Recommendation No. 120/2021

of 15 October 2021

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

on the assessment of Taltz (ixekizumab) in the following indication: under the drug programme "B.36. Treatment of active ankylosing spondylitis (AS) (ICD-10 M 45)"

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

- Taltz, ixekizumab, solution for injection, 80 mg/ml, 2, 1 ml injectors, GTIN code 05909991282950

in the indication: under the drug programme "B.36. Treatment of active ankylosing spondylitis (AS) (ICD-10 M 45)", in the existing limit group, and dispensing it free of charge **provided that** the proposed risk-sharing scheme is deepened so that the effective price of the drug health technology in question [information protected as a trade secret] of biopharmaceuticals so far reimbursed under the B.36 drug programme.

Grounds for the recommendation

The assessed technology represents another option in the treatment of AS. Currently, under the B.36 programme, other active substances such as adalimumab ADA, certolizumab pegol CER, etanercept ETA, golimumab GOL, infliximab INF and secukinumab SEC are funded.

The applicant made a direct comparison against ADA and an indirect comparison against SEC in the analyses. However, no indirect comparison was performed with the other active comparators currently funded under the B.36 drug programme. Given that ixekizumab (IKS) therapy may replace the above-mentioned drugs, the choice of the comparator and the scope of comparison should be considered insufficient.

There are no data on effectiveness.

The results of the direct comparison of IKS and ADA based on COAST-V revealed no statistically significant differences between the groups after 16 weeks of therapy in terms of ASAS20 (Assessment of SpondyloArthritis international Society criteria for 20% improvement), ASAS40 (Assessment of SpondyloArthritis international Society criteria for 40% improvement), BASDAI50 (Bath Ankylosing Spondylitis Disease Activity Index criteria for 50% improvement) response rates and the chance of developing inactive disease according to ASDAS (Ankylosing Spondylitis Disease Activity Score) (<1.3 points). However, the results above apply only to the population of AS patients who had not previously been treated with biopharmaceuticals (patients demonstrated a poor response to treatment with ≥2 NSAIDs (non-steroidal anti-inflammatory drugs).

The results of the indirect comparison of IKS and SEC, based on RCTs included in the analysis, indicate comparable efficacy after 16 weeks of therapy, as regards the endpoints of ASAS20, ASAS40 and BASDAI50 response rates, change in BASDAI scale result and quality of life as measured by the SF-36 PCS (Short Form 36-item Health Survey Physical Component Summary) questionnaire. There were no statistically significant differences between IKS and SEC for the above endpoints.

The safety profile assessment revealed no statistically significant differences between the IKS and SEC groups in the general population in the incidence of serious adverse events (SAEs), adverse events (AEs) overall and adverse events leading to treatment discontinuation. No death was reported during the 16-week treatment in the IKS and SEK arms of the studies.

For the direct comparison of IKS and ADA after 16 weeks of therapy, there were no statistically significant differences in the incidence of death, SAEs, treatment-emergent adverse events (TEAEs) overall and by severity, and AEs leading to treatment discontinuation, except for a statistically significant lower chance of neutropenia in the IKS group. The most common AEs (in >10% of patients) in the IKS group were infections in total, and in the ADA group -neutropenia and infections in total.

According to the results of the Deodhar 2020 network meta-analysis included in the assessment, there are no statistically significant differences between ixekizumab and the other drugs (reimbursed under the B.36 programme) used in this indication, i.e. etenercept, infliximab, certolizumab pegol, adalimumab, golimumab and secukinumab in terms of achieving ASAS20 response, BASFI (Bath Ankylosing Spondylitis Functional Index) and CRP change with respect to initial values, after 12-16 weeks of therapy.

According to the results of the economic analysis, [information protected as a trade secret] the applicant did not perform estimates for the other drugs currently funded under the B.36 programme. According to the Agency's estimates, in the variant with the RSS (risk-sharing scheme), the treatment with ixekizumab is [information protected as a trade secret] than the treatment with adalimumab, [information protected as a trade secret] etanercept, [information protected as a trade secret], infliximab, [information protected as a trade secret], golimumab [information protected as a trade secret] and certolizumab [information protected as a trade secret]. [information protected as a trade secret] The limitations of the economic analysis arise from the assumptions made regarding the choice of comparator, the proportion of patients receiving the 300 mg maintenance dose of secukinumab, the cost of drug administration and the length of the time horizon.

Therefore, the analysis presented by the applicant is not useful in the health technology assessment and decision-making process. During negotiations, it will be necessary to make reference to the costs of other drugs used in the B.36 drug programme.

The analysis of the impact on the applicant's budget showed that [information protected as a trade secret]. In the event of the reimbursement of Taltz, in the variant with the RSS, the expenditure [information protected as a trade secret] in the second year, while in the variant excluding the risk-sharing scheme, the expenditure [information protected as a trade secret] in the first and second year of reimbursement, respectively. The assumptions of the applicant's analysis may affect the uncertainty of the target population estimation and cause incremental costs to be underestimated.

Four reimbursement recommendations for the administration of IKS in the treatment of AS were identified (positive - French HAS 2021 and Australian PBAC 2021 and 2 positive subject to conditions - UK NICE 2021 and Canadian CADTH 2020). Conditional recommendations made the recommendation contingent upon ensuring an adequate price for the drug, and the UK NICE 2021 recommendation further narrowed the reimbursement to persons for whom the treatment with TNF-alpha inhibitors is not possible or on whom the inhibitors do not have sufficient effect. All of the reimbursement recommendations identified emphasise the clinical benefit of ixekizumab compared with placebo in adult patients with AS who have demonstrated a poor response to conventional therapy, but also underline the lack of added clinical value compared with TNF-alpha inhibitors and secukinumab in the treatment of this disease.

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. However, according to opinions of clinical experts, the possibility of applying a drug with a different mechanism of action gives a chance to achieve decreased disease activity of AS in a larger group of patients. Therefore, taking into account the position of the Transparency Council, it is considered justified to finance the assessed therapy from public funds provided that the proposed risk-sharing scheme is deepened so that the effective price of the drug health technology in question [information protected as a trade secret] of biopharmaceuticals so far reimbursed in the drug programme.

In addition, following the position of the Transparency Council, on the basis of expert opinion and clinical recommendations, it is suggested to define the time of ineffective treatment with two drugs from the NSAID group before biological treatment is introduced for a total of 4 weeks.

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:

- Taltz, ixekizumab, solution for injection, 80 mg/ml, 2, 1 ml injectors, GTIN code 05909991282950, net sales price: [information protected as a trade secret];

in the indication: under the drug programme "B.36. Treatment of active ankylosing spondylitis (AS) (ICD-10 M 45)''.

Proposed payment and dispensing category: patient payment level - free of charge, in the drug programme (DP), in the existing limit group 1184.0 Ixekizumab. The applicant has submitted a proposal for a risk-sharing scheme.

Health problem

Ankylosing spondylitis (AS), belonging to the group of inflammatory spondyloarthropathies (SpA), is a chronic, mostly progressive inflammatory process of unknown aetiology, mainly involving the sacroiliac joints, spinal joints, fibrous rings and ligaments of the spine, leading to their progressive stiffening.

The number of patients in Poland is estimated at approx. 150,000. The disease develops before the age of 40, but in most cases, the first symptoms are observed before the age of 30.

Chronic, progressive, untreated inflammatory disease leads to gradual stiffening of the sacroiliac and spine joints. Life expectancy in patients with AS is shorter compared to the general population due to complications, including those of a cardiological nature. Additionally, due to progressive disability, approximately 10-30% of patients discontinue their occupational activity after 10 years of the disease. AS may present with symptoms of inflammatory bowel disease and uveitis (ASAS-EULAR 2016).

Alternative health technology

The applicant as a comparator among the drugs currently funded under the B.36 drug program (i.e. adalimumab ADA, certolizumab pegol CER, etanercept ETA, golimumab GOL, infliximab INF and secukinumab SEC) accepted only secukinumab, which belongs to the same pharmacotherapeutic group as IKS - inhibitors of interleukin 17 (IL-17). The choice of comparator was considered insufficient because not all therapeutic options financed in Poland in the assessed indication were taken into account.

Description of the proposed intervention

Ixekizumab is a monoclonal antibody belonging to immunoglobulin G subclass 4 (IgG4), which binds with high affinity (< 3 pM) and specificity to interleukin 17A (both IL-17A and IL-17A/F).

According to the Summary of Product Characteristics (SmPC), Taltz is indicated, among other things, for the treatment of the active form of ankylosing spondylitis in adult patients who demonstrate poor response to conventional therapy.

The proposed reimbursement indication of Taltz (ixekizumab) is narrower than the registration

indication due to the eligibility criteria for the drug programme in question - Taltz is to be administered to patients with active and severe AS that demonstrated a poor response to at least two non-steroidal anti-inflammatory drugs.

Proposed risk-sharing scheme
[information protected as a trade secret]

Efficacy, effectiveness and safety assessment

This assessment involves collecting data on the health consequences (efficacy and safety) of the new therapy for the health problem in question and of other therapies that are currently reimbursed from public funds and represent alternative therapies available for the 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:

- two RCTs on the administration of the ixekizumab covered in this recommendation:
  - COAST-V (publications: van der Heijde 2018 (16 weeks data), Dougados 2020 and Dougados 2020a (52 weeks data) - a phase III study evaluating the efficacy and safety of IKS in patients with AS who had not previously been treated with biopharmaceuticals (patients demonstrated a poor response to treatment with ≥2 NSAIDs). Number of patients N=341, IKS (80 mg every 4 weeks): n=81; IKS (80 mg every 2 weeks): n=83; ADA (40 mg every 2 weeks): n=90; PLC: n=87;
  - COAST-W (publications: Deodhar 2019 (16 weeks data), Dougados 2020 (52 weeks data) - a phase III study evaluating the efficacy and safety of IKS in AS patients who demonstrated a poor response to treatment or intolerance to 1 or 2 TNF inhibitors. Number of patients N=316, IKS (80 mg every 4 weeks): n=114; IKS (80 mg every 2 weeks): n=98; PLC: n=104.

  In addition, results from the EMA 2020 and Taltz SmPC documentation and publications of Marzo-Ortega 2020 (data concerning productivity at work), Kiltz 2020 (data concerning functioning and health status), Mease 2019 (data concerning fatigue and sleep) were included – based on the COAST-V and COAST-W studies.
- two RCTs on the application of the alternative technology – secukinumab:
  - MEASURE 2 (published by Sieper 2017, Baeten 2015, abs. con. Braun 2015 (data for 16 and 52 weeks) - a phase III study evaluating the efficacy and safety of SEC (at 150 mg or 75 mg) in patients with AS who demonstrated a poor response to treatment or intolerance to ≤1 TNF inhibitor. Number of patients N=219 SEC 150 mg: n=72, SEC 75 mg: n=73, PLC: n=74;
  - MEASURE 4 (publication: Kivitz 2018, data for 16 and 104 weeks) - a phase III study evaluating the efficacy and safety of SEC (150 mg with saturating dose or 150 mg without saturating dose) in patients with AS who demonstrated a poor response to treatment or intolerance to ≤1 TNF inhibitor. Number of patients N=350, SEC 150 mg with saturating dose: n=116, SEC 150 mg without saturating dose: n=117, PLC: n=117.

The applicant presented the results of an indirect comparison for a 16-week follow-up period. In addition, the applicant presented results concerning the efficacy and safety of IKS±BSC based on COAST-V and COAST-W for 16- and 52-week period of therapy. In the present recommendation, only the results for the 52-week treatment period for clinically relevant endpoints according to the EMA

and the surveyed clinical experts are included.

The Cochrane Collaboration's assessment of the risk of bias for COAST-V, COAST-W and MEASURE 2 indicated a low risk of bias in all analysed domains. In contrast, for MEASURE 4, the assessment revealed an unclear risk of bias in the domain of blinding of effect assessment and low in the other domains analysed.

In addition, the applicant identified a total of 6 systematic reviews: Benucci 2020, CADTH 2020, Deodhar 2020, Lee 2020, Yin 2020, Wang 2021 complying with the inclusion criteria for the analysis.

Efficacy

Indirect comparison: ixekizumab vs secukinumab (IKS vs SEC)

In the absence of studies directly comparing IKS against SEC, the applicant conducted an indirect comparison using the Bucher method via placebo for the following endpoints:

- Treatment response according to ASAS criteria

Among patients who had not previously been treated with biopharmaceuticals, ASAS40 response after 16 weeks was reported in 48% after IKS therapy (COAST-V results) and in 41% after SEC therapy (MEASURE 2 and MEASURE 4 meta-analysis data results), respectively.

In the group of patients with iTNF ineffectiveness or intolerance, ASAS40 response after 16 weeks was observed in 25% of patients after IKS therapy (COAST-W results) and in 30.5% of patients treated with SEC (MEASURE 2 and MEASURE 4 meta-analysis data results), respectively.

In an indirect comparison, there were no statistically significant differences between the IKS and SEC treatment groups among both patients who had not previously been treated with biopharmaceuticals and those with iTNF ineffectiveness or intolerance regarding ASAS40 and ASAS20 response rates.

- Treatment response according to BASDAI scale

Among patients previously untreated with biopharmaceuticals, after 16 weeks of therapy, a reduction in BASDAI scale score of -2.92 points was observed in the IKS treatment group in COAST-V and of -2.6 and -2.54 points after SEC therapy in MEASURE 2 and MEASURE 4, respectively.

In contrast, in the group of patients after iTNF ineffectiveness or intolerance after 16 weeks of therapy, there was a reduction in the BASDAI score of -2.2 points in patients using IKS in COAST-W and -1.6 and -2.08 points in patients using SEC therapy in MEASURE 2 and MEASURE 4, respectively.

An indirect comparison presented no statistically significant differences for BASDAI scale score reduction between the IKS and SEC treatment groups among patients not previously being treated with biopharmaceuticals and those after iTNF ineffectiveness or intolerance.

The percentage of patients with a BASDAI50 response after 16 weeks of therapy was assessed on the basis of data from COAST-V and COAST-W as well as MEASURE 2 for SEC in the general population. The percentage of patients with a BASDAI50 response was 30.3% and 30.6% in the IKS and SEC groups, respectively. An indirect comparison indicated no statistically significant differences between the IKS and SEC groups after 16 weeks of therapy.

- Quality of life according to the SF-36 PCS questionnaire

In the population of patients not previously treated with biopharmaceuticals, the change in the SF-36 PCS questionnaire score was 7.7 points in the IKS group in COAST-V and 2 and 6.74 points in the SEC group in MEASURE 2 and MEASURE 4, respectively.

In the group of patients following iTNF ineffectiveness or intolerance, the change in the SF-36 PCS questionnaire score was 6.6 points in the IKS group in COAST-W and 4.5 and 5.21 points in the SEC group in MEASURE 2 and MEASURE 4, respectively.

Based on the results of the indirect comparison from the applicant, there were no statistically significant differences between IKS vs SEC among both patients not previously treated with biopharmaceuticals and those after iTNF ineffectiveness or intolerance in terms of a change in the SF-36 PCS questionnaire score compared to initial values after 16 weeks of therapy.

Long-term assessment of ixekizumab efficacy - 52 weeks (Dougados 2020, Dougados 2020a)

After 52 weeks of IKS treatment (80 mg dose every 4 weeks) among patients not previously treated with biopharmaceuticals, the percentages (depending on the method of analysis and reporting) who achieved:

- ASAS20 response ranged from 65.4% to 73.6%;
- ASAS40 response ranged from 53.1 to 59.7%;
- BASDAI 50 response ranged from 53.1% to 57.9%;
- inactive disease according to ASDAS (score <1.3 points) ranged from 22.2% to 25%;
- clinically significant improvement in ASDAS (≥1.1 change with respect to initial values) ranged from 63% to 70.8%.

However, among patients after iTNF ineffectiveness or intolerance, these percentages (depending on the method of analysis and reporting) ranged:

- from 52.6% to 68.2% with ASAS20 response;
- from 34.2% to 44.3% with an ASAS40 response;
- from 27.2% to 35.2% with the BASDAI50 response;
- from 8.8% to 11.8% with inactive disease according to ASDAS (score <1.3 points);
- from 46.5% to 62.4% with clinically significant improvement in ASDAS (≥1.1 change with respect to initial values).

Direct comparison: IKS vs ADA

The comparison of IKS and ADA was based on COAST-V. Only patients with AS not previously treated with TNF inhibitors (patients demonstrated a poor response to ≥2 NSAIDs) were examined in the study.

The results of the comparison indicated that there were no statistically significant differences between the IKS and ADA groups after 16 weeks of therapy in terms of ASAS20, ASAS40, BASDAI50 response rates and the chance of patients developing inactive disease according to ASDAS (<1.3 points).

Safety

Indirect comparison: ixekizumab vs secukinumab (IKS vs SEC) - general population

No death was reported during the 16-week IKS and SEK therapy.

Total serious adverse events (SAEs) were reported after 16 weeks of therapy in 2.6% of patients treated with IKS and in 3.2% of those treated with SEC. The incidence of total adverse events (AEs) and those leading to treatment discontinuation in the IKS group for the data presented in the main publications for COAST-V and COAST-W was 55% and 5%, respectively. In the SEC group, the incidence of total AEs and those leading to treatment discontinuation was 63% and 3%, respectively.

The result of the indirect comparison by the applicant indicates that there were no statistically significant differences between IKS and SEC therapy with regard to the incidence of death, total AEs and those leading to treatment discontinuation after 16 weeks of therapy.

Long-term assessment of ixekizumab efficacy - 52 weeks

Among patients from COAST-V and COAST-W who were treated with IKS at 80 mg every 4 weeks for 52 weeks, as well as patients on the ADA and PLC who switched to the IKS group (80 mg dose every 4

weeks) at 16 weeks of therapy, no deaths were reported. Serious adverse events (SAEs) were reported in 5.2% of patients.

Treatment-emergent adverse events (TEAEs) were reported in a total of 71.6% of patients and were mostly of a benign to moderate severity. TEAEs were serious in 5.5% of patients. Adverse events leading to treatment discontinuation were reported in 5.2% of patients. The most common TEAEs were upper respiratory tract infection, injection-site reaction and nasopharyngitis.

Direct comparison: IKS vs ADA

The comparison of IKS and ADA was based on COAST-V.

Results indicated no statistically significant differences between the IKS vs ADA groups after 16 weeks of therapy in the incidence of death, SAEs, TEAEs overall and by severity, and AEs leading to treatment discontinuation. The most common AEs (in >10% of patients) in the IKS group were infections in total, and in the ADA group -neutropenia and infections in total. The results of the comparison revealed a statistically significant 68% lower chance of grade 1 neutropenia in the IKS group than in the ADA group [OR=0.32 95%CI (0.12; 0.85)].

Additional efficacy and safety analysis

Assessment of effectiveness

The applicant has not identified data on effectiveness.

Secondary studies

The analysis included, among other things, the results of the Deodhar 2020 network meta-analysis for the comparison of the proposed IKS health technology (80 mg dose every 4 weeks) against drug health technologies currently reimbursed under the B.36 programme. programme administered at the dosage consistent with the SmPC (ETA, INF, CER, ADA, GOL, SEC). The meta-analysis demonstrated no statistically significant differences between the analysed therapies in terms of ASAS20 response, BASFI and CRP change from the initial values, after 12-16 weeks of therapy.

The conclusions of the authors of other secondary studies included in the applicant's analysis are similar or coherent with the conclusions obtained in the systematic review.

Information based on SmPC

In accordance with the Summary of Product Characteristics, very common adverse reactions (≥1/10) include injection site reactions and upper respiratory tract infections (most commonly nasopharyngitis).

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 additional safety communications on Taltz administration that are not in the Summary of Product Characteristics were found on the EMA, FDA, URPL websites.

Limitations

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

- lack of studies directly comparing IKS with the chosen comparator. Therefore, an indirect comparison was performed using the Bucher method by placebo, which displays certain limitations;
- the population covered by the studies included in the analysis differs from the population defined in the inclusion criteria for the analysis (e.g. with respect to prior intake of biopharmaceuticals other than iTNF). One of the exclusion criteria from the above-mentioned studies is the application of a biological therapy other than iTNF, whereas the content of the programme in question allows the administration of an IL-17 inhibitor prior to another IL-17 inhibitor. This means that in the drug programme it will be possible to administer IKS after SEC, contrary to the included studies;

- lack of comparison of efficacy and safety of the health technology covered in this recommendation with all optional technologies currently reimbursed under PL B.36, i.e. TNF inhibitors (adalimumab, certolizumab pegol, etanercept, golimumab, infliximab). It should be emphasised that under the current B.36 drug programme, the administration of particular drugs, including secukinumab and TNF inhibitors, is not limited to specific treatment lines;
- lack of data on effectiveness and long-term data for comparison of efficacy and safety of the drug technology covered in this recommendation for with SEC. The applicant presented only efficacy and safety results of IKS±BSC treatment after 52 weeks of therapy from COAST-V and COAST-W;
- no comparison of the efficacy of the drug technology covered in this recommendation with the SEC in relation to the endpoint concerning the percentage of patients with minimal clinically relevant improvement in ASDAS score (change ≥1.1 from initial values). It should be emphasised that according to the content of the B.36 drug programme, an adequate response to treatment after 3 months (±1 month) of therapy is defined as, among others, reduction in ASDAS value by 50% or ≥ 1.1 units in relation to the value before treatment. Also, according to the clinical experts surveyed by the Agency, improvement in ASDAS values is considered one of the clinically relevant endpoints.

In summary, the conclusions on the efficacy and safety of IKS based on 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.

The clinical analysis does not include randomised clinical trials proving the superiority of the technology covered in this recommendation over the comparators, so in the Agency's opinion the circumstances of Art. 13 of the Act on Reimbursement do arise.

The value estimated by the Agency of the official selling price of the medicinal product Taltz, at which the cost of its application is not higher than the cost of application of the reimbursed drug technology currently reimbursed in the indication analysed with the most favourable ratio of health effects achieved to the costs of their achievement, i.e. adalimumab (ADA), ranges from [information protected as a trade secret].

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, i.e. a result that indicates that given the wealth of Poland (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 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 assessment of the cost-effectiveness of ixekizumab (Taltz, IKS) therapy in Poland for the treatment of patients with ankylosing spondylitis (AS) was performed using cost-minimisation analysis (CMA).

Assumptions of the analysis:

- comparators: secukinumab (SEC);
- public payer perspective (NHF) and joint perspective (NHF and patient);
- time horizon: 18 months;
- costs included: drugs and administration of drugs.

According to the applicant's estimates, from both the public payer perspective and the joint perspective, the treatment with ixekizumab is [information protected as a trade secret] to the treatment with secukinumab [information protected as a trade secret] in the variant including the proposed RSS and [information protected as a trade secret] in the variant without the RSS.

The applicant calculated the net sales price of the technology covered in this recommendation at which the cost of its administration is no higher than the cost of secukinumab. It amounted to [information protected as a trade secret]

[information protected as a trade secret]

Limitations

The main limitations of the applicant's analysis relate to assumptions regarding the choice of comparator, the proportion of patients using the 300 mg maintenance dose of secukinumab, the cost of drug administration and the length of the time horizon.

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

Agency's own calculations

Considering the limitations of the applicant's economic analysis, taking into account the applicant's data on differential costs, efficacy parameters and analysis horizon, additional Agency's calculations were performed.

<u>CMA with consideration of all alternative technologies</u>

According to the Agency's estimates (only in the variant including the proposed RSS)
the treatment with ixekizumab is [information protected as a trade secret] with respect to the treatment with:

- secukinumab [information protected as a trade secret],
- adalimumab [information protected as a trade secret],
- etanercept [information protected as a trade secret],
- infliximab [information protected as a trade secret],
- golimumab [information protected as a trade secret]
- certolizumab [information protected as a trade secret]

<u>Testing alternatives to the applicant's input data</u>

Own calculations were applied to estimate the results of the analysis taking into account the 4-year

time horizon of the analysis, the percentage of patients receiving a maintenance dose of SEC 300 mg of 1 or 10% (the range of responses indicated by clinical experts), and the assumption that patients self-administer the assessed drugs and, thus, that the cost of administering the drugs is not different. In addition, the results of the variant assuming a minimum percentage of patients receiving the SEC 300 mg maintenance dose estimated by the applicant ([information protected as a trade secret]) and at the same time considering the cost of administering the drugs as non-differential are presented. It seems that such an alternative should be considered as the basic variant of the analysis.

[information protected as a trade secret]

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 financing of a new therapy may influence the organisation of service provision (particularly in the context of adaptation to the requirements of the implementation of the new therapy) and the availability of other healthcare services.

The budget impact analysis (BIA) was performed to estimate the public payer's expenditure in case of a positive decision on public funding of ixekizumab (Taltz) for the treatment of patients with ankylosing spondylitis under the drug programme covered in this recommendation.

Assumptions of the analysis:

- public payer perspective (NHF) and joint perspective (NHF and the patient);
- time horizon: 2 years (2022-2023);
- costs taken into account: analogous to those 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.

According to the results of the basic analysis, a positive decision on public financing of Taltz will result in [information protected as a trade secret] of public payer's expenditure regardless of whether the analysis variant includes the RSS. In the case of the variant not including the risk-sharing scheme, expenditure [information protected as a trade secret] in subsequent years of the adopted time horizon. However, in the variant involving the RSS, expenditure [information protected as a trade secret] in the second year of reimbursement.

The applicant conducted a sensitivity analysis that included an extreme value analysis and an analysis of 7 alternative scenarios in the variant with and without the RSS.

Incremental expenditure in the variant considering the RSS amounted to [information protected as a trade secret]. The largest increases in incremental expenditure were observed in the scenario assuming an alternative proportion of patients treated with secukinumab 300 mg in the maintenance phase of treatment amounting to [information protected as a trade secret] and with an increase in target IKS shares to 60%.

Incremental expenditure in the variant without the RSS amounted to [information protected as a trade secret] of the year of the analysis horizon. The largest increases in incremental expenditure were observed when target IKS shares were increased to 60% and when assuming a greater increase in

patients treated with IL-17 inhibitors under the B.36 drug programme.

Limitations

The main limitations of the analysis pertain to assumptions related to the omission of market share uptake of ixekizumab from TNF-alpha inhibitors funded under the B.36 drug programme, the assumption of the proportion of patients taking the increased maintenance dose of secukinumab (300 mg), the uncertainty regarding the proportion of subcutaneous drug administrations delivered in outpatient specialist care and the assumed time horizon of the analysis. These issues affect the uncertainty in the estimation of the target population and may result in the underestimation of incremental costs.

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

Agency's own calculations

Due to uncertainty regarding the values adopted by the applicant, the Agency's own calculations were performed for two parameters: costs of administration and proportion of patients treated with a higher maintenance dose of secukinumab. In the experts' opinion, basically all patients using subcutaneous drugs self-administer them at home, so it was decided not to include the costs of administration of IKS and SEC. In addition, the percentage of patients treated with a higher maintenance dose of secukinumab (300 mg) was adjusted, as according to the experts in Poland it ranges from 1% to 10%. By adopting the above assumptions, the incremental costs borne by the public payer in the variant with the RSS increase by over 40% (with 10% of patients treated with the higher dose of SEC) and by approx. 60% (with 1% of patients treated with the higher dose of SEC).

Comments on the proposed risk-sharing scheme

Taking into account the position of the Transparency Council and limitations of the conducted analyses, it is considered that the assessed technology may be financed from public funds if the proposed risk-sharing scheme is extended in such a way that the effective price of the drug health technology covered in this recommendation [information protected as a trade secret] of biopharmaceuticals reimbursed so far under the B.36 drug programme.

Comments on the drug programme

In conclusion, in the opinion of one of the clinical experts interviewed by the Agency, a proposal for changes to the provisions of the drug programme covered in this recommendation in terms of eligibility criteria was made. Two experts pointed out that according to ASAS recommendations and the standpoint of the Polish Society of Rheumatology, the duration of ineffective NSAID treatment before biological treatment initiation should amount to 4 weeks in total for the two drugs.

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.

[information protected as a trade secret]

Overview of recommendations in relation to the assessed technology

Clinical recommendations

The following clinical recommendations were identified:

- Polish Society of Rheumatology PTR 2021 (Poland),
- National Institute for Health and Care Excellence NICE Pathways 2021 (United Kingdom),

- American College of Rheumatology ACR/SAA/SPARTAN 2019 (USA),
- French Rheumatology Society SFR 2018 (France),
- Spanish Society of Rheumatology SSR 2018 (Spain),
- British Society for Rheumatology-British Health Professionals in Rheumatology BSR-BHPR 2017 (United Kingdom),
- Sociedade Portuguesa de Reumatologia SPR 2016 (Portugal),
- Assessment of SpondyloArthritis international Society/ European League Against Rheumatism ASAS-EULAR 2016 (international).

In conclusion, ixekizumab therapy is recommended by the ACR/SAA/SPARTAN 2019 and NICE 2021 guidelines in cases of ineffectiveness or where there are contraindications to TNF-alpha inhibitor therapy, in patients with active AS, and in patients who have not achieved the desired treatment effects after TNF-alpha inhibitor therapy. Additionally, in the PTR 2021 standpoint, it was noted that currently the most urgent positive decisions awaited by patients and physicians concerning the initiated reimbursement processes include ixekizumab for patients with AS and axial and peripheral forms of SpA (spondyloarthritis).

In some of the guidelines consulted, reference was made to biopharmaceuticals in general (TNF and IL-17 inhibitors). The PTR 2021 and SFR 2018 guidelines list IL-17 inhibitors as treatment options for people with ankylosing spondylitis when conventional NSAID therapy is ineffective. Furthermore, the PTR 2021 statement, citing the ASAS-EULAR 2016 guidelines, indicates that the current practice is to start treatment with biopharmaceuticals from iTNF administration. This is due to the long history of drugs from this group in clinical practice and the accumulated experience regarding their efficacy and safety. The guidelines also indicate that it does not limit the applicability of an iIL17 group drug in first-line biological treatment.

The PTR 2021, ACR/SAA/SPARTAN 2019, SFR 2018, SSR 2018 and ASAS-EULAR 2016 guidelines recommend the treatment with another iTNF or iIL17 after ineffectivenss of the first iTNF-α.

The BSR-BHPR 2017 and SPR 2016 guidelines do not list IL-17 inhibitors as a recommended biological therapy option. That being said, these guidelines were developed prior to the registration date of ixekizumab in the indication covered in this recommendation (EMA: 28/04/2020).

Reimbursement recommendations

Four reimbursement recommendations related to the assessed technology were identified:

- Haute Autorité de Santé HAS 2020 (France) - positive,
- Pharmaceutical Benefits Advisory Committee PBAC 2020 (Australia) - positive,
- National Institute for Health and Care Excellence NICE 2021 - positive subject to conditions,
- Canadian Agency for Drugs and Technologies in Health CADTH 2020 - positive subject to conditions.

In conclusion, the conditional recommendations made the recommendation contingent on ensuring that the drug was appropriately priced. The Canadian CADTH 2020 recommendation included a reservation that ixekizumab should provide savings compared with the least expensive biological therapy reimbursed for the treatment of AS. The UK NICE 2021 recommendation further narrowed reimbursement to people for whom TNF-alpha inhibitors administration is not possible or for whom TNF-alpha inhibitors are not sufficiently effective. All of the recommendations identified highlight the clinical benefit of ixekizumab compared with placebo in adult patients with AS who have demonstrated an inadequate response to conventional therapy, but also underline the lack of clinical added value compared with TNF-alpha inhibitors and secukinumab in the treatment of the disease. The HAS 2020, PBAC 2020 and CADTH 2020 recommendations also emphasise the omission in the analysis of comparisons with all possible comparators (i.e. in addition to secukinumab, also with TNF-

alpha inhibitors funded in the indication covered in this recommendation).

According to the information submitted by the applicant, Taltz (ixekizumab) [information protected as a trade secret].

Legal basis for the recommendation

The recommendation was prepared based on the order of 20 July 2021 of the Minister of Health (ref. no.: PLR.4500.1319.2021.10.RBO) concerning the preparation of the President's recommendation on the assessment of the following drug: Taltz, ixekizumab, solution for injection, 80 mg/ml, 2, 1 ml injectors, GTIN code 05909991282950, in the following indication: under the drug programme ''Treatment of active ankylosing spondylitis (AS) (ICD-10 M 45)'', 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 received Position of the Transparency Council No. 120/2021 of 11 November 2021 on the assessment of Taltz (ixekizumab) under the drug programme ''Treatment of active ankylosing spondylitis (AS) (ICD-10 M 45)''.

References

1. Position of the Transparency Council No. 120/2021 of 11 November 2021 on the assessment of Taltz (ixekizumab) under the drug programme ''Treatment of active ankylosing spondylitis (AS) (ICD-10 M 45)''.
2. Report No. OT.4231.37.2021 "Application for the reimbursement of Taltz (ixekizumab) under the drug programme »Treatment of active ankylosing spondylitis (AS) (ICD-10 M 45)«". Completion date: 30 September 2021