Recommendation No. 1/2021

of 4 January 2021

of the President of the Agency for Health Technology Assessment and Tariff System

on the evaluation of Jinarc (tolvaptan) under the drug programme indicated for "Treatment of autosomal dominant polycystic kidney disease (ICD-10 Q 61.2)"

The President of the Agency does not recommend the inclusion of the following medicinal products in the reimbursement scheme:

- Jinarc (tolvaptan), tablets, 30 mg; 90 mg, 56 tablets, EAN: 05038256002139,
- Jinarc (tolvaptan), tablets, 30 mg; 60 mg, 56 tablets, EAN: 05038256002122,
- Jinarc (tolvaptan), tablets, 15 mg; 45 mg, 56 tablets, EAN: 05038256002115,

under the drug programme indicated for "Treatment of autosomal dominant polycystic kidney disease (ICD-10 Q 61.2)" as part of a new limit group and dispensing it free of charge.

Explanation for recommendation

The President of the Agency, taking into account the position of the Transparency Council, available scientific evidence, clinical guidelines and reimbursement recommendations, considers the public financing of the technology named in the application to be unjustified

The efficacy assessment of the technology named in the application is mainly based on the results of RCTs (TEMPO 3:4, REPRISE) comparing the use of TOL vs BSC in a population of adult patients with autosomal dominant polycystic kidney disease (ADPKD) and a single-arm trial (TEMPO 4:4) extending the TEMPO 3:4 trial and assessing the long-term efficacy and safety of TOL. However, it is important to consider that the trial results do not address the endpoints of greatest importance to patients.

According to the results of TEMPO 3:4, the use of TOL reduced the annual rate of increase in total kidney volume (TKV), the primary endpoint) in the general population of the study by 2.7%, and the difference between groups was statistically significant in favour of TOL vs BSC (the relative reduction in the rate of increase in TKV in the treatment group vs control group was 49.2%). In TEMPO 4:4, in the general population of patients continuing tolvaptan treatment, there was an increase in TKV of approximately 30% from the baseline value in TEMPO 3:4, i.e. after approximately 60 months of treatment.

For the key secondary endpoint – estimated glomerular filtration rate *(eGFR)*– according to TEMPO 4:4 in the TOL continuation group, the total change in eGFR was -16.7 ml/min/1.73m^2. In contrast, in the primary efficacy analysis of REPRISE (which included all patients who completed the trial as well as those who terminated participation early), the difference in terms of annual mean change in eGFR after 12 months of therapy between the TOL+BSC group (eGFR change of -2.34 ml/min/1.73 m^2) and the PLC+BSC group (eGFR change of -3.61 ml/min/1.73 m^2) was 1.27 ml/min/1.73 m^2.

Referring to the safety profile in TEMPO 4:4, thirst, polyuria and hypertension were the most frequent findings in patients. According to the REPRISE results, severe liver-related events were significantly more frequently reported in the treatment group.

The results of the economic analysis concerning the use of tolvaptan in place of the comparator (BSC) (trade secret) show that the ICUR from the perspective of the National Health Fund (NFZ) is (trade secret). On the other hand, the budget impact analysis concerning the public payer from the perspective of the National Health Fund showed (trade secret).

Reimbursement recommendations from other countries that indicate a health problem were also considered. However, it is also important to note (following the CADTH recommendation) that the use of tolvaptan in ADPKD patients is associated with significant therapy safety issues, e.g. renal damage, hyponatraemia, increased uric acid levels and gout, polyuria, thirst disorders and skin cancer. In addition, this recommendation indicates that there is insufficient evidence to show that tolvaptan treatment results in improvements in the endpoints of greatest importance to patients. Taking into account the above doubts and the results of the economic and financial analysis, the inclusion of the evaluated technology in the reimbursement scheme was considered unjustified.

Subject of the application

The order of the Minister of Health concerns the assessment of the validity of public financing of medicinal products:

- Jinarc (tolvaptan), tablets, 30 mg; 90 mg, 56 tablets, EAN: 05038256002139, with the proposed net sales price of (trade secret)
- Jinarc (tolvaptan), tablets, 30 mg; 60 mg, 56 tablets, EAN: 05038256002122, with the proposed net sales price of (trade secret)
- Jinarc (tolvaptan), tablets, 15 mg; 45 mg, 56 tablets, EAN: 05038256002115, with the proposed net sales price of (trade secret),

under the drug programme indicated for "Treatment of autosomal dominant polycystic kidney disease (ICD-10 Q 61.2)".

Proposed payment and dispensing category: free of charge, the drug is to be used under a drug programme as part of a new limit group. The applicant did not propose a risk-sharing scheme (RSS).

Health problem

According to the ICD-10, autosomal dominant polycystic kidney disease is assigned to code Q61.2 Polycystic kidney, autosomal dominant (adult type).

Polycystic kidney disease (PKD) is a genetically determined occurrence of multiple cysts in the renal cortex and medulla. There are two PKD types, i.e. autosomal dominant and autosomal recessive. Autosomal dominant polycystic kidney disease (ADPKD) is a systemic genetic disorder inherited in an autosomal dominant manner. It is characterised by the development and growth of cysts in the kidneys and other organs and additional systemic symptoms. It occurs in adults and is the most common genetically determined kidney disease.

The earliest clinical manifestation of the disease is hypertension, which may present in adolescence. The characteristic sign is the polycystic kidney, which presents at various ages, at the latest by 40. A mutation in one of the genes encoding proteins polycystin 1 or polycystin 2 (PKD1 or PKD2) is responsible for the development of the disease. A PKD1 mutation is responsible for about 85% of cases in individuals with a recognised mutation, while a PKD2 mutation accounts for 15%. In 5–10% of patients, there is no family history of this disorder, as a mutation arising *de novo* is responsible for the development of the disease.

The incidence of the disease is estimated to be from 1:400 to 1:1000 live births. It is usually detected between the age of 10 and 30 . It accounts for 5–15% of cases of end-stage renal disease requiring renal replacement therapy.

The incidence of ADPKD is estimated at 4 cases per 10,000 in the European Union, which means the disease meets the criteria of a rare disease (according to the definition, a rare disease occurs in no more than 5 people per 10,000 cases).

ADPKD is associated with an increased age-standardised mortality rate compared to the general population. This rate is 60% higher than in the general population. The most common causes of death in ADPKD patients include cardiovascular disease and infection.

Alternative health technology

All guidelines and expert opinions found indicate that symptomatic treatment of ADPKD is currently used.

In the opinion of the clinical expert, symptomatic treatment is currently used in the evaluated population.

In accordance with the notice of the Minister of Health of 21 October 2020 on the list of reimbursable drugs, foodstuffs intended for particular nutritional uses and medical devices (Official Journal of the Minister of Health, item 88), there are no reimbursable drugs for the indication named in the application.

Moreover, currently in Poland, ADPKD is treated symptomatically, e.g. with hypotensive drugs, analgesics, antibiotics or drugs affecting lipid metabolism.

The drugs used for symptomatic treatment in the indication mentioned in the application that are currently reimbursed in Poland include:

- Hypotensive drugs: angiotensin-converting enzyme inhibitors, angiotensin II receptor antagonists, calcium channel blockers (cardioselective calcium antagonists; phenylalkylamine derivatives);
- Analgesics: analgesic drugs; natural opium alkaloids;
- Antibiotics: fluoroquinolones and cyclosporins;
- Drugs affecting lipid metabolism: HMG-CoA reductase inhibitors.

The applicant adopts best supportive care (BSC) as a reimbursable comparator in the target population for Jinarc based on the clinical guidelines described. The BSC consists of drugs used for the symptomatic treatment of ADPKD and includes hypotensive drugs, analgesics, antibiotics and drugs affecting lipid metabolism.

Considering the above, the applicant's choice of comparator was considered reasonable.

Description of the benefit named in the application

Tolvaptan is a vasopressin antagonist that specifically blocks the binding of arginine vasopressin (AVP) to V2 receptors in the distal nephron. Tolvaptan's affinity for V2 receptors in humans is 1.8 times that of a natural AVP.

According to the Summary of Product Characteristics (SmPC), Jinarc is indicated for the slowing of cyst formation and progression of renal impairment in autosomal dominant polycystic kidney disease (ADPKD) in adult patients with stage 1 to 4 chronic kidney disease (CKD) at treatment baseline who show rapid disease progression.

The indication mentioned in the application concerns treatment of adult patients with autosomal dominant polycystic kidney disease (ADPKD) (ICD-10 Q 61.2) under a drug programme and is narrower than the approved indication due to the eligibility criteria for the drug programme.

Evaluation of efficacy (clinical and practical) and safety

This evaluation consists of collecting data on the health consequences (efficacy and safety) of a new therapy for a given health problem and other therapies that are currently publicly funded and represent alternative treatments available for the particular health problem. Subsequently, this evaluation involves determining the reliability of the collected data and comparing the efficacy and safety results of the new therapy against therapies that are already available for the treatment of the health problem in question.

Based on the above, the assessment of efficacy and safety provides an answer to the question of the measure of health outcome (in terms of both efficacy and safety) to be expected for the new therapy compared to other therapeutic options considered.

The applicant's systematic review included the following studies:

- TEMPO 3:4 – a randomised, double-blind, multicentre, phase III study. A comparative evaluation of the efficacy and safety of tolvaptan (TOL) versus best supportive care (BSC) was performed in a population

of adult ADPKD patients with chronic kidney disease stage 1 to 3. Study period: January 2007 to January 2009 (36 months). Hypothesis type: superiority. The number of patients: Group A (TOL): 961, Group B (BSC): 484. The study was evaluated according to the Jadad scale: 5/5 points.

- TEMPO 4:4 – a single-arm, open-label, multicentre, phase III extension of the TEMPO 3:4 study. Trial duration: 24 months. (After accounting for the study period of TEMPO 3:4, the total trial duration was 60 months). Hypothesis type: superiority / non-inferiority. Number of patients: Group A (TOL): 557. The study was evaluated according to NICE: 7/8 points.
- REPRISE – a randomised, double-blind, multicentre, phase IIIb study (the report includes only data on the double-blind treatment phase of REPRISE). Results are presented regarding the evaluation of the efficacy and safety profile of TOL versus BSC in an adult ADPKD patient population. Trial duration: 15 months. (8 weeks before randomisation, 12 months during the double-blind phase and an additional 2 weeks of a follow-up period). Hypothesis type: superiority. Number of patients: Group A (TOL): 683 Group B (BSC): 687. The study was evaluated according to the Jadad scale: 5/5 points.
- Bern ADPKD – a prospective observational registry (a single-centre cohort study), which presented results on the efficacy and safety profile of TOL+BSC versus no TOL+ BSC. Patient assignment to groups: between October 2015 and July 2019, 125 ADPKD patients treated at the Department of Nephrology and Hypertension of the Bern University Hospital were included in the Bern ADPKD registry. Patients were assigned to groups according to the use of TOL therapy. Study period: 12 months. (data cut-off date: March 2019). Hypothesis type: superiority. The number of patients: Group A: 30 (TOL+BSC), Group B (no TOL + BSC): 68. The study was evaluated according to the NOS for cohort studies: Sample selection: **, Comparability: **, Endpoint: ***.

The following parameters, among others, were used to show effectiveness:

- HR – *hazard ratio*,
- MD – *mean difference*,
- NNT – *number needed to treat*.

Effectiveness

Effectiveness assessment of TOL versus BSC based on TEMPO 3:4 outcomes

The efficacy analysis of TOL versus BSC in adult ADPKD patients was based on the outcomes of TEMPO 3:4 (Torres 2012). The results were supplemented with additional data for TEMPO 3:4 from the 2015 EMA report.

TEMPO 3:4 involved a larger patient population than the target population considered in this analysis. Therefore, in addition, the report also includes data from TEMPO 3:4 on patients in the target population (i.e. patients with CKD stage 2 or 3 at treatment baseline) from Torres (2016), which presented the post-hoc analysis results according to CKD stage at baseline of TEMPO 3:4.

In addition, the report also presents TEMPO 3:4 results on patients in the target population (i.e. patients with CKD stage 2 or 3 at treatment baseline) from the 2017 Grantham article, which presents a post-hoc analysis on the effect of tolvaptan on urinary excretion of monocyte chemotactic protein-1 (µMCP-1).

The TEMPO 3:4 trial duration was 36 months.

Efficacy was evaluated against the following endpoints:

- TKV

  Annual rate of increase in TKV

  The primary endpoint in TEMPO 3:4 was the assessment of the annual rate of change in total kidney volume (TKV).

  The results concerning the magnitude of change in TKV in patients randomised to TOL treatment compared to the change in patients in the control group were statistically significant. In the general patient population, the rate of TKV increase over 36 months of the trial was lower in patients treated with TOL than in those receiving PLC+BSC, at 2.80% per year vs 5.51% per year, respectively. The use of TOL resulted in a 2.7% lower increase in the annual rate of TKV (the ratio of geometric means for the

increase rate was 0.974 according to the study authors $p < 0.0001$). The relative reduction in TKV increase rate in the treatment group relative to the control group was 49.2%.

The results concerning the general population were also confirmed when analysed in subgroups of patients listed according to the study protocol, including the subgroup of patients with CKD stage 2 and 3 at baseline of TEMPO 3:4. According to the post-hoc analysis results depending on the stage of CKD, the application of TOL resulted in a 3.12% reduction in the annual TKV increase rate in patients with CKD stage 2 (relative reduction of TKV increase rate in the treatment group compared to the control group was 60.4%) and a 2.61% reduction in patients with CKD stage 3 (relative reduction of TKV increase rate in the treatment group compared to the control group was 39.8%).

Change in TKV relative to baseline

The results of the MMRM analysis of the mean change in TKV relative to baseline confirmed the analysis results concerning the primary endpoint. According to the data presented by the study authors, in patients using TOL, total kidney volume increased by an average of about 9.6% after 36 months of therapy. In comparison, in the control group, this change was about 18.8%. The difference between the groups was statistically significant (in favour of the TOL treatment group).

Similar results were obtained when analysing subgroups of patients stratified by CKD stage at baseline of TEMPO 3:4. In patients with CKD stage 3, at baseline of TEMPO 3:4, total kidney volume after 36 months of therapy increased by an average of about 7%. In comparison, in the control group, this change was about 18%. In patients with CKD stage 3, at baseline of TEMPO 3:4, total kidney volume after 36 months of therapy increased by an average of about 11%, and in the control group, this change was about 22%. In both cases, the difference between the groups was statistically significant (in favour of the TOL treatment group).

- Clinical progression

The TEMPO 3:4 secondary composite endpoint assessed the time to clinical progression as assessed by the investigator, which was defined as the occurrence of the following ADPKD events:

- ✓ deterioration of renal function (defined as a persistent, i.e. a 25% reduction in the inverse of serum creatinine lasting at least 2 weeks during the treatment period (from the end of dose adjustment to the last visit during treatment));
- ✓ clinically significant renal pain (defined as the need for sick leave, use of last resort analgesics, narcotic analgesics and radiological or surgical intervention to treat nociceptive pain);
- ✓ increase in hypertension (changes in blood pressure or intensification of blood pressure lowering therapy);
- ✓ increase in proteinuria (according to gender-specific categories).

Deterioration of renal function

In TEMPO 3:4, during 36 months of treatment, renal function deterioration in the general population was reported less frequently in the treatment group than the control group (number of events/100 patient-years were 2 and 5, respectively). The risk of renal function deterioration events was statistically significantly lower by about 61% in the TOL treatment group compared to the control group ($HR = 0.39$; $p < 0.001$).

Analysis of subgroups of patients with CKD stage 2 and 3 at study baseline also showed that deterioration of kidney function was less common in the treatment group compared to the control group. According to data presented by the study authors, the risk of renal function deterioration in these subgroups of patients was statistically significantly lower in the TOL treatment group compared to the control group.

Clinically significant renal pain

TEMPO 3:4 evaluated clinically significant renal pain requiring sick leave, drug treatment or invasive intervention.

During 36 months of treatment, clinically significant renal pain in the general population was reported less frequently in the treatment group compared to the control group (number of events/100 patient-

years was 5 and 7, respectively). The risk of clinically significant renal pain events was statistically significantly lower by about 36% in the TOL treatment group compared to the control group (HR = 0.64; p = 0.007).

Analysis of subgroups of patients with CKD stage 3 at study baseline also showed that clinically significant renal pain occurred less frequently in the treatment group compared to the control group (number of events/100 patient-years was 4 and 9, respectively). According to data presented by the study authors, the risk of clinically significant renal pain events in this subgroup of patients was statistically significantly lower in the TOL treatment group than in the control group (p = 0.007). No statistically significant differences between groups were shown in the subgroup of patients with CKD stage 2 at baseline of TEMPO 3:4.

Hypertension

TEMPO 3:4 analysed the occurrence of hypertension increase events, defined as changes in blood pressure defined in the study protocol or hypertension exacerbation requiring an increase in the dose of blood pressure-lowering medication.

During 36 months of treatment, hypertension increase in the general population was reported slightly less frequently in the treatment group compared to the control group (number of events/100 patient-years was 31 and 32, respectively). The risk of events related to an increase in hypertension was 6% lower in the TOL treatment group than in the control group, but the difference between groups was not statistically significant (HR = 0.94 [95% CI: 0.81; 1.09]; p = 0.42).

Proteinuria

In TEMPO 3:4, the incidence of events related to increased proteinuria was analysed. During 36 months of treatment, increased proteinuria in the general population was reported with similar frequency in the treatment and control groups (number of events/100 patient-years was 8). Thus, the risk of events associated with increased proteinuria was similar in the TOL treatment group and the control group (HR = 1.04 [95%CI: 0.84; 1.28] p = 0.74).

- Renal function assessment

  Change in the inverse of serum creatinine

  The results presented in TEMPO 3:4 indicate that the use of TOL was associated with a slower decline in renal function compared to the control group. The estimated change in the inverse of serum creatinine was -2.61 $(mg/ml)^{-1}$ /year in the general population in the treatment group and -3.81 (mg/ml)-1 /year in the control group. Thus, an increase of 1.20 $(mg/ml)^{-1}$ /year was noted. In contrast, the relative treatment effect was 31.6%. According to data presented by the study authors, the difference between the groups was statistically significant (in favour of the TOL treatment group).

  The study authors point out that this treatment effect was confirmed by comparing pre-treatment and post-treatment visit data. There was a significant increase in the score of 4.93 $(mg/ml)^{-1}$ at 3 years for the treatment group compared to the PLC+BSC group (p < 0.001). The study authors also point out that MMRM analysis showed a significant difference in favour of TOL+BSC from year 1 of therapy (difference between groups was 2.02 $(mg/ml)^{-1}$; p < 0.001) to year 3 (difference between groups was 3.68 (mg/ml)-1; p < 0.001).

  Creatinine concentration

  In TEMPO 3:4, after 36 months of therapy, there was an increase in mean creatinine levels in the TOL treatment group from 1.05 mg/dl to 1.21 mg/dl. In the PLC+BSC group, mean creatinine levels increased from 1.04 mg/dl to 1.27 mg/dl. The difference between the groups with respect to mean creatinine concentration after 36 months of treatment was statistically significant (in favour of the treatment group).

  CKD stage

  In the subgroup of CKD stage 2 patients at baseline, after 36 months of therapy, a statistically significantly higher percentage of patients had CKD stage 1 and 2 than in the control group. After 36 months of therapy, CKD stage 3 was noted in the considered subgroup of patients in about 33% of TOL

patients and about 45% of the control group patients. The difference between the groups was statistically significant (in favour of the treatment group), with an NNT of 9.

In the subgroup of CKD stage 3 patients at baseline, after 36 months of therapy, CKD stage 3 was statistically significantly more frequent in the treatment group than in the control group. CKD stage 4 and 5 was observed in the subgroup of patients considered but more frequently in the control group than in the treatment group. In CKD stage 4, the difference between the groups was statistically significant (in favour of the treatment group), with an NNT of 9.

- Blood pressure evaluation

  Change in blood pressure

  TEMPO 3:4 investigated the change in mean resting blood pressure from baseline in subjects without hypertension. The mean increase in blood pressure was about 2.6% in both groups. According to the data presented by the study authors, there was no statistically significant difference between the groups with respect to the endpoint considered (p = 0.55).

  Events associated with an increase in hypertension

  According to data presented by the TEMPO 3:4 authors over 36 months, the risk of events involving an increase in hypertension in those without hypertension was not statistically significantly higher in the TOL treatment group than in the control group (HR = 0.99; p = 0.97).

- Renal pain evaluation

  In TEMPO 3:4, the other secondary endpoints assessed the change in renal pain intensity from baseline. As part of the assessment, patients were asked to indicate the change in the intensity of their renal pain from their last visit. Pain was rated on a scale of 0 to 10 points. All results are presented as the mean area under the curve for the difference between baseline and last visit (or last visit before medical or surgical treatment).

  There were no statistically significant differences between groups for this endpoint. However, as the authors of the study pointed out, it should be noted that although 50.9% of the general patient population reported a history of renal pain, only a small proportion of patients reported pain at study baseline (mean population score was <1). According to the study authors, the method used to assess renal pain over an extended period (a four-month interval between visits) was insufficient to evaluate renal pain in patients with ADPKD, probably because of the more episodic nature of pain events in most ADPKD patients.

<u>Evaluation of the long-term efficacy of TOL based on TEMPO 4:4</u>

The analysis of the long-term efficacy of TOL in adult ADPKD patients was based on TEMPO 4:4 (Torres 2018), an open-label extension of TEMPO 3:4 that included patients who completed TEMPO 3:4.

The TEMPO 4:4 trial duration was 24 months. Some patients participating in TEMPO 4:4 had previously used TOL for 36 months as part of TEMPO 3:4, meaning the total duration of TOL exposure in these patients was 60 months. Data for patients who used placebo in TEMPO 3:4 were not included in the analysis.

Torres (2018) also presents results concerning subgroups of patients by CKD stage, PKD genotype, classification on imaging studies and gender. This section presents results for the subgroups listed, only for patients who had previously used TOL as part of TEMPO 3:4 (TOL → TOL group).

The long-term efficacy was evaluated against the following endpoints:

- TKV

  Change in TKV

  The primary endpoint in TEMPO 4:4 was the change in TKV at month 24 in TEMPO 4:4 relative to the baseline of TEMPO 3:4. In the group of patients who continued treatment with TOL, the increase in TKV was 29.9%. A greater increase in TKV was observed in males (38.6%) compared to females (19.9%). A 29.5% increase in TKV was observed in patients with CKD stage 1, while in patients with CKD stage 2 or 3, it was 26.9%. The difference in TKV increase between groups differing in PKD (polycystic kidney disease) genotype was insignificant at 28.6% (PKD1-NT/PKD2) and 28.1%, respectively. In patients with

more severe CKD according to the Mayo classification (1C–1E), there was a 28.2% increase in TKV, while in the other group (1B or 2A–2B), it was 21.8%.

- Estimated glomerular filtration rate *(eGFR)*

  Change in eGFR

  The key secondary endpoint in TEMPO 4:4 was the change in eGFR after 24 months of therapy as part of TEMPO 4:4 relative to the baseline of TEMPO 3:4. In the group of patients continuing treatment with TOL, the total change in eGFR was -16.7 ml/min/1.73m^2.

  Males and females showed a similar change in eGFR of -16.4 and -16.7 ml/min/1.73m^2, respectively. The change in eGFR was greater in patients with CKD stage 1 (-20.4 ml/min/1.73m^2) compared to patients with CKD stage 2 or 3 (-17.7 ml/min/1.73m^2). The change in eGFR in groups differing in PKD genotype was -16.9 (PKD1-NT/PKD2) and -17.4 (PKD1-T), respectively. In patients with more severe CKD according to the Mayo classification (1C–1E), there was an eGFR change of -17.8 ml/min/1.73m^2, while in the other group (Mayo classification 1B or 2A–2B), it was -11.9 ml/min/1.73m^2.

  Decline in eGFR

  Another secondary endpoint was a decline in eGFR at month 24 of TEMPO 4:4 relative to the baseline of TEMPO 4:4. Over 24 months in TEMPO 4:4, patients continuing treatment with TOL experienced a decline in eGFR of 3.26 ml/min/1.73m^2 per year.

Evaluation of the efficacy of TOL versus BSC based on REPRISE

Based on the randomised, double-blind REPRISE trial, an assessment of the efficacy of tolvaptan versus BSC in ADPKD patients with advanced CKD (stage 2 to late stage 4) was presented (Torres 2017). The results were supplemented with additional data for REPRISE from the 2018 EMA report. Results concerning the longest available study period were included, i.e. the double-blind phase lasting 12 months or an additional follow-up period after the study lasting an additional 2 weeks. The efficacy of tolvaptan was evaluated based on

- eGFR

  Change in eGFR

  The change in eGFR between baseline and the end of treatment was the primary endpoint of REPRISE. In the primary efficacy analysis (which included all patients who completed the trial as well as those who terminated participation early), the difference in terms of annual mean change in eGFR after 12 months of therapy between the TOL+BSC group (eGFR change of -2.34 ml/min/1.73 m2) and the PLC+BSC group (eGFR change of -3.61 ml/min/1.73 m2) was 1.27 ml/min/1.73 m2. According to the data presented by the study authors, the reduction in eGFR was statistically significantly smaller in patients receiving TOL than in the control group, demonstrating the effectiveness of the studied intervention. This difference corresponded to a 35% change in eGFR over a year.

  Decline in eGFR change

  The key secondary endpoint in REPRISE was to assess the annualised slope of eGFR change at all measured time points during the trial.

  The results for the comparison of TOL+BSC versus PLC+BSC treatment regarding the annualised slope of eGFR change are analogous to the results for the primary endpoint. The primary analysis showed greater efficacy of TOL (annual mean decline in eGFR of 3.16 ml/min/1.73 m2) than the control group (annual mean decline in eGFR of 4.17 ml/min/1.73 m2). According to the study authors, the difference between the groups was 1.01 ml/min/1.73 m2 and was statistically significant (in favour of the treatment group). Statistically significant differences in favour of the studied intervention in reducing the rate of eGFR decline were also observed for both genders, both ranges of baseline eGFR values considered in the study, patients with CKD stage 3 and 4, both geographical regions, patients ≤55 years and Caucasian patients. Statistically significant benefits were not observed in the smaller groups – patients over 55, patients other than Caucasian and patients with CKD stage 2.

Effectiveness assessment of TOL versus BSC based on the Bern ADPKD registry results

The analysis of the practical effectiveness of TOL relative to BSC in adult ADPKD patients was based on the results of the prospective observational Bern ADPKD registry.

It included data presented in Anderegg (2020), which analysed results on the effect of the compared therapies on patients' health-related quality of life, and data presented in Bargagli (2020), which assessed the effect of TOL on the urinary lithogenic risk profile in patients with ADPKD.

The Bern ADPKD registry involved a larger patient population than the target population considered in this analysis. However, it should be noted that CKD stage 2 or 3 was present in 61.2% of the general study population and 60.0% of the TOL treatment group (as reported in Anderegg 2020).

The trial duration was 12 months.

The evaluation was based on the following endpoints:

- Quality of life

  The Bern ADPKD registry assessed the quality of life with the SF-36 questionnaire (T-score) and KDQOL-SF.

  In most domains assessed, the mean score in the TOL group after 12 months was higher (indicating better quality of life) than in the non-TOL group. Exceptions include scores for MCS, effects of kidney disease, burden of kidney disease, quality of social interaction and sleep. Differences between groups were statistically significant (in favour of the treatment group) only for the physical functioning domain. Otherwise, there were no statistically significant differences between the groups. Higher scores concerning kidney-specific domains were associated with higher scores at baseline.

  As the authors point out, after 12 months of using TOL, patients showed improvement in bodily pain scores. In addition, their physical functioning score was higher than in the general population of Switzerland. The group that did not use TOL had a lower overall health score than the general population and a higher bodily pain score.

  According to the data presented in the paper, the ANCOVA results for the SF-36 and KDQOL-SF questionnaires, after adjusting for relevant factors (i.e. baseline, gender and age), showed no effect of TOL on health-related quality of life after 12 months of follow-up. The exception was patient satisfaction with treatment, which was higher in the TOL treatment group.

- Urine parameters

  According to the data presented in Bargagli (2020), after 12 months of follow-up, the median change in urinary parameter values from baseline for most of the parameters assessed was greater in the TOL treatment group than in the group without TOL. However, based on the available data, inference of statistical significance for differences between groups was not possible.

  The authors of the paper additionally performed analyses of the associations between tolvaptan treatment and urinary parameters relevant to kidney stone formation using linear mixed-effects regression. The multivariate analysis was adjusted for age, sex, body mass index, eGFR, endogenous net acid production estimated by NAE and height-adjusted TKV. In both the unadjusted and multivariate analysis, treatment with tolvaptan was significantly associated with lower relative supersaturation ratios for calcium oxalate, brushite and uric acid, higher urine volume, plasma copeptin and net gastrointestinal alkali absorption (NGIA) and lower NAE. In addition, in the unadjusted analysis, tolvaptan was associated with higher urine pH and urine oxalate excretion and lower urine ammonium excretion, but these associations were no longer significant after multivariable adjustment. After multivariable adjustment, higher urine citrate and urine calcium excretion became significantly associated with tolvaptan treatment.

Safety

<u>Evaluation of the safety of TOL versus BSC based on TEMPO 3:4 outcomes</u>

The safety analysis of TOL versus BSC in adult ADPKD patients was based on the outcomes of TEMPO 3:4, a randomised, double-blind trial (Torres 2012). The results were supplemented with additional data for TEMPO 3:4 from the 2015 EMA report.

TEMPO 3:4 involved a larger patient population than the target population considered in this analysis. Therefore, in addition, the report also includes data from TEMPO 3:4 on patients in the target population (i.e. patients with

CKD stage 2 or 3 at treatment baseline) from Torres (2016), which presented the post-hoc analysis results of TEMPO 3:4 according to CKD stage at baseline of TEMPO 3:4.

The TEMPO 3:4 trial duration was 36 months.

Safety was evaluated against the following endpoints:

- Death

  Over 36 months in TEMPO 3:4, there were no patient deaths in the treatment or control group.

- Serious adverse events

  In the general population of patients participating in TEMPO 3:4, during the 36-month period, total serious adverse events (SAEs) occurred slightly less frequently in the treatment group than in the control group (i.e. 18.4% and 19.7% of patients, respectively). However, the difference between the groups was not statistically significant.

  In TEMPO 3:4, the TOL treatment group showed a lower incidence of SAEs associated with ADPKD worsening or ADPKD complications, i.e. urinary tract infection, pyelonephritis, renal pain, hypertension and renal cyst haemorrhage. However, there were no statistically significant differences between groups for most reported events within the individual SAE categories considered. A statistically significant difference (in favour of the control group) was noted only for the incidence of adverse events related to anaphylactic reactions (these events were reported in 1.0% of patients in the TOL group and 0.2% of patients in the control group).

- Adverse events (selected for which there were statistically significant differences between TOL vs BSC)

  - ✓ Total adverse events

    In total, adverse events (AEs) occurred with similar frequency in the treatment and control groups (i.e. 97.9% of patients in the TOL group and 97.1% of patients in the control group, respectively) Severe AEs in TEMPO 3:4 were also reported in a similar proportion of patients in the treatment and control groups (the difference between the groups was not statistically significant).

    Both the general patient population participating in TEMPO 3:4 and the analyses of patient subgroups with CKD stage 2 and 3 showed that AEs leading to discontinuation of participation in the trial was reported more frequently in the treatment group than in the control group, and the difference between the groups was statistically significant (in favour of the control group).

  - ✓ Infections and infestations

    The incidence of AEs considered parasitic infections and infestations was mostly similar in the treatment and control groups of TEMPO 3:4. Statistically significant differences between the groups (in favour of the treatment group) were noted for the incidence of urinary tract infections in the general population and the subgroup of patients with CKD stage 3 at baseline of TEMPO 3:4, and the incidence of renal cyst infection in the general population. No statistically significant differences between groups were found for the other analysed events in terms of infections and infestations.

  - ✓ Metabolic and nutritional disorders

    Over 36 months in TEMPO 3:4, hyperglycaemia was statistically significantly less frequent in the treatment group than in the control group (0.6% and 2.1% of patients, respectively). However, polydipsia, decreased appetite, hyperuricaemia, hyperglycaemia/new-onset diabetes and hypernatraemia were more frequent in the treatment group than in the control group, and the difference between groups for the listed events was statistically significant (in favour of the control group). No significant difference between groups was noted in terms of the incidence of hypercholesterolemia, dehydration and gout.

  - ✓ Arrhythmias

In TEMPO 3:4, arrhythmia-related events were reported a higher proportion of patients in the treatment group than the control group, and the difference between groups was statistically significant in favour of the control group. In contrast, myocardial infarction and chest pain occurred in a similar proportion of patients in the treatment and control groups (the difference between groups was not statistically significant).

- ✓ Gastrointestinal disorders

  The incidence of adverse events considered gastrointestinal disorders was mostly similar in the treatment and control groups of TEMPO 3:4. Statistically significant differences between groups (in favour of the control group) were noted only for the incidence of dry mouth, constipation and indigestion. No statistically significant differences between groups were found for the other analysed events.

- ✓ Hepatic and biliary disorders

  The incidence of adverse events considered hepatic and biliary disorders was mostly similar in the treatment and control groups of TEMPO 3:4. A statistically significant difference between the groups (in favour of the control group) was noted only for the incidence of liver function abnormalities leading to discontinuation of participation in the trial (this event was reported in 0.6% of patients in the treatment group and did not occur in any patient in the control group). No statistically significant differences between groups were found for the other analysed events.

- ✓ Skin and subcutaneous tissue disorders

  In TEMPO 3:4, dry skin, eczema and rash were reported a higher proportion of patients in the treatment group than the control group, and the difference between groups was statistically significant in favour of the control group. On the other hand, pruritus occurred in a similar proportion of patients in the treatment and control groups (the difference between groups was not statistically significant).

- ✓ Musculoskeletal and connective tissue disorders

  The incidence of adverse events considered musculoskeletal and connective tissue disorders was mostly similar in the treatment and control groups of TEMPO 3:4. Statistically significant differences between groups (in favour of the treatment group) were noted only for the incidence of back pain (this event was reported in 13.7% of patients using TOL versus 18.2% of patients in the control group). No statistically significant differences between groups were found for the other analysed events.

- ✓ Renal and urinary tract disorders

  Over 36 months in TEMPO 3:4, ADPKD-related adverse events (i.e. renal pain and haematuria) were less frequent in patients who received tolvaptan than in the control group. The difference between the groups was statistically significant in favour of the treatment group for the incidence of renal pain in the general population and the subgroup of patients with CKD stage 3, and the incidence of haematuria in the general population.

  While polyuria (including cases leading to discontinuation of trial participation), nocturia and pollakiuria (including cases leading to discontinuation of trial participation) were statistically significantly more often in the TEMPO 3:4 treatment group than in the control group. As indicated in the 2015 EMA report, adverse events related to increased water loss (including polyuria, nocturia) in the treatment group were observed more frequently during the first 3 months of therapy than during maintenance treatment.

  No statistically significant differences between groups were found for the other adverse events reported in the trial under renal and urinary tract disorders.

- ✓ General disorders and administration site conditions

  Over 36 months in TEMPO 3:4, fever occurred in 4.4% of patients using TOL and 8.7% of patients in the control group. The difference between the groups was statistically significant (in favour of the treatment group). Thirst (general population and subgroups of patients with

CKD stage 2 and 3) and fatigue (general population) were statistically significantly more frequent in the treatment group than in the control group. No statistically significant differences between groups were found for the other adverse events reported in the trial and analysed under general disorders and administration site conditions.

- ✓ Diagnostic tests

  In TEMPO 3:4, adverse events related to increased sodium and increased uric acid were reported in the general population with a statistically significantly higher frequency in the treatment group than in the control group. No statistically significant differences between groups were found for the other adverse events reported in the trial and analysed under abnormalities in diagnostic test results.

- ✓ Injuries, poisonings and complications after surgery

  Over 36 months in TEMPO 3:4, anaphylactic reactions were reported slightly more frequently in the treatment group than in the control group, but the difference between groups was statistically significant (in favour of the control group). In contrast, desmectasis occurred less frequently in the treatment group than in the control group, but the difference between groups was not statistically significant.

- Laboratory parameters

  - ✓ Laboratory parameter values

    In TEMPO 3:4, mean serum sodium concentration (in the additional post-treatment follow-up period) and blood urea nitrogen (after 36 months and in the additional post-treatment follow-up period) were statistically significantly lower in the TOL treatment group compared to the control group.

    In contrast, mean serum sodium and uric acid concentration (after 36 months) and ALT activity (in the additional post-treatment follow-up period) were higher in the treatment group than in the control group, and the difference between the groups was statistically significant.

    No statistically significant differences between groups were found for the other analysed laboratory parameters.

    In addition, as indicated by the study authors, there were no statistically significant differences between the groups with regard to the mean change in body weight, (systolic and diastolic) blood pressure and heart rate.

    The 2015 EMA report stated that in the general patient population of TEMPO 3:4 after 36 months of treatment, the mean change in serum glucose from baseline was 0.90 mg/dl in the treatment group and -0.36 mg/dl in the control group. However, the difference between the groups was not statistically significant.

  - ✓ Frequency of potentially clinically significant change in laboratory parameters

    In TEMPO 3:4, potentially clinically relevant increases in serum creatinine and blood urea nitrogen were reported less frequently during 36 months of therapy in the treatment group than in the control group, and the difference between groups was statistically significant in favour of the studied intervention.

    Potentially clinically significant increases in serum sodium and uric acid levels (in the general population and patients with CKD stage 2 and 3) and increases in ALT activity (in the general population and patients with CKD stage 2) and increases in AST activity (in the general population and patients with CKD stage 2), on the other hand, occurred statistically significantly less frequently in the control group than in the treatment group.

<u>Evaluation of the long-term safety of TOL based on TEMPO 4:4</u>

The analysis of the long-term safety of TOL in adult ADPKD patients was based on TEMPO 4:4 (Torres 2018), an open-label extension of TEMPO 3:4 that included patients who completed TEMPO 3:4.

The total duration of TOL exposure of patients was 60 months (combined for TEMPO 3:4 and TEMPO 4:4 trials) because patients participating in TEMPO 4:4 continued TOL treatment after TEMPO 3:4 ended.

The analysis included results for patients who continued TOL treatment (the group of patients who took a placebo in TEMPO 3:4 and then started TOL in TEMPO 4:4 were excluded).

The analysis was based on the following endpoints:

- Death

  Over 24 months in TEMPO 4:4, there were 4 deaths in patients continuing TOL treatment. Causes of death included cardiac arrest, gunshot wound, intracranial aneurysm and subarachnoid haemorrhage.

- Serious adverse events

  Over 24 months in TEMPO 4:4, at least one serious adverse event was reported in 89 (16.0%) patients continuing TOL treatment.

- Treatment-emergent adverse events

  Over 24 months in TEMPO 4:4, in total, adverse events were reported in 516 (92.6%) patients in the group continuing TOL treatment. In contrast, adverse events leading to discontinuation of trial participation occurred in 30 (5.4%) patients.

  Thirst (46.7% of patients), polyuria (41.1% of patients), hypertension (28.7% of patients), nocturia (25.5% of patients) and renal pain (17.6% of patients) included the most common adverse events reported. Other reported adverse events occurred in TEMPO 4:4 not more frequently than in approximately 11.0% of patients.

Evaluation of the safety of TOL versus BSC based on REPRISE

The safety of tolvaptan versus best supportive care in ADPKD patients in the general population was evaluated using results from the double-blind phase of the randomised REPRISE trial (Torres 2017). The results were supplemented with additional data for REPRISE from the 2018 EMA report.

The double-blind treatment period was 12 months.

Safety was evaluated against the following endpoints:

- Death

  Over 12 months in the trial, there was one death reported in the PLC+BSC group. No death occurred in any patient in the TOL+BSC group. The difference between the groups was not statistically significant. No deaths due to adverse events were reported in any group.

- Serious adverse events

  Serious treatment-emergent adverse events were statistically significantly more frequent in the TOL+BSC group (12.5% of patients) than in the PLC+BSC group (8.8% of patients). Serious liver-related events, i.e. those corresponding to one of the five Standardised MedDRA Queries used, were also statistically significantly more frequent in the treatment group (4.6% of patients in the treatment group vs 0.6% of patients in the placebo group).

  The analysis performed by the EMA for serious adverse events of special interest indicated a higher incidence of abnormalities in diagnostic test results in the treatment group than in the control group. Elevation of liver enzymes and ALT activity occurred in 1.6% and 0.1% and 1.2% and 0% of patients in the TOL+BSC and PLC+BSC groups, respectively. The differences between groups were statistically significant (in favour of the control intervention).

  The other serious adverse events reported in the trial occurred in less than 0.6% of patients in each group, and the differences between groups were not statistically significant.

  According to the data indicated in the 2018 EMA report, the intensity of serious adverse events was mostly rated as severe.

- Adverse events

Adverse events were reported in most patients in both the treatment (85.3%) and control (82.3%) groups. All reported adverse events emerged during the trial. Significantly, the intensity of events in most cases was defined as "other than severe" (83.6% of patients in the TOL+BSC group and 81.2% of patients in the PLC+BSC group). There were no statistically significant differences between groups for the incidence of total adverse events, severe adverse events, or adverse events other than severe.

Patients using TOL were more likely to discontinue treatment due to adverse events than patients in the control group (9.5% vs 2.2%). Treatment was discontinued by 2.1% of patients in the TOL+BSC group due to adverse events related to water loss compared to 0.1% in the control group. Liver-related adverse events were the reason for medication discontinuation in 1.6% of cases in the treatment group and 0.1% in the control group. The differences between groups were statistically significant (in favour of the control group).

Among the adverse events that were statistically significantly more frequent in the TOL+BSC group than in the PLC+BSC group were liver-related events (10.9% vs 5.3%, respectively). In the TOL+BSC treatment group, thirst was present in 4.0% of patients and 1.9% of patients in the PLC+BSC group, while polydipsia was present in 1.8% and 0.4% of patients, respectively. There were statistically significant differences between groups in disfavour of the studied intervention. Diarrhoea (6.9% vs 3.4%), polyuria (5.3% vs 1.6%), nocturia (4.7% vs 1.8%) and fatigue (6.8% vs 3.5%) were also significantly more frequent in patients in the treatment group compared to the control group. Elevated ALT activity was statistically significantly more frequent in the treatment group (3.7% of patients) than in the control group (1.3% of patients). Elevated liver enzymes (2.5% vs 0.4%) and blood uric acid level (1% vs 0%) were also statistically significantly more common in the treatment group compared to the control group.

Among other adverse events, renal pain (16.6% of patients in the TOL+BSC group vs 19.0% of patients in the PLC+BSC group), hypertension (10.7% and 11.5% in the treatment and control groups, respectively) and viral upper respiratory tract infection (10.6% vs 12.3%) were the most common adverse events. Despite the numerical superiority in the treatment group, the differences between groups were not statistically significant. Other adverse events occurred in less than 10% of patients, and there were no statistically significant differences between groups.

No cases of glaucoma were reported in either group during the trial. In contrast, skin cancer was more common in the control group than in the treatment group; however, the number of cases was small (no data shown in the retrieved documents).

- Laboratory parameters

  Patients in the TOL+BSC group were statistically significantly more likely than those in the PLC+BSC group to have ALT elevated above 3 x GGN (5.6% vs 1.2%, respectively), ALT elevated above 5 x GGN (3.4% vs 0.7%, respectively), and AST elevated above 3 x GGN (3.5% vs 0.9%, respectively).

  In contrast, patients in the control group were more likely to have elevated blood urea nitrogen levels (31.8% vs 23.9%, respectively), elevated creatinine levels (18.8% vs 6.8%, respectively) and decreased sodium levels (2.6% vs 1.2%, respectively). The differences between groups were statistically significant (in favour of the studied intervention).

  No statistically significant differences between groups were found for the other abnormalities in laboratory parameters considered in the trial.

<u>Additional efficacy and safety analysis</u>

According to the Jinarc SmPC, the prevalent adverse reactions (i.e. ≥1/10) include polydipsia (increased thirst), headache, dizziness, diarrhoea, dry mouth, nocturia, pollakiuria, polyuria, fatigue and thirst.

On the websites of institutions monitoring the safety of medicinal products (Office for Registration of Medicinal Products, Medical Devices and Biocidal Products [Pol. URPL]; European Medicines Agency [EMA] and the United States Food Food and Drug Administration (FDA)), no notices or information relating to the technology named in the application were found.

Limitations

The reliability of the results presented is mainly affected by the following:

- the trials included in the analysis involved a broader population of patients than stated in the application (i.e. patients with CKD stage 1 to 3 In TEMPO 3:4, patients with CKD stage 2 to 4 in REPRISE and patients with CKD stage 1 to 5 in the Bern ADPKD registry);
- in TEMPO 4:4, all patients received TOL. Long-term data are therefore presented only for the group of patients continuing TOL treatment. Due to the lack of long-term data for the comparator, it is not possible to perform a long-term comparative assessment of the efficacy and safety of TOL relative to the comparator considered in this analysis;
- part of the results of TEMPO 3:4 have not been published in full, so data from the 2015 and 2018 EMA reports are presented as part of the analysis;
- some of the TEMPO 3:4 data presented in the report originate from post-hoc analyses;
- some of the trial results included in the analysis were read from figures, which involves a risk of uncertainty regarding the reliability of these data.

Proposed risk-sharing scheme

No risk-sharing scheme was proposed.

Economic evaluation, including estimates of cost to health outcomes achieved

Economic evaluation involves estimating and comparing the costs and health outcomes that may be associated with using the new therapy for an individual patient in place of already reimbursed therapies.

The costs of therapy are estimated in the currency of our country, and health outcomes are usually expressed in life-years gained (LYG) or quality-adjusted life years (QALY) as a result of the therapy.

By comparing the cost and outcome values of the new therapy to the costs and outcomes of already reimbursed therapies, one can answer the question of whether the health outcome achieved for an individual patient with the new therapy is associated with a higher cost compared to already reimbursed therapies.

The obtained results of the cost to health outcome ratio are compared with the use of the so-called break-even point, i.e. a result that indicates that given the wealth of our country (expressed in GDP), the maximum cost of the new therapy that is expected to produce a unit of health outcome (1 LYG or 1 QALY) compared to already available therapies should not exceed three times the GDP per capita.

Currently, the break-even point is PLN 155,514 (3 x PLN 51,838).

The cost to health outcome ratio does not estimate or determine the value of life, it only enables its assessment and, among others, on this basis, choose the therapy related to potentially the best outcome.

The cost-effectiveness of tolvaptan (Jinarc medicinal product) to slow cyst formation and progression of renal impairment in autosomal dominant polycystic kidney disease in adults with chronic kidney disease stage 2 or 3 at baseline who have rapid disease progression was carried out using cost-utility analysis *(CUA)* and cost-effectiveness analysis *(CEA)*. The intervention indicated in the application was compared to best supportive care (BSC).

Analysis assumptions:

- public payer perspective (NFZ), joint perspective (NFZ+patient, same as NFZ perspective),
- lifetime time horizon (80 years),
- costs included: tolvaptan therapy; monitoring; nephrology outpatient clinic visits; CKD treatment; vascular access; end-stage renal disease treatment.

According to the applicant's estimates, the use of tolvaptan in place of BSC is (trade secret). The estimated incremental cost-utility ratio (ICUR) for TOL vs BSC comparison was (trade secret). On the other hand, the estimated incremental cost-effectiveness ratio (ICER) for TOL vs BSC comparison was (trade secret). These values are within the (trade secret) profitability threshold referred to in the Reimbursement Act (i.e. PLN 155,514).

The value of the official selling price of Jinarc medicinal product at which the cost of its use is not higher than the cost of using the optional reimbursable technology with the most favourable ratio of health outcomes to the cost of getting them is, respectively:

- For the 45 mg + 15 mg package – (trade secret),
- For the 60 mg + 30 mg package – (trade secret),
- For the 90 mg + 30 mg package – (trade secret).

The sensitivity analysis included unidirectional and multidirectional analysis.

As part of the unidirectional sensitivity analysis, the applicant conducted a stress-value and scenario analysis for changes in the 30 parameters that most affect the cost-effectiveness estimate.

(trade secret)

According to the results of the multivariate sensitivity analysis (trade secret)

Limitations

The limitations of the economic analysis are mainly due to the limitations of the clinical analysis and the clinical trials included.

Indication whether the circumstances referred to in Art. 13 sec. of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs intended for particular nutritional uses and medical devices (Journal of Laws of 2020, item 357, as amended).

If the applicant's clinical analysis does not include randomised clinical trials proving the superiority of the drug over health technologies already reimbursed in a particular indication, the official sales price of the drug must be calculated in such a way that the cost of use of the drug whose reimbursement is applied for is not higher than the cost of health technology with the most favourable ratio of obtained health outcome to the cost of obtaining them.

In view of the finding of a randomised trial demonstrating the superiority of TOL over BSC, in the Agency's opinion, the circumstances of Art. 13 of the Reimbursement Act do not apply.

Assessment of the impact on the healthcare system, including the impact on the budget of the public payer

The health system impact assessment has two major parts.

First, a payer budget impact analysis allows estimating the potential expenses associated with public funding of the new therapy.

Estimates of expenses associated with the new therapy (the "tomorrow" scenario) are compared to how much is currently spent on treating a health problem (the "today" scenario). On this basis, it is possible to assess whether a new therapy will require more resources to treat a given health problem or is associated with savings in the payer's budget.

A budget impact assessment determines whether a payer has adequate resources to fund a particular technology.

The assessment of health system impact in the second part answers the question of how the decision to fund the new therapy may affect the organisation of service delivery (particularly in the context of adjusting to the requirements of delivering the new therapy) and the availability of other healthcare services.

The budget impact analysis in case of a decision on reimbursement of the medicinal product Jinarc (tolvaptan) used to slow down cyst formation and progression of renal impairment in the autosomal dominant form of polycystic kidney disease in adults with chronic kidney disease stage 2 or 3 at baseline who show rapid disease progression, was performed from the perspective of the public payer (NFZ). The cost of the applied technology was taken into account, except for one of the sensitivity analyses, where (trade secret) was included. The target population was estimated at (trade secret) patients in year 1 and (trade secret) patients in year 2 of the analysis.

According to the results of the budget impact analysis, from the perspective of the NFZ, the issuance of a favourable decision on public financing of the medicinal product Jinarc will entail additional expenses for the public payer in the amount of (trade secret) in the 1st year of reimbursement and (trade secret) in the 2nd year of reimbursement.

The applicant has conducted sensitivity analyses:

(trade secret)

Parameters that affected the result of the primary analysis by at least ±10% included

(trade secret)

Limitations

The main limitation of the above analysis is related to the applicant's assumption regarding the estimation of the population of patients in whom the technology will be used in case of a favourable reimbursement decision. The population was estimated based on, among other things, the proportion of patients with rapidly progressive disease. It should be noted that the inclusion criteria for the population in the reimbursement application are not the same as the criteria presented in the final approved drug programme. They differ with regard to the definition of rapidly progressive disease, and it is, therefore, unclear whether the percentages estimated by the applicant based on the criteria in the original version of the drug programme will be the same as those resulting from the wording of the inclusion criteria in the final approved drug programme.

Comments on the proposed risk-sharing scheme

No risk-sharing scheme was proposed.

Comments on the drug programme

One clinical expert commented on the drug programme regarding the diagnostic tests performed under the programme. According to the expert, it will be safe if the first 18 months, sodium and uric acid levels are also determined in monthly tests (and every 3 months thereafter).

Discussion of the solutions proposed in the rationalisation analysis

The rationalisation analysis aims to identify a mechanism whose introduction will result in the release of public funds in an amount corresponding to at least the increase in costs resulting from a positive decision on reimbursement of the health technology named in the application.

A rationalisation analysis is submitted if the budget impact analysis for the entity responsible for funding shows an increase in reimbursement costs.

As part of the rationalisation analysis, proposed solutions, which offset the NFZ expenditures related to reimbursement of tolvaptan in the evaluated drug programme for most of the scenarios considered. The exception is the variant of sensitivity analysis taking into account (trade secret)

Discussion of recommendations in relation to the evaluated technology

Four clinical recommendations related to the indication named in the application were found:

- Canadian Society of Nephrology (CSN 2018) – CANADA
- Horie 2016 – JAPAN
- Kidney Health Australia – Caring for Australian and New Zealanders with Kidney Impairment (KHA-CARI 2016) – AUSTRALIA
- Spanish Working Group on Inherited Kidney Diseases (SWGIKD 2014) – SPAIN.

All clinical guidelines found focus on symptomatic treatment of ADPKD. Only the more recent ones – Canadian (CSN 2018) Japanese (Horie 2016) guidelines identify tolvaptan as the only therapeutic option that slows the increase in total kidney volume and deterioration of renal function in ADPKD patients with relatively good renal function. With that said, the Canadian guidelines (CSN 2018) recommend tolvaptan for patients:

- meeting TEMPO 3:4 inclusion criteria, i.e. age between 18 and 50 years; TKV > 750 ml; eGFR > 45 ml/min/1.73 m2;
- meeting REPRISE inclusion criteria (referring to patients with enlarged kidneys), i.e. age between 18 and 55 years with eGFR of 25 to 65 ml/min/1.73 m2 or age between 56 and 65 years. with eGFR between 25 and 44 ml/min/1.73 m2 and a history of documented eGFR decline > 2.0 ml/min/1.73 m2/year;
- with chronic kidney disease stages 1–4 (eGFR > 25 ml/min) and a Mayo classification of 1D or 1E. Treatment with tolvaptan may be considered in patients with a Mayo classification of 1C who are under

50 and have a risk factor for disease progression (i.e. annual decline in eGFR of > 2.5 ml/min/1.73 m2/year and/or annual increase in TKV > 5%.

The Australian guidelines (KHA-CARI 2016) only mention that tolvaptan has been shown in a single randomised controlled trial in early-stage ADPKD to reduce the rate of increase in TKV and decline in eGFR (as well as improvement in chronic renal pain). However, probably due to insufficient evidence, its use is not recommended.

In contrast, the Spanish guidelines (SWGIKD 2014) do not mention tolvaptan at all in the recommendations. Bearing in mind that tolvaptan was registered by the EMA in 2015, therefore after the publication date of the above-mentioned guidelines.

The search also yielded 7 reimbursement recommendations relating to the financing of the technology named in the application, including:

- 4 favourable ones
    - ✓ Haute Autorité de Santé (HAS 2015) – France
    - ✓ Haute Autorité de Santé (HAS 2019) – France
    - ✓ Pharmaceutical Benefits Advisory Committee (PBAC 2018) – Australia
    - ✓ Scottish Medicines Consortium (SMC 2016) – Scotland
- 2 conditionally favourable ones
    - ✓ National Centre for Pharmacoeconomics (NCPE 2018) –Ireland
    - ✓ National Institute for Health and Care Excellence (NICE 2015) – UK
- 1 unfavourable one:
    - ✓ Canadian Agency for Drugs and Technologies in Health (CADTH 2016) – Canada.

In summary, the favourable recommendations (HAS 2015 and 2019, PBAC 2018, SMC 2016) mainly note that tolvaptan significantly slowed disease progression in patients with ADPKD who were at increased risk of disease progression and who had relatively preserved renal function.

The conditionally favourable recommendations (NCPE 2018 and NICE 2015) mainly note that clinical evidence has demonstrated the capacity of tolvaptan to reduce the rate of renal function deterioration. Given the above, tolvaptan is expected to delay rather than eliminate the need for renal replacement therapy. Favourable recommendations from NICE are conditional on a reduction in the price of the drug under the risk-sharing scheme and from NCPE on improving the cost-effectiveness of tolvaptan relative to existing technologies in the indication being appraised.

The unfavourable recommendation (CADTH 2016) mainly notes that the use of tolvaptan in patients with ADPKD is associated with significant therapy safety issues, e.g. renal damage, hyponatraemia, increased uric acid levels and gout, polyuria, thirst disorders and skin cancer. In addition, this recommendation indicates that there is insufficient evidence to show that tolvaptan treatment results in improvements in the endpoints of greatest importance to patients.

According to the information provided by the applicant, Jinarc is funded by (trade secret)

Basis for the recommendation

The recommendation was prepared under the order of the Minister of Health of 13 October 2020 (reference number: PLR.4500.239.2020.20.MN, PLR.4500.238.2020.20.MN, PLR.4500.237.2020.20.MN) regarding the preparation of the President's recommendation on the evaluation of the drug Jinarc (tolvaptan), tablets 30mg, 60 mg, 56 tablets, EAN: 05038256002122, Jinarc (tolvaptan), tablets, 15 mg, 45 mg, 56 tablets, EAN: 05038256002115, under the drug programme indicated for: B.33 "Treatment of autosomal dominant polycystic kidney disease (ICD-10 Q 61.2)", pursuant to 35 sec. 1 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs intended for particular nutritional uses and medical devices (Journal of Laws of 2020, item 357, as amended), following Transparency Council Position No. 1/2021 of 4 January 2021 on the evaluation of the drug Jinarc (tolvaptan) under the drug programme "Treatment of autosomal dominant polycystic kidney disease (ICD-10 Q 61.2)"

PRESIDENT

dr n. med. Roman Topór-Mądry

/document signed electronically/

References

1. Stanowisko Rady Przejrzystości nr 1/2021 z dnia 4 stycznia 2021 roku w sprawie oceny leku Jinarc (tolvaptanum) w ramach programu lekowego „Leczenie autosomalnie dominującej postaci zwyrodnienia wielotorbielowatego nerek (ICD-10 Q 61.2)" (The Transparency Council Position No. 1/2021 of 4 January 2021 on the evaluation of the drug Jinarc (tolvaptan) under the drug programme "Treatment of autosomal dominant polycystic kidney disease (ICD-10 Q 61.2)").
2. Raport nr OT.4331.44.2020 „Wniosek o objęcie refundacją leku Jinarc (tolwaptan) we wskazaniu: „Leczenie autosomalnie dominującej postaci zwyrodnienia wielotorbielowatego nerek (ICD-10 Q 61.2)" (Report No. OT.4331.44.2020 "Application to include the drug Jinarc (tolvaptan) in the indication: "Treatment of autosomal dominant polycystic kidney disease (ICD-10 Q 61.2)")" Verification analysis. Date of completion: 23 December 2020