Recommendation No.
122/2021 of 2 November 2021
of the President of the Agency for Health Technology Assessment and Tariff System on the assessment of Kineret (anakinra) in the indication under the drug programme "B.33. Treatment of active rheumatoid arthritis and aggressive course of juvenile idiopathic arthritis (ICD-10 M 05, M 06, M 08)"

The President of the Agency recommends the reimbursement of the following medicinal product:

- Kineret 100 mg/0.67 ml solution for injection in pre-filled syringe with a scale EAN: 07350031442090

in the drug programme "Treatment of active rheumatoid arthritis and aggressive course of juvenile idiopathic arthritis (ICD-10 M 05, M 06, M 08)" in the existing limit group and dispensing it free of charge **provided that [information protected as a trade secret]**

Grounds for the recommendation

The application in question concerns the extension of reimbursement indications for Kineret - if reimbursed, anakinra (ANA) would be an additional reimbursement option for patients with systemic juvenile idiopathic arthritis (SJIA) from the age of 2 and for patients with Still's disease (AOSD) who start treatment under the B.33 drug programme and a new therapeutic option in patient subgroups where there is currently no active standard treatment, i.e.: patients with SJIA from 8 months to 2 years of age and patients with SJIA or AOSD who have experienced treatment failure with drugs reimbursed under the B.33 drug programme.

The applicant made an indirect comparison in relation to tocilizumab (TOC) of patients with SJIA despite the use of glucocorticosteroids (GCSs) and disease-modifying antirheumatic drugs (DMARDs). The results indicate that the use of ANA vs TOC (over a follow-up period of 1-3 months) is associated with a statistically significantly lower probability of achieving a response according to ACRpedi30. There were no statistically significant differences between the compared therapies for the other endpoints assessed, for which an indirect comparison was performed.

In contrast, no randomised trials were found comparing the effects of administering ANA versus PLC (placebo) in the subpopulation of SJIA patients aged 8 months to 2 years or in the patient population who has experienced treatment failure with drugs under B.33 drug programme. Therefore, only results based on available studies for ANA patient groups are presented.

The applicant has adopted tocilizumab (TOC) as a comparator in the population of patients with SJIA from 2 years of age and patients with AOSD who start treatment under the B.33 drug programme. In

the subpopulations of patients with AOSD who experienced treatment failure with almost all drugs reimbursed under the B.33 drug programme, patients with SJIA from 8 months to 2 years of age and patients with SJIA who experienced treatment failure with drugs reimbursed under the B.33 drug programme, the applicant adopted placebo (PLC) as a comparator.

However, two economic comparisons were ultimately performed in the applicant's analysis: in relation to tocilizumab (CMA - cost-minimisation analysis) and in relation to standard treatment (CUA - cost-utility analysis) among all patients in the population (without distinguishing between patients with JIA and patients with AOSD). This approach was justified by the limited availability of clinical data on the analysed patient population (the analysed indication meets the criteria of an ultra-rare disease).

According to the results of the economic analysis, in the general population (patients with JIA and AOSD) in whom ANA would be used as part of the first-line treatment, the use of anakinra instead of tocilizumab, regardless of the perspective adopted (NHF, joint), is [information protected as a trade secret] In the population of patients in whom all possible options available in the B.33 programme were exhausted, the estimated ICUR (incremental cost-utility ratio) for the comparison of anakinra vs comparator amounted, from the NHF perspective, to [information protected as a trade secret] and, from the joint perspective, to [information protected as a trade secret] In the population of treatment, patients under 2 years of age for whom anakinra will be used in the first-line the estimated ICUR for the comparison of anakinra vs comparator amounted, from the NHF perspective, to [information protected as a trade secret] and, from the joint perspective, to [information protected as a trade secret]: [information protected as a trade secret] These values are below the cost-effectiveness threshold referred to in the Reimbursement Act. At the same time, the estimates provided under the CUA are characterised by low reliability.

The budget impact analysis for the applicant indicated an increase in costs for the public payer in the amount of [information protected as a trade secret]. The assumptions of the applicant's analysis may affect the uncertainty of the target population estimation and cause incremental costs to be underestimated.

Three reimbursement recommendations for the use of the technology under this application were identified (positive - French HAS 2019 and Scottish SMC 2018 and 1 conditionally positive - British NICE 2021). In summary, the above-mentioned recommendations underline the lack of data allowing efficacy to be compared with another biological treatment, while pointing out the superiority of ANA over PLC. The 2021 NICE conditional recommendation indicated that the use of ANA should be restricted to patients with AOSD who had an inadequate response to treatment with ≥2 conventional DMARDs and to patients with SJIA aged ≥8 months and weighing ≥10 kg who have failed to respond to ≥d1 conventional DMARD.

In summary, it should be noted that the conclusions of the efficacy of the assessed technology on the basis of available scientific evidence are uncertain. Moreover, the limitations of the applicant's estimates of the cost of anakinra in the proposed patient subpopulations should be taken into account. Nevertheless, according to clinical experts' opinions, the possibility of using the proposed technology responds to an unmet health need and creates opportunities for active treatment in a larger group of patients. Therefore, in view of the above and of the position of the Transparency Council, it is considered justified to finance the therapy under assessment from public funds provided that [information protected as a trade secret]

Furthermore, it is considered reasonable to detail provisions defining the target population for the proposed technology. Among other things, it is advisable to clarify the eligibility criteria so that ANA treatment does not include patients after failure of oral or subcutaneous methotrexate therapy, which was applied for at least 3 months in patients with the presence of poor prognosis factors in accordance with the current EULAR recommendations. In addition, it is suggested to add the assessment of patients' quality of life at eligibility and during treatment monitoring in the programme in order to obtain real data from Polish clinical practice.

Subject of the application

The order of the Minister of Health concerns the assessment of the appropriateness of public reimbursement of the following medicinal product:

- Kineret 100 mg/0.67 ml solution for injection in pre-filled syringe with a scale,
  EAN: 07350031442090, the proposed net sales price is [information protected as a trade secret];

"Treatment of active rheumatoid arthritis and aggressive course of juvenile idiopathic arthritis (ICD-10 M 05, M 06, M 08)".

Proposed payment and dispensing category: patient - free of charge, under the drug programme, in existing limit group 1153.0 Anakinra. [information protected as a trade secret]

Health problem

Juvenile idiopathic arthritis (JIA) is the most common chronic, immune-mediated connective tissue disease of the developmental age. According to the ILAR (International League Against Rheumatism) definition, JIA is a heterogeneous group of arthritis beginning before the age of 16 and lasting at least 6 weeks. According to the 2001 ILAR classification, there are several forms of JIA.

Systemic-onset JIA (SJIA) is characterised by: fever for at least 2 weeks (every day for at least 3 consecutive days), inflammation of ≥ 1 joint and at least one of the following: recurrent skin rashes, generalised lymphadenopathy, liver or spleen enlargement, serositis.

Adult-onset Still's disease (AOSD) is a rare connective tissue disease classified as a systemic form of JIA that presents with fever, rash, lymphadenopathy and splenomegaly, and inflammation of serous membranes and multiple organs in adults.

AOSD and SJIA are defined as the same disease entity, with the distinction being based on the age of the patients - patients under 16 years of age are diagnosed with SJIA, while adult patients with AOSD.

JIA is the most common rheumatic disease of the developmental age. The incidence rate ranges from 1.6 to 23 cases/100,000/year and is the lowest in Asia and the highest in Scandinavian countries. The prevalence rate ranges from 3.8 to as many as 167 (Belgium) and 400 (Australia) cases/100,000. Available epidemiological data for Poland are fragmentary. According to data from Łódzkie and Świętokrzyskie voivodships, the incidence rate was 5-6.5/100,000/year. The annual prevalence rate of SJIA in Poland between 2008 and 2021 was 0.243-0.298 per 1,000 inhabitants. In line with the information provided by experts surveyed by the Agency, patients with SJIA represent approximately 5-10% of all patients with JIA. The annual incidence rate of AOSD is 0.1-1.0/100,000 people aged 16-35.

There is an increased risk of death in patients with JIA, with a mortality rate of 2-4%. In AOSD, the 5-year survival rate is 90-95%.

Alternative health technology

The applicant has adopted tocilizumab (TOC) as a comparator in the population of patients with SJIA from 2 years of age and patients with AOSD who start treatment under the B.33 drug programme.

In subpopulations of AOSD patients who experienced treatment failure with almost all drugs reimbursed under the B.33 drug programme, patients with SJIA from 8 months to 2 years of age and SJIA patients who experienced treatment failure with drugs reimbursed under the B.33 drug programme, the applicant adopted placebo (PLC) as a comparator.

Taking clinical guidelines into account, expert opinions and therapeutic options financed in Poland, the choice of comparators was considered acceptable.

Description of the proposed intervention

Anakinra neutralises the biological activity of interleukin-1α (IL-1α) and interleukin-1β (IL-1β) through the competitive inhibition of binding to the type I interleukin receptor (IL-1RI).

According to the Summary of Product Characteristics (SmPC), Kineret is indicated for use in e.g. adults, adolescents, children and infants aged 8 months and older weighing 10 kg or more suffering from systemic juvenile idiopathic arthritis (SJIA) and adult-onset Still's Disease (AOSD), with active systemic symptoms indicative of moderate to severe disease activity or in patients with persistent disease activity after treatment with non-steroidal anti-inflammatory drugs (NSAIDs) or glucocorticosteroids (GCSs).

The proposed indication matches the registered indication, but is further specified by drug programme selection criteria.

[information protected as a trade secret]

Efficacy, effectiveness and safety assessment

This assessment 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 that health problem. Furthermore, this assessment requires determination of the reliability of data collected and a comparison of the efficacy and safety results of the new therapy against the therapies already available to treat the health problem in question.

On the basis of the above, the efficacy and safety assessment allows answering the question of the scale of the health outcome (both in terms of efficacy and safety) to be expected from the new therapy compared with other therapeutic options under consideration.

The applicant's systematic review included 3 randomised controlled trials (RCTs) including 2 studies used for indirect comparison of ANA and TOC,

- ANA vs PLC in patients with SJIA (ANAJIS study - Quartier 2010): Follow-up period 1 year (RCT phase – 1 month, extended phase 2 to 12 months). Number of patients: 24 (ITT - intention-to-treat analysis) (RCT phase: ANA group N=12, PLC group N=12, extended phase: ANA group N=22). The Cochrane risk-of-bias assessment showed unclear risk in the domains of allocation concealment, selective presentation of results, other factors and no risk in other domains;
- TOC vs PLC in patients with SJIA (TENDER study - Benedetti 2021, Benedetti 2015, Brunner 2020): Follow-up period: RCT phase 12 weeks, open phase up to 5 years; Number of patients: 112 (ITT) (RCT phase: TOC group N=75, PLC group N=37, extended phase: ANA group N=112). The Cochrane risk-of-bias assessment pointed out unclear risk in the domains of randomisation procedure, selective presentation of results, other factors and no risk in other domains;

and 1 comparative study

- ANA vs DMARD in patients with AOSD (NordicAOSD05 - Nordstrom 2012, Schanberg 2020): the follow-up period was 24 weeks. Twenty-two patients with AOSD after prior GCS and/or sDMARD therapy were included in the study.

Furthermore, publications with a lower level of credibility were included in the applicant's review, including:

- concerning SJIA:
  - ✓ Prospective studies, concerning ANA, single-arm: Klein 2019, Gomes 2011, Gattorno 2008, Pascual 2005;
  - ✓ Retrospective, single-arm studies: Gattorno 2011, Naselli 2011, Naselli 2013, Sag 2018, Sag

2019, Zeft 2009, Ohlsson 2008, Pardeo 2013, Pardeo 2015, Pardeo 2021, Saccomanno 2019, Tibaldi 2018, Tibaldi 2019, Giancane 2020;

- ✓ A retrospective study on ANA in a population of patients with various diseases, with isolated results for SJIA: Miettunen 2011;
- ✓ Two-arm studies: Atemnkeng 2020 (ANA not treated biologically/DMARD/GCS vs ANA after biological treatment/DMARD/GCS, Lainka 2021 (ANA vs KAN); o Studies comparing ANA with TOC: Kearsley-Fleet 2019, Shenoi 2017;

- concerning SJIA and AOSD:
  - ✓ Lequerre 2008 (single-arm ANA), Vitale 2016 (ANA vs KAN) retrospective studies;
- concerning AOSD
  - ✓ Two-arm studies comparing ANA vs TOC: Palmou 2015, Riancho- Zarrabeitia 2015, Toz 2015, Toz 2016, Vercruysse 2019, Campochiaro 2020 (in the applicant's clinical analysis Farina 2020);
  - ✓ retrospective study, single-arm (ANA): Vitale 2019, Vitale 2020, Cavalli 2013 Cavalli 2014, Cavalli 2015, Della Torre 2013, Giampietro 2013, Ortiz-Sanjuan 2015, Riancho- Zarrabeitia 2014, Colafrancesco 2017, Iliou 2013, Sfriso 2016, Riera 2011, Ugurlu. 2018, Gerfaud-Valentin 2014, Franchini 2010, Giampietro 2010;
  - ✓ case series descriptions: Naumann 2010, Fitzgerald 2005, Haraoui 2004, Priori 2008, Maria 2014;
- studies included in additional safety assessment (ANA): RCT Ilowite 2009 (residual results in the subgroup of patients with systemic-onset JIA are also presented in the main part of the analysis) and Smith 2018 case report.

The applicant's clinical analysis also considered

- 3 unpublished studies (2005-004008-36, NCT03932344, 2015-004393-16).
- secondary studies:
  - ✓ systematic reviews with meta-analysis: patients with SJIA (Otten et al. 2013, Tarp 2016, Song, 2021); patients with AOSD (Ruscitti 2017, Hong 2014, Ruscitti 2020);
  - ✓ Systematic reviews without meta-analysis: the SJIA patient population (Gartlehner 2008, Swart 2010, Sönmez 2018, Boom 2015, Diamantopoulos 2013, Kuemmerle-Deschner 2019, Anink 2012); 5 concerning the AOSD patient population (Ramos-Casals 2008, Junge 2017, Zhou 2018, Homood 2014, Giacomelli 2021);
- and 12 references included in the additional safety assessment: Kineret's SmPC, summary and full text of 3 EPARs for Kineret, public notice on increased risk of serious infection and neutropenia in patients receiving Kineret and Enbrel concurrently, FDA-approved patient leaflet - Kineret announcement regarding an increased risk of serious infections and neutropenia in patients receiving Kineret and Enbrel concurrently, communication to healthcare professionals regarding complaints associated with Kineret relating to the presence of solid material on the surface of needles, extracts from PRAC (Pharmacovigilance Risk Assessment Committee) recommendations on the new content of Kineret information note for medicinal products, Lareb adverse events report, a cohort study report on adverse reactions to biopharmaceuticals commissioned by the Netherlands Pharmacovigilance Centre Lareb, a summary of adverse event reports submitted to Lareb and the WHO.

Efficacy

<u>Population of patients with SJIA (despite administering GCSs and DMARDs)</u>

According to the results of an indirect comparison, the use of ANA vs TOC (during a follow-up period of 1-3 months) is associated with a statistically significantly lower probability of achieving a response

according to ACRpedi30. There were no statistically significant differences between the compared therapies for the other endpoints assessed, for which an indirect comparison was performed.

On the basis of the summary of results after one month of ANA vs PLC therapy, a statistically significant improvement was observed in the mean change of: ESR, number of joints with active disease process and overall VAS score of disease activity according to the doctor in comparison to initial values. For TOC vs PLC, a significantly statistical improvement in the means of all analysed endpoints was observed after 3 months of therapy compared to initial values. Moreover, the ANAJIS study reported that after one month of treatment with ANA, fever was not observed in any of the 4 patients in whom it was recorded at baseline. On the other hand, in the TENDER study, after 3 months of TOC treatment, fever subsided in 85% of participants who had it at baseline. Twenty-two patients were included in the open-label phase of the ANAJIS study, 16 of whom were treated up to 12 months. Of the 7 persons with response, 6 discontinued treatment with GCSs and in 5 persons, the disease was inactive.

In the Ilowite 2009 RCT, during the 12-week run-in phase after ANA therapy, response was observed in 73% (11 out of 15) of SJIA patients. In contrast, in the blinded phase after 28 weeks of ANA treatment, disease exacerbation was noted in 22% (2 out of 9) of SJIA patients

Patient population with refractory AOSD (after failure of GCSs and DMARDs)

In the NordicAOSD05 RCT (Nordstrom 2012), after 24 weeks of treatment with ANA, the following results were observed: treatment response in 50% (6 out of 12) of the patients, a reduction in mean GCSs dose compared to initial values (by 10.8 mg), a reduction in mean CRP concentration compared to initial values, and an improvement in physical and mental quality of life scores in SF-36 compared to initial values. Discontinuation of GCS was possible in 25% (3 out of 12) of the patients. In the open-label phase of the study, 50% (7 out of 14) of persons achieved remission at week 52 of ANA therapy.

Safety

Population of patients with SJIA (despite administering GCSs and DMARDs)

An indirect comparison of ANA vs. TOC (over a follow-up period of 1-3 months) indicated no statistically significant differences regarding withdrawal from the study for any reason and discontinuation of therapy due to adverse events.

According to the summary of results based on the ANAJIS study, adverse events occurred with similar frequency in the ANA and PLC groups. On the other hand, adverse events were more common in the TENDER study in the TOC group than in the PLC group. However, it is worth considering the differences in the duration of exposure of patients to active treatment (for ANA - 1 patient-year, for TOC - 14.4 patient-years).

No deaths were reported in any of the above randomised phase studies.

In the ANAJIS study, 22 patients had ANA exposure during a total of 182 months of the open-label phase (8 patients were withdrawn from the study between months 1-6). Discontinuation of therapy due to adverse events was reported in 2 (9%) patients, any adverse event in 89% of patients ([5.71] patient-years), serious adverse events in 5% of patients ([0.33] patient-years).

Patient population with refractory AOSD (after failure of GCSs and DMARDs)

In the 2012 Nordstrom study, Grade 1 (n=7/12, 58%) and Grade 2 (n=1/12, 8%) injection site reactions were reported after 24 weeks of ANA treatment. A serious adverse event was also reported in 1 patient. No participant was withdrawn from the study. Injection site reactions were also observed in 4 additional patients in an extended open-label phase of the study lasting 28 weeks.

Additional efficacy and safety analysis

Assessment of effectiveness

Population of patients with SJIA (despite administering GCSs and DMARDs)

This analysis presents efficacy results based on the 2019 Kearsley-Fleet study, where the comparison

with an appropriate comparator was possible. Safety results are presented as a summary based on all studies included in the applicant's analysis.

The 2019 Kearsley-Fleet study indicated that the use of ANA vs TOC (over a follow-up period of 1 year) was associated with a statistically significantly greater improvement in ESR. No statistically significant differences were reported between the compared therapies for other endpoints. Moreover, the study reported that treatment was discontinued due to remission in 1 person in ANA group, failure - 4 in the ANA group and 2 in TOC group, other - 1 person in the TOC group. The Kearsley-Fleet 2019 study reported that treatment was discontinued due to adverse events: in 4 (18%) patients in the ANA group (gastric cramps and diarrhoea, injection site reaction - patient switched to ETA therapy, difficulty with daily injections - 2 patients switched to TOC therapy) and 3 (6%) patients in the TOC group (drug-induced worsening of rash, neutropenia and active MAS - the patient was switched to ANA therapy).

In the Atemnkeng 2020 study, 51 people (11 in first-line and 40 in second-line) received ANA at some point during treatment. After one year of ANA therapy, minimal disease activity according to JADAS was observed in 62% of the patients, remission according to JADAS in 45% and inactive disease according to ACR in 65% of the patients. A statistically significant improvement in mean JADAS10 scores (from 11.4 to 1.1, p=0.0014) was observed in second-line ANA treatment compared with initial values. In the last follow-up period after second-line ANA treatment, 60% of patients had minimal disease activity according to JADAS, 45% had remission according to JADAS and 70% had inactive disease according to ACR. There was also a statistically significant improvement after three months of ANA second-line treatment in clinical parameters: CRP (p=0.03) and ESR (p=0.02) compared to initial values. There was also an improvement in physical disability scores according to CHAQ-DI (0.8 ± 1 at baseline to 0.4 ± 0.8 when assessed for the last time). Second-line ANA therapy was discontinued by 20 (50%) patients due to failure (n=12), remission (n=7) and serious adverse event (n=1).

Eighty-four children with SJIA were treated in the Leinka 2021 ANA study. The therapy lasted for 34 (range: 6-116) months. ANA therapy reduced or managed systemic disease symptoms in 95% (n=80/84) of the children. Absence of symptoms was observed in 23% of patients. CRP levels returned to normal in 16 out of 83 patients who received ANA. Inactive disease according to the Wallace criteria could be determined for 28 out of 55 children (51%) who received ANA at any time during the 12-month period. The time from the first documented inactive disease was 89 days (range: 7-260). During ANA therapy, 24% (n=13/55) of the children achieved disease remission for ≥6 months. The following were observed: good clinical response in 68% (n=54/80) of persons, poor clinical response in 27% (n=22/80), intermediate response in 5% (n=4/80). 61% (51/84) of patients discontinued ANA therapy due to no response (16/51), good clinical response (15/51), change of study (10/51), short-term on-demand therapy (3/51), adverse events (2/51), trypanophobia (2/51) and other, unknown (3/51).

Permanent discontinuation of ANA therapy due to adverse events was reported in: 2.5-31% of the persons (Atemnkeng 2020, Leinka 2021, Zeft 2009, Saccomanno 2019).

The most common adverse events after ANA therapy included: injection site reactions, infections (e.g. reactivations of latent viruses, upper respiratory tract, gastrointestinal infection), skin reactions, elevated transaminases, neutropenia, headache, trypanophobia, proteinuria, haematuria, urticaria, acne, gastrointestinal disorders, blood and lymphatic disorders (Gattorno 2008, Pascual 2005, Pardeo 2005, Atemnkeng 2020, Leinka 2021, Lequerre 2008, Zeft 2009).

Serious adverse events following ANA included injection site reactions, macrophage activation syndrome, fever, visceral leishmaniasis, and elevated liver enzymes (Gattorno 2008, Atemnkeng 2020, Lequerre 2008, Saccomanno 2019, Zeft 2009).

Patient population with refractory AOSD (after failure of GCSs and DMARDs)

This recommendation presents efficacy results based on studies: Campochiaro 2020 and Vitale 2019, where it was possible to compare or contrast ANA results with TOC. Safety results are presented as a summary based on all studies included in the applicant's analysis.

In the 2020 Campochiaro study, 42 patients were treated with ≥1 biopharmaceutical (79 courses of therapy in total). ANA was the most common treatment that the participants received (mainly as first-line treatment), followed by TOC. One biopharmaceutical was received by 21 patients, 2 biopharmaceuticals by 11, 3 biopharmaceuticals by 6, 4 biopharmaceuticals by 3 and 6 biopharmaceuticals by 1 person. The median duration of biological treatment was 12 months (IQR: 6-56).

The percentage of patients with an overall response was comparable between ANA and TOC (73% vs 81%, p=1.000). At the time of initiation of biological treatment, all participants received GCSs. The percentage of patients who discontinued GCSs was comparable between ANA and TOC (46% vs 52%, p=0.789). In total, ANA therapy was discontinued at 24 months in 37% of the patients and TOC in 29% of the patients. The most common reasons for treatment discontinuation included treatment ineffectiveness (24% in the ANA group vs 14% in the TOC group) and the occurrence of adverse events (10% each in the ANA and TOC groups).

In the Campochiaro 2020 study, treatment was discontinued due to adverse events by 10% each in the ANA and TOC groups. ANA therapy was discontinued due to injection site reactions, while TOC treatment was discontinued due to neutropenia and anaphylaxis.

According to Vitale 2019, ANA was administered for an average of 35.96 (±36.05, median=23) months. ANA treatment was provided to 141 patients who had previously received NSAIDs (69%), GSK (98%), sDMARDs (86%) and biopharmaceuticals (21%). ANA treatment was discontinued due to adverse events in 18% (25/141) of the persons, long-term remission (permanent disappearance of all clinical and serological changes) in 14% (20/141) of the persons, and primary and secondary efficacy failure in 11% (16/141) and 8% (11/141) of the persons, respectively. Cumulative risk of loss of ANA efficacy was estimated to be 3% during the first 12 months of therapy, 14% when assessed after 60 months and 18% after 120 months.

Permanent discontinuation of ANA therapy due to adverse events in 7-13% of patients (Giampietro 2013, Ortiz-Sanjuan 2015, Lequerre 2008).

In the median follow-up (16 months-5 years) after ANA therapy, the most frequently observed adverse events/effects were: injection site reactions, skin lesions (e.g. rash), infections (including: pneumonia, hepatitis virus reactivations), leukopenia, angioedema, macrophage activation syndrome (Cavalli 2015, Ortiz-Sanjuan 2015, Naumann 2010, Giampietro 2013, Lequerre 2008).

Three deaths were reported (due to macrophage activation syndrome, myocarditis and congestive cardiomyopathy) (Vitale 2016).

Information based on SmPC

According to the Kineret SmPC, the most commonly reported adverse reaction in all PLC-controlled ANA post-therapy studies conducted in rheumatoid arthritis patients was injection site reactions, most of mild to moderate severity. Very common adverse reactions (≥ 1/10) included headache, increased cholesterol and injection site reactions.

Information on the basis of safety communications for Taltz administration on the websites of the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPL), the European Medicines Agency (EMA) and the United States Food and Drug Administration (FDA)

No safety communications for Kineret administration were found on EMA, FDA, URPL websites.

Limitations

The main limitations of the analysis are related to the following aspects:

- There is a lack of randomised trials, in both SJIA and AOSD populations, directly comparing the efficacy and safety of ANA and TOC. Therefore, an indirect comparison by placebo was performed, which is characterised by limitations;

- no randomised trials were found comparing effects of ANA versus PLC in the subpopulation

of SJIA patients aged 8 months to 2 years as well as in the population of patients after failure of the B.33 drug programme. Therefore, results are presented based on the available studies for ANA patient groups;

- in the studies included in the analysis, heterogeneity was identified regarding inclusion criteria, patient numbers, follow-up periods, definition of endpoints assessed (response to treatment), prior treatment, severity of disease symptoms, therapies concomitantly used with ANA in observational studies making it difficult to unambiguously attribute the identified studies to the subpopulations of AOSD patients identified within the proposed indications.

Summing up, conclusions on the efficacy and safety of ANA on the basis of the available scientific evidence are burdened with uncertainty.

Indication whether the circumstances referred to in Art. 13 sec. 3 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional uses and medical devices (Dz. U. /Journal of Laws/ of 2021, item 523) do arise.

If the applicant's clinical analysis does not include randomised clinical trials proving the superiority of the drug over health technologies already reimbursed, the official selling price of the drug must be calculated so that the cost of the drug to be reimbursed is not higher than the cost of the health technology with the most favourable cost–effectiveness ratio.

Comparison: anakinra vs tocilizumab

Clinical analysis does not include randomised clinical trials proving the superiority of the technology applied for over the comparator and therefore, in the Agency's opinion, the circumstances of Art. 13 of the Act on Reimbursement do arise.

The net official selling price at which the cost of the two therapies over a one-year horizon is equal is [information protected as a trade secret] per unit pack of Kineret (anakinra).

Comparison: anakinra vs placebo

Given that there are no reimbursed active comparators in the patient population in which all possible options available in the B.33 programme have been exhausted and in the patient population below 2 years of age in which anakinra will be used as the first-line treatment, the Agency is of the opinion that the circumstances of Art. 13 of the Act on Reimbursement do not arise.

Economic evaluation, including a cost-effectiveness estimation

Economic evaluation involves estimating and comparing the costs and health outcomes that may be associated with the administration of the new therapy to an individual patient instead of already reimbursed therapies.

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

Juxtaposing the values concerning the costs and outcomes of a new therapy and comparing them to the costs and outcomes of already reimbursed therapies allows answering the question of whether the health outcome achieved in an individual patient owing to a new therapy is associated with a higher cost in comparison with already reimbursed therapies.

The obtained results of the cost-effectiveness ratio are compared with the so-called cost-effectiveness threshold, a score that signals that given our country's affluence (expressed in GDP), the maximum the cost of a new therapy to be associated with a unit health outcome (1 LYG or 1 QALY) compared to therapies already available should not exceed three times GDP per capita.

Currently, the cost-effectiveness threshold amounts to PLN 155,514.00 (3 x PLN 51,838.00).

The cost-effectiveness ratio does not estimate or determine the value of life, but it only enables its assessment and on that basis, among other things, choosing the therapy related to potentially best

outcome.

The cost-effectiveness of anakinra (Kineret) therapy for the treatment of systemic forms of juvenile idiopathic arthritis and AOSD in adults in Poland was assessed using cost-utility analysis (CUA) for the comparison of ANA versus standard treatment and cost-minimisation analysis (CMA) for the comparison of ANA vs tocilizumab.

Assumptions of the analysis:

- comparators:
    - tocilizumab (TOC): in patients with JIA aged ≥ 2 and patients with AOSD, in whom anakinra would be used as the first drug in the programme;
    - standard treatment (ST): in patients with JIA aged 8 months to 2 years for whom anakinra would be used as the first drug in the programme; in patients with JIA and patients with AOSD for whom all possible options available in the B.33 programme have been exhausted;
- public payer perspective (NHF) and joint perspective (NHF and the patient);
- time horizon: CUA over a lifetime horizon (66 years), CMA over a one-year horizon;
- Included costs: drugs, administration of drugs, diagnostics, additional medical care (cost of outpatient visits outside the programme, cost of treatment in threatening and present complications of macrophage activation syndrome (MAS), cost of Bone Marrow Transplant (BMT).

However, two economic comparisons were ultimately performed in the applicant's analysis: in relation to TOC and in relation to ST among all patients in the population (without distinguishing between patients with JIA and patients with AOSD). This approach was justified by the limited availability of clinical data on the analysed patient population (the analysed indication meets the criteria of an ultra-rare disease).

<u>CMA results: anakinra vs tocilizumab</u>

General population (patients with JIA and AOSD) in whom ANA would be used as first-line treatment

According to applicant's estimates, replacing tocilizumab with anakinra, regardless of the perspective adopted (NHF, joint), is [information protected as a trade secret]

The net sales price at which the cost of the two therapies equalises over a one-year horizon is [information protected as a trade secret] per unit pack of Kineret (anakinra). The estimated thresholds are [information protected as a trade secret] than the proposed net sales price.

<u>CUA results: anakinra vs standard treatment (ST)</u>

Population of patients for whom all possible options available under the B.33 programme have been exhausted

According to the applicant's estimates, the use of anakinra instead of a comparator, in the population of patients for whom all possible options available in the B.33 programme have been exhausted, is [information protected as a trade secret]

The estimated ICUR for the comparison between anakinra and comparator was from the NHF perspective [information protected as a trade secret] and from the joint perspective [information protected as a trade secret] The values are [information protected as a trade secret] the cost-effectiveness threshold referred to in the Act on Reimbursement.

The net sales price at which the cost of the two therapies equalises over a one-year horizon is [information protected as a trade secret] per unit pack of Kineret (anakinra).

The population of patients younger than 2 years of age for whom anakinra will be used as first-line treatment

According to the applicant's estimates, the use of anakinra instead of a comparator, in a population of patients aged less than 2 years in which anakinra would be used as the first drug in the programme, is [information protected as a trade secret]

The estimated ICUR for the comparison of anakinra vs comparator amounted, from the NHF perspective, to [information protected as a trade secret] and from the joint perspective: [information protected as a trade secret] These values are [information protected as a trade secret] the cost-effectiveness threshold referred to in the Act on Reimbursement.

With the ICUR value estimated in the basic analysis, the applicant's estimate of the threshold net sales price of Kineret (anakinra) at which the cost of an additional quality-adjusted life year is equal to the threshold amount referred to in Art. 12 point 13 and Art. 19 sec. 2 point 7 of the Act is [information protected as a trade secret]. The estimated thresholds are [information protected as a trade secret] than the proposed net sales price. The CUA is based on the assumption of comparable efficacy of ANA in first- and last-line biological treatment; moreover, the data are from the ANAJIS study (which did not include patients aged 8 months to 2 years), so the result is burdened with considerable uncertainty

The applicant conducted deterministic (a total of 45 scenarios for the comparison of anakinra vs tocilizumab and 89 scenarios for the comparison of anakinra vs placebo) and probabilistic sensitivity analyses.

Comparison: anakinra vs tocilizumab

According to the applicant's estimates, the greatest impact on incremental costs related to the use of ANA instead of TOC and on changing the conclusion [information protected as a trade secret] was to include assumptions about: [information protected as a trade secret]

Comparison: anakinra vs ST

Population of patients for whom all possible options available under the B.33 programme have been exhausted

According to the results of the analysis [information protected as a trade secret]. However, in [information protected as a trade secret] out of the 89 tested scenarios [information protected as a trade secret] the ICUR [information protected as a trade secret] The highest ICUR values were obtained when including [information protected as a trade secret] The lowest ICUR value was obtained when including [information protected as a trade secret].

The population of patients younger than 2 years of age for whom anakinra will be used as first-line treatment

According to the results of the analysis, [information protected as a trade secret] tested scenarios [information protected as a trade secret] in the case of [information protected as a trade secret]

Probabilistic sensitivity analysis (PSA)

According to the probabilistic analysis performed by the applicant, the probability of the cost-effectiveness of ANA therapy compared to the comparator, with the assumed cost-effectiveness threshold [information protected as a trade secret]

Limitations

The main limitation to the applicant's analysis is related to the lack of reliable clinical data to infer true differences between ANA and TOC and ANA and ST in the patient subgroups assessed.

In the applicant's analysis, the population was defined according to the provisions of the proposed drug programme. Finally, as part of the basic analysis, when comparing ANA with ST, the use of the compared interventions in the last line of biological treatment was taken into account, i.e. among patients having exhausted all available treatment options in the B.33 programme, thus omitting patients aged 8 months to 2 years for whom ANA would be used as part of first-line biological treatment. The applicant arbitrarily assumed the same value of the proposed technology among these patients as among patients using anakinra in the last line of biological treatment. It is worth noting that the scientific evidence included in the CUA does not cover the population aged more than 2 and does not fully meet the definition of population in the last line of biological treatment according to the programme. Scientific evidence for comparing ANA with TOC was not considered either, yet the assumption of their comparable efficacy was made. The comparison of ANA vs ST among SJIA patients younger than 2, taking into account subsequent lines of treatment, was carried out only as one variant of sensitivity analysis. In contrast, the economic model allowed estimates to be made separately for the population of patients less than 2 years of age in whom anakinra will be used as first-line treatment.

The reduction in the reliability of applicant's estimates is affected by the inclusion of ANA with TOC in the basic analysis for comparison, [information protected as a trade secret] and taking into account the comparator price (TOC) only on the basis of data from the Ministry of Health announcement [information protected as a trade secret]. The assumption may overestimate the actual cost of TOC therapy. It should be noted that CMA results [information protected as a trade secret] indicate that ANA therapy is [information protected as a trade secret] therapy, whereas the inclusion of [information protected as a trade secret] indicates that ANA therapy is [information protected as a trade secret] to TOC therapy [information protected as a trade secret].

It should also be noted that the applicant's clinical analysis did not demonstrate clinical equivalence, lack of clinically meaningful differences between the compared therapies or therapeutic equivalence in health outcomes of the compared substances. The applicant did not include data from the indirect comparison performed as part of the economic analysis, which among other things indicated statistically significant differences for the ANA vs TOC comparison. Therefore, there are doubts as to the correctness of the applicant's choice of the analytical technique, i.e. CMA to compare ANA with TOC.

A detailed description of limitations is presented in the Agency Verification Analysis.

Agency's own calculations

With regard to the availability of NHF data on reimbursement in drug programmes for the period from January to June 2021 (NHF announcement for the period from January to June 2021), which presents the amount of TOC reimbursement for the aforementioned period as well as data on the number of settled billing units in individual scopes (i.e. TOC administered subcutaneously and TOC administered intravenously) and the number of people covered by the B.33 drug programme under inpatient treatment the Agency's own calculations were used for update estimates.

According to Agency's estimates, the use of anakinra instead of tocilizumab [information protected as a trade secret]. It is worth noting, however, that the calculations presented may not fully reflect the currently applicable [information protected as a trade secret] for TOC.

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

Healthcare system impact assessment has two major parts.

First, the analysis of the impact on the payer's budget allows estimating the potential expenses associated with public reimbursement of the new therapy.

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

A budget impact assessment determines whether a payer has adequate resources to reimburse

particular technology.

Healthcare system impact assessment in the second part answers the question of how the decision on the reimbursement of a new therapy may affect the organisation of the provision of services (particularly in terms of adaptation to the requirements of the implementation of the new therapy) and the availability of other healthcare services.

Budget impact analysis (BIA) was conducted to estimate the public payer's expenditure in the case of a positive decision on public funding of anakinra (Kineret) in the treatment of patients meeting criteria for inclusion in the drug programme: "Treatment of active rheumatoid arthritis and aggressive course of juvenile idiopathic arthritis (ICD-10 M 05, M 06, M 08)".

Assumptions of the analysis:

- public payer (NHF) perspective;
- time horizon: 2 years;
- costs included: direct medical costs as in the economic analysis;
- population size - [information protected as a trade secret] patients in the first year and [information protected as a trade secret] patients in the second year of the analysis.

The results of the applicant's analysis indicate that the reimbursement of Kineret will [information protected as a trade secret] the public payer's costs by [information protected as a trade secret]

The applicant has carried out sensitivity analysis which included the analysis of [information protected as a trade secret]

[information protected as a trade secret]

Limitations

The main limitation related to the assessment of expenditure from public payer's budget is the lack of data enabling assessment of the percentage of use of the applied technology in case of its reimbursement. The projected share of anakinra in the new scenario is uncertain and may not reflect the actual market situation.

Major uncertainties associated with the applicant's AWB arise from assessing patient population size in the clinical condition identified in the application. In the case of AOSD, studies from other countries were included, which consequently may not reflect the actual number of patients with the assessed indication. Moreover, in the absence of other data, patients eligible for the drug programme among all AOSD patients were defined on the basis of data for patients with JIA. Furthermore, a conservative approach was applied to determine the number of patients for whom anakinra could be used after failure of other biopharmaceuticals taking into account the failure of only one line of treatment before starting anakinra (the drug programme allows patients to be included also after the failure of several lines of treatment: e.g. with two TNF inhibitors and tocilizumab).

What is more, the calculations included [information protected as a trade secret] for tocilizumab based on NHF data, which may not fully reflect the actual one.

A detailed description of limitations is presented in the Agency Verification Analysis.

Agency's own calculations

With regard to the availability of NHF data on reimbursement in drug programmes for the period from January to June 2021 (NHF announcement for the period from January to June 2021), which presents the amount of TOC reimbursement for the aforementioned period as well as data on the number of settled billing units in individual scopes (i.e. TOC administered subcutaneously and TOC administered intravenously) and the number of people covered by the B.33 drug programme under

inpatient treatment the Agency's own calculations were used for update estimates.

According to the Agency's calculations, the reimbursement of Kineret will increase public payer's costs by [information protected as a trade secret] in relation to the result of applicant's analysis.

[information protected as a trade secret]

Comments on the drug programme

In summary, the proposed drug programme mostly corresponds to the inclusion and exclusion criteria of the current B.33 drug programme. However, some provisions remain unclear and need to be specified, in particular the new provisions defining the target population for the proposed technology. Moreover, it would be advisable to clarify the content of the eligibility criteria so that ANA treatment does not include patients after failure of oral or subcutaneous methotrexate therapy, which has been used for at least 3 months in patients with the presence of poor prognosis factors according to the current EULAR recommendations.

In addition, it is suggested to add the assessment of patients' quality of life at eligibility and during treatment monitoring in the programme in order to obtain real data from Polish clinical practice.

Detailed clinical expert comments are presented in the Agency Verification Analysis.

Discussion on the solutions proposed in the rationalisation analysis

The subject of the rationalisation analysis is the identification of a mechanism, the introduction of which 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 the reimbursement of the health technology covered in this recommendation.

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

According to the results of the rationalisation analysis, the solution proposed by the applicant covers an increase in public payer's costs related to the reimbursement of the proposed drug.

Applicant's detailed proposals were set out in the Agency Verification Analysis.

Overview of recommendations in relation to the assessed technology

Clinical recommendations

The following clinical recommendations were identified:

- Rutkowska-Sak 2016 Paediatric Rheumatology Expert Panel 2013 (Poland),
- American College of Rheumatology ACR 2013 (USA),
- Childhood Arthritis and Rheumatology Research Alliance CARRA 2012 (USA),
- Rheumatology Expert Panel 2019 (Italy),
- PCCRA 2016 (Canada),
- PRO-KIND subcommittee German Society for Pediatric Rheumatology (GKJR) 2018 (Germany).

In conclusion, IL-1 inhibitors are recommended for the treatment of SJIA with predominant systemic symptoms in the first (Rutkowska-Sak 2016, ACR 2013, CARRA 2012) or subsequent lines of treatment (ACR 2013, CARRA 2012 - ANA listed). The guidelines recommend ANA in patients with JIA in the first or subsequent line of treatment (GKRJ 2018) and in patients not responding to GCS or MTX (PCCRA 2018). The guidelines did not refer to the treatment of patients under 2 years of age Most guidelines indicate that following the failure of standard treatment (NSAIDs and/or GCS, sDMARDs), biological treatment is indicated in patients with SJIA (iIL-1, iIL-6 and iTNF are mentioned as part of biological treatment; however, the GKRJ 2019 and PCCRA 2019 guidelines indicate limited use of iTNF in patients with SJIA).

The only guidelines relating to AOSD (Rheumatology Expert Panel of Italy 2019) recommend iIL-1 in

the first or subsequent line of treatment. The guidelines did not refer to other groups of drugs.

Reimbursement recommendations

Four reimbursement recommendations related to the assessed technology were identified:

- National Institute for Health and Care Excellence (Great Britain) NICE 2021 - conditionally positive,
- Haute Autorité de Santé HAS 2019 (France) – positive,
- Scottish Medicines Consortium SMC 2018 (Scotland) – positive.

In conclusion, the recommendations note the lack of data allowing comparison of efficacy with other biological treatments, while pointing out the superiority of ANA over PLC. The 2021 NICE conditional recommendation indicated that the use of ANA should be restricted to patients with AOSD who have had an inadequate response to treatment with ≥2 conventional DMARDs and to patients with JIA aged ≥8 months and weighing ≥10 kg who have failed to respond to ≥1 conventional DMARD. In addition, the British recommendation indicated similar costs for the use of ANA and TOC.

According to the information provided by the applicant, Kineret is funded in [information protected as a trade secret] EU and EFTA countries (out of 31 indicated). It is publicly reimbursed at 100% (in 10 countries), 65% (in 2 countries) or individually (in 6 countries). [information protected as a trade secret].

Legal basis for the recommendation

The recommendation was prepared on the basis of the order of 16 July 2021 of the Minister of Health (ref. no.: PLR.4500.1067.2021.11.RBO) on the preparation of the President's recommendation on the assessment of the drug: Kineret (anakinra) 100 mg/0.67 ml solution for injection in pre-filled syringe with a scale, EAN: 07350031442090, in the indication: within the drug programme "Treatment of active rheumatoid arthritis and aggressive course of juvenile idiopathic arthritis (ICD-10 M 05, M 06, M 08)", pursuant to Art. 35 sec. 1 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs intended for particular nutritional uses and medical devices (Dz. U. /Journal of Laws/ of 2021, item 523), having obtained Position of the Transparency Council No. 122/2021 of 2 November 2021 on the assessment of Kineret (anakinra) within the drug programme "Treatment of active rheumatoid arthritis and aggressive course of juvenile idiopathic arthritis (ICD-10 M 05, M 06, M 08)".

References

1. Position of the Transparency Council No. 122/2021 of 2 November 2021 on the assessment of Kineret (anakinra) within the drug programme "Treatment of active rheumatoid arthritis and aggressive course of juvenile idiopathic arthritis (ICD-10 M 05, M 06, M 08)".
2. Report No. OT.4231.35.2021 "Application for the reimbursement of Kineret (anakinra) within the drug programme »Treatment of active rheumatoid arthritis and aggressive course of juvenile idiopathic arthritis (ICD-10 M 05, M 06, M 08)«" Completion date: 21 October 2021.