translation may nevertheless have resulted in discrepancies. Rights may only be derived on the basis of the Dutch version of Zorginstituut Nederland's advice.
Furthermore, Zorginstituut Nederland points out that only the summary of this report was translated. A proper understanding of all relevant considerations and facts would require familiarity with the Dutch version of this report, including all appendices.