Recommendation No. 109/2019

of 12 December 2019

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

on whether Hyrimoz (adalimubab), solution for injection in pre-filled syringe, 40mg, 2 injectors; Hyrimoz (adalimubab), solution for injection in pre-filled syringe, 40mg, 2 pre-filled syringes with protection, should be reimbursed in the following indication: treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate

The President of the Agency does not recommend reimbursing the following medicinal product:

- Hyrimoz (adalimumab), solution for injection in pre-filled syringe, 40 mg, 2 injectors, EAN: 07613421020880;
- Hyrimoz (adalimumab), solution for injection in pre-filled syringe, 40 mg, 2 pre-filled syringes with protection, EAN: 07613421020897

in the following indication: treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

Statement of reasons for the recommendation

The President of the AOTMiT, taking into account the position of the Transparency Council and the available scientific evidence, as well as the results of pharmacoeconomic analyses and clinical guidelines, has concluded that financing of the health technology in question from public funds is not justified.

The assessment of efficacy and safety of adalimumab (ADA) in patients with psoriatic arthritis was conducted on the basis of several primary studies, including 3 RCTs. For the purpose of a systematic review and comparison of the efficacy and safety of ADA with the relevant comparators, three subpopulations have been identified: A – patients with psoriatic arthritis not meeting the inclusion criteria in the current B.35 drug programme, B – patients eligible for

the B.35 drug programme, C – patients excluded from the B.35 drug programme as a result of the permitted treatment duration being exceeded or a sustained response to treatment.

The efficacy analysis demonstrated a statistically significant advantage of ADA±conventional synthetic DMARD over PLC±conventional synthetic DMARD regarding the majority of quality-of-life endpoints in population A. For population B, only statistically significant advantage of ADA over INF was demonstrated in the assessment of the physical health in the SF-36 questionnaire. Quality of life was not assessed in population C.

In terms of response to treatment, ADA±conventional synthetic DMARD demonstrated a statistically significant advantage in population A over PLC±conventional synthetic DMARD at all endpoints indicated as clinically relevant by experts: ACR20, ACR50, ACR70, PsARC, DAS-28. For population B, no statistically significant differences in efficacy of ADA vs. ETA and ADA vs. INF were observed on the basis of included primary studies. The frequency of relapses after discontinuation of biological treatment and the time to relapse were used to assess the efficacy in population C. The relapse occurred in approx. 80% of patients, and the average time to its occurrence ranged from 10.6 weeks to 52 weeks.

The safety analysis was conducted only for populations A and B. No death was reported in the studies included for population A. No statistically significant differences were identified in the incidence of serious adverse events, whereas the incidence of serious adverse events (SAEs) for population A in the ADA arm in both studies did not exceed 2%. With regard to all adverse events (AEs), a statistically significantly lower chance of AEs in general in the ADA arm than in the PLC arm was noted. Furthermore, a statistically significant decrease of risk of two AEs: exacerbation of psoriasis and exacerbation of psoriatic arthritis in the arm using ADA was also demonstrated. For population B, the analysis of the incidence of AEs in general did not demonstrate statistically significant differences between ADA, INF and ETA arms.

The main limitation of the clinical analysis is the lack of scientific evidence on the efficacy and safety of ADA therapy for population C. Although an additional systematic review has been conducted to assess efficacy in this arm, the included studies do not comply with the inclusion and exclusion criteria in the systematic review in terms of population, intervention and comparator. It should be noted that population C represents a large part of the target population in which Hyrimoz is to be used after reimbursement is introduced, and drawing conclusions on the basis of the identified scientific evidence for this patient arm is, in principle, impossible.

Furthermore, it should be noted that OPAL Broaden (population A) was a study designed to demonstrate the advantage of tofacitinib (TOF) over no treatment (PLC), and the comparison of ADA vs. PLC was also a part of the study. Nevertheless, the superiority hypothesis only applied to the TOF vs. PLC comparison. In Genovese 2007 (population A), the comparison conducted in 32.7% of the studied sample probably did not apply to the adopted comparator.

The primary studies identified for population B refer only to some of the adopted comparators (infliximab, etanercept). No evidence was identified for the other comparators: golimumab, secukinumab and certolizumab pegol, which are also available in the B.35 drug programme. In population B, the safety assessment of ADA is made difficult by the scarce data available in the analysed scope.

In addition, the primary studies included in the clinical analysis provide little data on the efficacy of ADA after previous iTNF treatment and, given the indication in question, such a clinical situation is possible.

In line with the results of the applicant's economic analysis, the use of Hyrimoz in the treatment of psoriatic arthritis as part of pharmacy reimbursement *[information protected as a trade secret]*.

It should be noted that the applicant's economic analysis is subject to many limitations. The estimations were carried out for 3 subpopulations reflecting possible treatment sequences, however, none of the sequences fully reflects the comparison with comparators defined in the scoping analysis.

The applicant's budget impact analysis demonstrated that taking a positive decision about public funding of Hyrimoz as part of pharmacy reimbursement in the indication in question *[information protected as a trade secret]*. In line with the results of the analysis, the NHF's expenditure *[information protected as a trade secret]*.

One serious limitation of the above-mentioned analysis consists in the uncertainty as to the correctness of the estimates concerning the target population, which is also confirmed by the results of the sensitivity analysis carried out by the applicant. The applicant adopted the assumption that initiation of Hyrimoz reimbursement under the open list of reimbursed products would result in the discontinuation of the reimbursement of other drugs containing ADA under the B.35 drug programme, but did not explain how patients who have hitherto used adalimumab under this programme would be treated. In addition, in the opinion of the AOTMiT, the assumption made by the applicant may result in a significant part of the patients, who had previously used adalimumab under the drug programme, being further treated with ADA as part of pharmacy reimbursement. This would mean that the target population was underestimated by the applicant.

In addition, it should be noted that the change in the reimbursement category for Hyrimoz will result in changes to the current B.35 "Treatment of aggressive psoriatic arthritis (ICD-10 L 40.5, M 07.1, M 07.2, M 07.3)" drug programme, i.e. drugs containing adalimumab other than Hyrimoz, currently financed from public funds (Humira, Amgevita, Imraldi) will no longer be financed under the drug programme in case of a change in the reimbursement category for Hyrimoz.

Subject of the application

The order of the Minister for Health concerns assessing whether the following medicinal product should be reimbursed:

- Hyrimoz (adalimumab), solution for injection in pre-filled syringe, 40 mg, 2 injectors, EAN: 07613421020880 with the net ex-factory price of PLN *[information protected as a trade secret]*;
- Hyrimoz (adalimumab), solution for injection in pre-filled syringe, 40 mg, 2 pre-filled syringes with protection, EAN: 07613421020897 with the net ex-factory price of PLN *[information protected as a trade secret]*;

in the following indication: treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

The proposed reimbursement availability category – prescription drug available in the indication specified by the clinical condition. The proposed patient co-payment level – lump sum. The drug would be financed under a new limit group. No risk-sharing scheme was proposed.

Health problem

Psoriatic arthritis (ICD-10: L40.5, M07.1, M07.2, M07.3) is a chronic immunological joint inflammatory disease in patients with psoriasis, belonging to the spondylarthritis category.

The aetiology of the disease is unknown, but the probable causes include genetic predisposition as well as injuries and viral or bacterial infections.

Psoriatic arthritis is primarily associated with inflammation of peripheral joints, spine joints, sacroiliac joints and/or entheses. The disease has a variable course, with periods of exacerbation and remission; with time, it leads to disability.

No detailed data on the incidence or prevalence of psoriatic arthritis in Poland is available. Assuming that psoriasis affects about 2% of the population, the number of patients with psoriatic arthritis can be estimated to range between approx. 40,000 and 230,000.

According to the NHF's data, approx. 19,700 patients with psoriatic arthritis (with a diagnosis under one of the following ICD-10 codes: L40.5 or M07.1 or M07.2 or M07.3) were treated in Poland in 2018. However, the number of patients treated under the B.35 "Treatment of aggressive psoriatic arthritis" drug programme between 2016 and 2018 amounted to: 1,189, 1,390 and 1,622, respectively.

Alternative health technologies

The most recent clinical practice guidelines for primary treatment of patients with psoriatic arthritis after failure of conventional disease-modifying antirheumatic drugs (DMARD) recommend TNF-alfa inhibitors (etanercept, infliximab, adalimumab, golimumab, certolizumab pegol), followed by IL-17 inhibitors (secukinumab, ixekizumab, brodalumab), which are preferred over the IL-12/23 inhibitor (ustekinumab). In case of patients with active psoriatic arthritis despite treatment with TNF inhibitor monotherapy, the guidelines recommend changing the therapy to another TNF-alfa inhibitor, which is preferred over a change to IL-17 inhibitor. In line with the guidelines, the IL-17 inhibitor is preferred over the IL-12/23 inhibitor, which is, in contrast, recommended over abatacept and tofacitinib.

Pursuant to the announcement of the Minister of Health of 27 June 2019 on the list of reimbursed drugs, foodstuffs for particular nutritional uses and medical devices as of 1 July 2019, the following active substances are currently financed from public funds in Poland: secukinumab, certolizumab pegol, adalimumab, etanercept, infliximab and golimumab under the B.35 "Treatment of aggressive psoriatic arthritis (ICD-10 L40.5, M07.1, M07.2, M07.3)" drug programme. In addition to the treatment of patients with psoriatic arthritis under the current drug programme, the following drugs are also reimbursed: non-steroidal anti-inflammatory drugs (NSAIDs),

glucocorticoids, conventional disease-modifying antirheumatic drugs: methotrexate and sulfasalazine, and immunosuppressive drugs: cyclosporine A.

Hyrimoz is currently reimbursed under the "Treatment of aggressive psoriatic arthritis (ICD-10 L40.5, M07.1, M07.2, M07.3)" drug programme B.35. Adult patients with active and progressive psoriatic arthritis, in whom the response to previous disease-modifying antirheumatic drugs has been insufficient, are eligible for the above-mentioned drug programme. Insufficient response was identified in the drug programme as:

- in the case of the peripheral form of psoriatic arthritis – persistent active and severe form of the disease despite the use of at least two disease-modifying immunosuppressive drugs, such as methotrexate, leflunomide, sulfasalazine and cyclosporine;

- in the case of the axial form of psoriatic arthritis – persistent active and severe form of the disease despite the use of at least two non-steroidal anti-inflammatory drugs.

If the reimbursement category of Hyrimoz is changed from a drug programme to pharmacy reimbursement, in addition to the population in which the drug is currently reimbursed (to simplify, the population is called population B), the target population will be extended by two additional populations:

- adults with active and progressive psoriatic arthritis, in whom the response to previous disease-modifying antirheumatic drugs was insufficient, who are not eligible for treatment under the current drug programme as they do not meet all the required inclusion criteria (population A);
- adult patients with active and progressive psoriatic arthritis, in whom the response to previous disease-modifying antirheumatic drugs was insufficient, who were qualified for the current drug programme and who discontinue the effective treatment under drug programme due to meeting the exclusion criteria (population C).

Given that the indication in question for Hyrimoz does not specify how many drugs must be ineffective before adalimumab can be administered to the patient (which means that ineffectiveness of a single drug is sufficient), it may happen that if ADA needs to be changed to another tumour necrosis factor inhibitor (iTNF alfa), the patient may have difficulty in accessing further treatment because he/she will not meet the criteria for inclusion to the B.35 drug programme.

As comparators for Hyrimoz (adalimumab), the applicant chose:

- in population A: Conventional synthetic disease-modifying antirheumatic drugs used as monotherapy or in combination therapy (methotrexate, leflunomide, sulfasalazine, cyclosporine, azathioprine, chloroquine);
- in population B: drugs currently financed under the drug programme (adalimumab, etanercept, infliximab, golimumab, certolizumab pegol and secukinumab);
- in population C: Conventional synthetic disease-modifying antirheumatic drugs.

In the AOTMiT's opinion, the choice of the comparators is justified. *[information protected as a trade secret]*.

Description of the proposed intervention

Hyrimoz, with its active substance being adalimumab, binds specifically to TNF and neutralises the biological function of TNF by blocking its interaction with the p55 and p75 cell surface TNF receptors. Furthermore, adalimumab modulates biological responses that are induced or regulated by TNF, including changes in the levels of adhesion molecules responsible for leukocyte migration (ELAM-1, VCAM-1, and ICAM-1 with an IC50 of 0.1–0.2 nM).

In line with the summary of product characteristics (SPC), the registered indications of Hyrimoz include:

- psoriatic arthritis – Hyrimoz is indicated for the treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

The indication in question corresponds to the registered indication.

Efficacy, effectiveness and safety assessment

The assessment consists in the collection of data on health consequences (efficacy and safety) resulting from the use of a new therapy in a given health problem and other publicly financed therapies which constitute an alternative treatment option available in a given health problem. Then, the assessment

requires determining the reliability of the collected data and comparing the results regarding the efficacy and safety of the new therapy with those of therapies already available in a given health problem.

Based on the above, the efficacy and safety assessment allows for obtaining information about the extent of the health effect (with regard to both efficacy and safety) to be expected in relation to the new therapy compared to the other considered therapeutic options.

Fourteen primary studies (described in 20 publications) were included in the efficacy and safety assessment of adalimumab; for particular populations:

in population A:

- 2 RCTs
    - OPAL Broaden (Mease 2017, Strand 2019, Helliwell 2018) – multi-centre, prospective, phase III randomised, double-blind, controlled clinical trial. Tofacitinib (TOF) was the assessed intervention. ADA and placebo (PLC) arms constituted the control arm. In addition, patients received stable doses of methotrexate (MTX), sulfasalazine (SSA) or leflunomide (LEF). Study hypothesis: superiority for TOF vs. PLC comparisons; no hypothesis has been presented for the comparison of ADA with another intervention. Observation period: 3 months. After this time, patients from PLC arm started treatment with TOF. Total number of patients N=422, including in the ADA arm N=106, in the PLC arm N=105. The quality of the study was assessed using the Cochrane Handbook criteria. The risk of bias was assessed to be low;
    - Genovese 2007 – multi-centre, prospective, phase III, randomised, double-blind controlled clinical trial. ADA vs. PLC was compared. In both arms patients received simultaneously stable doses of MTX or other disease-modifying antirheumatic drugs (except cyclosporine and tacrolimus) and oral glucocorticoids at a stable dose not higher than the equivalent of 10 mg of prednisone per day. Observation period: 12 weeks, followed by an open phase in which all participants received ADA for a period of up to 24 weeks. Total number of patients N=100, in the ADA arm N=51, in the PLC arm N=49. The quality of the study was assessed using the Cochrane Handbook criteria. The risk of bias was deemed to be impossible to determine in the following domains: blinding of researchers and patients, blinding of assessment of effects and selective reporting, while in the remaining domains it was assessed to be low;

in population B:

- 1 RCT:
    - Atteno 2010 – single-centre, 3-arm, open, randomised trial. The following substances were compared: ADA, INF, ETA. Observation period: 12 months. Total number of patients N=100, in the ADA arm N=34, in the INF arm N=30, in the ETA arm N=36. The quality of the study was assessed using the Cochrane Handbook criteria. The risk of bias was assessed to be high in the following domains: blinding of researchers and patients, blinding of assessment of effects; in the following domains: randomisation method, concealment of randomisation code, incomplete data and other factors, to be impossible to determine and to be low in the domain of selective reporting;
- 2 controlled observational studies:
    - BSRBR registry (publications: Saad 2010, Saad 2010a; observation period up to 18 months; N=596 patients);
    - GISEA registry (publications: Iannone 2014 – observation period up to 24 months, Iannone 2016 – observation period up to 48 months; N=328 patients);

in population C:

- 2 single-arm prospective observational studies:
    - Araujo 2013 (observation period: 6 months or up to relapse, N=26 patients);
    - CORRONA study/registry (publications: Huynh 2017 – N=325 patients, Harrold 2018 – N=94 patients; observation period: no data);
- 1 single-arm retrospective observational study: Chimenti 2013 (the study lasted from January 2006 to February 2010; N=47 patients);
- 1 observational case-control study: Cantini 2008 (6 years in total, observation period of the population of patients with psoriatic arthritis after discontinuation of treatment with biological disease-modifying antirheumatic drugs amounted to 19 months on average; the analysis included 236 patients with psoriatic arthritis (study arm) and 268 patients with rheumatoid arthritis (control arm)).

In addition, the applicant also included single-arm studies for the efficacy and safety of adalimumab not directly related to any of the populations listed in the application:

- Three single-arm experimental studies Hellman 2019 (observation period: 12 weeks, N=20 patients), ACCLAIM (observation period: 12 weeks, N=90 patients), STEREO (observation period: 12 weeks, N=414 patients),
- Two single-arm observational studies Behrens 2018 (observation period: 6 months, NN=1166 patients), Teoli 2012 (observation period: up to 24 weeks; N=40 patients).

The summary of the results of the above mentioned single-arm studies was presented as a supplement to the data for population A.

The following parameters were used to assess efficacy and safety:

- OR – odds ratio;
- MD – mean difference;

The following scales and questionnaires were used in the presented studies:

- American College of Rheumatology 20/50/70 criteria – dedicated to rheumatoid arthritis (RA). Improvement defined as a reduction in the number of painful and swollen joints by 20% (ACR20), 50% (ACR50) or 70% (ACR70) and an improvement of 20%, 50% or 70% respectively in three of the five criteria: overall patient assessment of disease activity, overall physician assessment of disease activity, measurement of functional capacity [most commonly Health Assessment Questionnaire (HAQ)], visual analogue pain score and ESR or C-reactive protein (CRP) score. The percentage of patients with an ACR20/50/70 improvement represents the percentage of patients with a 20%/50%/70% reduction in the number of painful and swollen joints together with an improvement in the three (out of 5) parameters mentioned above. The higher ACR score, the greater the improvement. ACR20 is considered as the minimum clinically relevant response, ACR50 is assumed to be the indicator of a clinically relevant response, and ACR70 is considered to be a reduction of disease similar to remission. Treatment efficacy criteria according to ACR allow for describing only the change of disease activity and not its final activity as a result of the applied treatment.
- Psoriatic Arthritis Response Criteria (PsARC) – The response according to the modified PsARC criteria is defined as an improvement in at least 2 of the 4 criteria (at least one of which must include the number of joints that are tender or swollen) and no deterioration of the result for the following 4 criteria: number of tender joints (n = 78); number of swollen joints (n = 76); overall patient assessment of disease activity (measured on the basis of the VAS scale – 100

mm, 0 mm being the lowest and 100 mm the highest activity of the disease); overall physician assessment of disease activity (ditto). An improvement or deterioration in the number of the tender/swollen joints was defined as a reduction or increase, respectively, in the number of joints by at least 30% compared to the initial values.

- Health Assessment Questionnaire-Disability Index (HAQ-DI) assesses a patient's level of functional ability and includes questions of fine movements of the upper extremity, locomotor activities of the lower extremity, and activities that involve both upper and lower extremities. The questionnaire describes 20 activities that the patient assesses on a 4-stage scale in terms of the difficulty of performing the described activity. Disability rate ranges from 0 (no disability) to 3 (very serious disability). The higher the score, the more severe the disease. Minimal Clinically Relevant Difference (MCRD) = 0.35 points
- Short Form (36) Health Survey (SF-36) assesses quality of life with the disease. The SF-36 survey consists of 36 questions divided into 8 categories that assess pain, physical functioning, general health condition, fatigue/vitality, mental health, social functioning and limitations caused by physical or mental problems. SF-36 is a general measure in which comparisons between different diseases are possible. The higher the score, the higher the quality of life. MCRD= 2.5 points for PCS and MCS. MCRD= 5 points for each domain.
- EuroQoL, 5 Dimension (EQ-5D) – A two-part questionnaire, including a descriptive and visual part. The descriptive part includes the basic domains of the health condition: mobility, self-care, usual activities, pain/discomfort and anxiety/depression. A scale of 1 to 5 points is available, and better physical fitness and quality of life corresponds to a lower score. The parameters assessed in such a way allow for calculating the index value, where the value of 1,000 is the highest possible. The visual scale allows to assess the quality of life from 0 to 100, where 0 means the worst imaginable health condition and 100 stands for the best. The higher the score, the worse the quality of life assessment. MCRD= 0.05 points for the descriptive part, MCRD= 10 points for the visual part.
- Ankylosing Spondylitis Quality of Life (ASQoL) – The Ankylosing Spondylitis Quality of Life questionnaire assesses motivation, daily activity, lack of dependence on mood and social interactions. The questionnaire result ranges from 0 to 18 points. The higher the score, the worse the quality of life assessment. MCRD= 1.8 points
- Dermatology Life Quality Index (DLQI) – A 10-point dermatological questionnaire that assesses the quality of life related to the patient's health condition in the following areas: symptoms and feelings, daily activities, leisure, work and school, personal relationships, treatment. The response to each question is rated on a scale ranging from 0 to 3 points. The final score constitutes the sum of all points and amounts to 0-30 points. It is the most commonly used to assess QoL in patients with psoriatic arthritis >16 years of age. The higher the score, the worse the quality of life assessment. MCRD= 3-5 points
- Disease Activity Score-28 with C-Reactive Protein (CRP) (DAS28-CRP) is used to assess the activity of the disease on the basis of the following criteria: joint swelling – number of tender joints (on a scale ranging from 0 to 28), the patient's assessment of general health condition or disease activity and the current concentration of C-reactive protein. On the basis of the obtained score, the disease activity is interpreted as follows: disease remission (<2.6), low disease activity (2.6 -3.2), moderate disease activity (3.2 -5.1), high disease activity (>5.1).
- Visual Analog Scale (VAS) – Visual Analog Scale is used in cases where there is a need for the patient to quantify – on a special scale with values ranging from 0 to 100 mm (0 – no pain, 100 – unbearable pain), the activity of the disease or the general health condition. The higher the score, the higher the severity of the disease.

Efficacy

The results concerning efficacy were presented for the analysed endpoints in particular populations:

Quality of life

Population A

In OPAL Broaden and Genovese 2007, the patients' quality of life was assessed using the following questionnaires: HAQ-DI, DLQI, EQ-5D, ASQoL and SF-36.

The results of both studies demonstrated a statistically significant improvement in the quality of life assessment in patients using ADA±conventional synthetic DMARDs in comparison to the control arm regarding the general HAQ-DI questionnaire.

For the SF-36 questionnaire, a statistically significant improvement has been demonstrated in the PCS (physical component score) area and in the domains of physical functioning, pain and general health. The Least Squared Mean Difference (LSMD) amounted respectively to:

- in the PSC area LSMD=3.55 (the value of p-value parameter p<0.001 was indicated);
- for physical functioning LSMD= 3.2 95%Cl (1.0;5.3);
- in the case of pain LSMD= 3.75 (the value of p-value parameter p<0.001 was indicated);
- for the domain of general health LSMD= 2.09 75 (the value of p-value parameter p≤ 0.05 was indicated);

However, the minimal clinically relevant difference (MCRD) in the ADA vs. PLC arm has only reached the result for PCS. The result in the domain of general health was borderline statistically significant (p-value parameter p≤0.05), but was not clinically relevant.

In the case of the study using the EQ-5D questionnaire, the improvement of results in the ADA arm concerning mobility and pain or discomfort has reached both statistical significance and clinical relevance in relation to PLC:

- for mobility LSMD= -0.2 95%Cl (-0.3;-0.1);
- for pain or discomfort LSMD= -0.2 95%Cl (-0.3;-0.1).

However, according to the EQ-VAS graphic scale, the improvement of the quality of life was borderline statistically significant (p≤0.05), but did not exceed the clinical relevance threshold.

In OPAL Broaden, the ASQoL assessment demonstrated a statistically significant and clinically relevant improvement in the quality of life of patients treated with ADA in relation to PLC: LSMD=-1.90 (the value of p-value parameter p<0.01 was indicated);

Mease 2017 and Strand 2019 (OPAL Broaden study) also describe the percentage of patients in whom a clinically significant change in the results of particular quality of life assessment questionnaires occurred during 3 months of observation. A statistically significant and clinically relevant improvement in the quality of life assessment was observed in the questionnaire:

- HAQ-DI – in 53.1% of patients in the ADA arm vs. 30.9% of patients in the PLC arm; the chance of the occurrence of the aforementioned endpoint was 2.54 times higher in the ADA vs. PLC arm, OR=2.54 95% (1.40; 4.60);
- SF-36 PCS – in 64% of patients in the ADA arm vs. 40.2% of patients in the PLC arm; the chance of the occurrence of the aforementioned endpoint was 2.64 times higher in the ADA vs. PLC arm, OR=2.64 95% (1.50; 4.67);

- HAQ-DI – in 59.4% of patients in the ADA arm vs. 42.2% of patients in the PLC arm; the chance of the occurrence of the aforementioned endpoint was 2.01 times higher in the ADA vs. PLC arm, OR=2.01 95% (1.15; 3.51)**.**

Population B

In Atteno 2010, a randomised trial and BSRBR, a registry study, the quality of life of patients using (ADA, INF or ETA)±conventional synthetic DMARD was assessed using the HAQ-DI questionnaire.

The results of the above-mentioned studies demonstrate that there are no statistically significant differences in the quality of life measured with the HAQ-DI questionnaire between the ADA arm and INF and ETA arms in both the 6th and 12th month of treatment.

In the BSRBR study, the quality of life was additionally assessed using the SF-36 questionnaire in the domain of physical and mental health. The study demonstrated a statistically significant advantage of ADA over INF in terms of functioning in the domain of physical health: the difference in averages amounted to MD=3.9 95%CI (0.5; 7.3). However, the result did not exceed the minimal clinically relevant difference.

The other results were not statistically significant.

Population C

The quality of life was not assessed in studies identified for population C.

<u>Clinically relevant endpoints related to the course of the disease</u>

Population A

- Dichotomous variables

  The ADA treatment was statistically significantly more efficient than PLC regarding all endpoints identified by experts as clinically relevant. The greatest differences in favour of the ADA vs. PLC arm in the Genovese 2007 and OPAL Broaden studies were reported for:

  - ACR50
    - ✓ OPAL Broaden – the chance to improve the ACR50 index was 4.68 times greater in the ADA vs. PLC arm; OR= 4.68 95%CI (2.17; 10.09);
    - ✓ Genovese 2007 – the chance to improve the ACR50 index was 16.42 times greater in the ADA vs. PLC arm; OR= 16.42 95%CI (2.06; 131.18);
  - ACR70:
    - ✓ OPAL Broaden – the chance to improve the ACR70 was 4.65 times greater in the ADA vs. PLC arm; OR= 4.65 95%CI (1.67; 19.92);
    - ✓ Genovese 2007 – the chance to improve the ACR50 was 8.06 times greater in the ADA vs. PLC arm; OR= 8.06 95%CI (1.75; 37.2).

- Continuous variables

  In the scope of DAS-28 CRP index, a statistically significant advantage of using ADA over PLC was noted. LSMD amounted to -0.7 95%Cl (-1.0;-0.5).

Population B

- Dichotomous variables

  The response to treatment in Atteno 2010 was assessed according to ACR20 criteria. No statistically significant differences were identified between arms using ADA, INF and ETA

(±xLMPCh). The percentage of patients in the above-mentioned arms who achieved a response in line with ACR20 amounted to: 70.6%, 76.7% and 72.2%, respectively.

- Continuous variables

  In the BSRBR registered study, the activity of the disease was assessed using the DAS-28 scale. No statistically significant differences between patients receiving ADA±conventional synthetic DMARD and those receiving INF±conventional synthetic DMARD or ETA±conventional synthetic DMARD were observed after 18 months of therapy.

Population C

The studies identified as part of the additional stage of the review allow for assessing the incidence of relapse and the time to relapse after discontinuation of bLMPCh treatment with or without conventional synthetic DMARD. Due to the limitations of the review, the results should be considered only illustratively. In line with the included studies, the percentage of patients experiencing a relapse after the discontinuation of bLMPCh±conventional synthetic DMARD treatment ranged from 76.9% (Araujo 2013) to 83.3% (CORRONA). The mean time to relapse ranges from 10.6 weeks (Araujo 2013) to 52 weeks (Cantini 2008). According to data published in CORRONA, the mean time to relapse amounts to 34.7 weeks.

Additional efficacy assessment on the basis of single-arm studies

An additional efficacy assessment was carried out on the basis of single-arm experimental studies: Hellman 2019, ACCLAIM (Gladman 2010), STEREO (Van den Bosch 2010, Van den Bosch 2015) and observational studies: Behrens 2018, Teoli 2012.

The quality of life assessment demonstrated a statistically significant improvement measured by the HAQ-DI questionnaire in Hellman 2019 and STEREO. The clinical importance of the change in Hellman 2019 cannot be clearly defined, while in ACCLAIM the change was clinically relevant.

Safety

Within the framework of the safety profile analysis, the identified scientific evidence relates only to populations A and B. In population C, no scientific evidence concerning safety is available, only endpoints concerning the incidence of relapse and the time to relapse were evaluated.

The results concerning the safety profile were presented for the analysed endpoints in particular populations:

Death

Population A

During the 3-month observation period in OPAL Broaden and Genovese 2007, no case of death was reported.

Population B

In the description of Atteno 2010 and GISEA (Iannone 2014, Iannone 2016) the authors do not provide any information on deaths during the study. In the BSRSR study, 2 deaths (2.2%) were reported within 18 months in the arm receiving ADA±conventional synthetic DMARD and 8 (4.7%) and 15 (4.5%) in the INF±conventional synthetic DMARD arm and ETA±conventional synthetic DMARD arm, respectively. The differences in the incidence of deaths between the arms were not statistically significant.

Adverse events

Population A

Adverse events in general occurred statistically significantly 71% less frequently in the ADA arm than in the PLC arm in Genovese 2007: 52.9% vs. 79.6%; OR = 0.29 95%CI (0.12; 0.70).

In OPAL Broaden, however, no statistically significant differences in the incidence of adverse events in general were observed, and the percentage of patients with adverse events in general amounted to 46.2% in the ADA arm vs. 35.2% in the PLC arm.

The particular adverse events (AEs) occurring statistically significantly less frequently in patients using adalimumab in comparison to the PLC arm in Genovese 2007 were as follows:

- 79% lower chance of exacerbation of psoriasis (3.9% in ADA arm vs. 16.3% in PLC arm); OR = 0.21 95%CI (0.04; 1.04);
- 88% lower chance of exacerbation of psoriatic arthritis (2.0% in ADA arm vs. 14.3% in PLC arm); OR = 0.12 95%CI (0.01; 1.01).

According to the authors of Genovese 2007, the most frequent AEs in patients treated with ADA±conventional synthetic DMARD were parasitic infections (17.6%) in general, parasitic infections of the upper respiratory tract (13.7%) and pain at the injection site (11.8%), but their occurrence was not statistically significantly more frequent in the ADA arm than in the PLC arm.

The differences in the incidence of serious adverse events in the ADA arm vs. PLC arm in both OPAL Broaden and Genovese 2007 were not statistically significant, and the incidence of serious adverse events (SAEs) in the ADA arm in both studies did not exceed 2%.

In OPAL Broaden and Genovese 2007, there were also no statistically significant differences in the incidence of adverse events leading to treatment discontinuation, and that percentage in the ADA arm amounted to 1.9-2.0%.

Additional safety assessment on the basis of the open, extension phase of Genovese 2007

97 patients from both arms of the first blinded phase of the study were qualified for safety assessment in the additional phase of the study. No deaths occurred during the 12-week observation period (weeks: 12 – 24) of this phase of Genovese 2007. SAEs occurred in 3 (3.1%) patients. AEs in general were reported in 53 (54.6%) patients and parasitic infections in 29 (29.9%) patients. AEs leading to treatment discontinuation were reported in 6 (6.2%) patients.

Population B

The analysis of total AEs incidence in Atteno 2010 demonstrated no statistically significant differences between ADA, INF and ETA arms. The authors of the study do not describe the occurrence of serious adverse events and adverse events leading to treatment discontinuation.

Additional safety assessment on the basis of single-arm studies

The additional safety assessment was carried out on the basis of the following studies: ACCLAIM (Gladman 2010) and STEREO (Van den Bosch 2010). No case of death has been reported in the ACCLAIM, and publications describing STEREO do not refer to this endpoint.

Severe adverse events (SAEs) occurred in 2.4% of patients in ACCLAIM and 4.1% of patients in STEREO. The most common SAEs were parasitic infections (0.7%; STEREO). In ACCLAIM and STEREO, adverse events in general occurred in 63.8% and 70.1% of patients, respectively. The most frequently reported AEs were infections and parasitic infections (18.1%; ACCLAIM).

Additional safety information

No alerts on the safety of use of adalimumab have been identified on the websites of organisations monitoring safety of care (i.a. the Office for Registration of Medicinal Products, Medical Devices and Biocidal Products (URPL), the European Medicines Agency (EMA), the Food and Drug Administration (FDA); the Medicines and Healthcare products Regulatory Agency (MHRA).

- URPL

2008 – The announcement describes the occurrence of 3 cases of hepatosplenic T-cell lymphoma between 2002-2008. Hepatosplenic T-cell lymphoma is a neoplasm with a bad prognosis. In 2 out of 3 cases the patient was simultaneously taking azathioprine or 6-mercaptopurine because of a comorbid inflammatory bowel disease, however, a potential link between hepatosplenic T-cell lymphoma and adalimumab cannot be excluded. In the event of symptoms of lymphoma and/or hepatosplenomegaly with or without generalised peripheral lymph node enlargement or significant peripheral blood lymphocytosis in patients treated with ADA, the diagnosis of hepatosplenic T-cell lymphoma should be taken into account. The warning has been included in the SPC and patient leaflet.

- EMA

  2016 – The announcement mentions the need for a detailed analysis of cases of acute febrile neutrophilic dermatosis (Sweet's syndrome, SS) in patients taking adalimumab. The available data confirm 5 cases of relief of SS symptoms after discontinuation of taking adalimumab and a case of recurrence of SS symptoms after the therapy was resumed. The MAH has been called upon to submit a detailed review of the reported cases of Sweet's syndrome considered to be linked to ADA. It was recommended to correct product information and to propose appropriate changes to the SPC.

  2013 – The announcement refers to cases of immune reconstitution inflammatory syndrome (IRIS) associated with the use of adalimumab. EMA recommended investigating the IRIS cases and determining the time after which the first symptoms of IRIS appear following discontinuation of adalimumab therapy.

- FDA

  2018 – The announcement draws attention to the increased risk of severe, potentially fatal infections possible during treatment with ADA, which include: tuberculosis, bacterial sepsis, invasive fungal infections and infections caused by other opportunistic pathogens. In case of severe infection or sepsis, the treatment with ADA should be discontinued. Before the initiation of treatment with adalimumab, a test for latent tuberculosis should be performed and patients should be monitored for symptoms of tuberculosis during treatment. Moreover, the cases of lymphomas and other malignant neoplasms in patients treated with iTNF, including ADA, were also indicated. Currently, it cannot be excluded whether fatal cases of hepatosplenic T-cell lymphoma are associated with the administration of iTNF in combination with azathioprine or 6-mercaptopurine.

In line with the SPC for Hyrimoz, very common adverse events (≥1/10) include:

- Parasitic infections and infections (infections of the respiratory tract, including infections of the lower and upper respiratory tract, pneumonia, sinusitis, pharyngitis, nasal pharyngitis and pneumonia caused by the herpes virus);
- Blood and lymphatic disorders (leukopenia, including neutropenia and agranulocytosis, as well as anaemia);
- Metabolism and nutrition disorders (increased lipid levels);
- Nervous system disorders (headaches);
- Stomach and intestinal disorders (stomach pains, nausea and vomiting);
- Hepatic and biliary disorders (increased liver enzyme activity);
- Skin and subcutaneous tissue disorders (rash, including peeling rash);
- Musculoskeletal and connective tissue disorders (reaction at injection site, including erythema at injection site).

Limitations of the analysis

The following aspects impact the reliability of the clinical analysis:

- The main limitation of the clinical analysis consists in the lack of scientific evidence on the efficacy and safety of therapy with the assessed drug for population C. The studies included as scientific evidence for the efficacy of adalimumab in population C in fact concern biological drugs other than adalimumab and can therefore only be considered as an additional, illustrative assessment of the duration of treatment response after discontinuation of bLMPCh treatment and of the prevalence of relapse in such a situation. At the same time, the evidence does not provide a comparison of the efficacy of the use of ADA vs. conventional synthetic DMARD in population C. Although an additional systematic review has been conducted to assess efficacy in this arm, the included studies do not comply with the predefined PICO scheme in terms of population, intervention and comparator. It should be noted that population C represents a large part of the target population in which Hyrimoz is to be used after reimbursement, and drawing conclusions on the basis of the identified scientific evidence for this arm is impossible.
- The studies on populations A and B do not allow to draw comprehensive conclusions on the efficacy and safety of adalimumab.

  OPAL Broaden (population A) was designed to demonstrate the advantage of tofacitinib (TOF) over no treatment (PLC), and a comparison of ADA vs. PLC has also been part of the study. Nevertheless, the superiority hypothesis only applied to the TOF vs. PLC comparison. In Genovese 2007 (population A) the comparison conducted in 32.7% of the studied sample probably did not include the adopted comparator.

  The primary studies identified for population B refer only to some of the adopted comparators (infliximab, etanercept). No evidence has been identified for golimumab, secukinumab and certolizumab pegol, which are also available under the current drug programme and therefore represent comparators for ADA in population B. In addition, in population B, the safety assessment of adalimumab is hampered by the scarce data.
- The use of scales and questionnaires dedicated to diseases other than psoriatic arthritis also constitutes a limitation (e.g. the ACR scale is designed for rheumatoid arthritis and the ASQoL questionnaire for patients with ankylosing spondylitis). This also applies to the primary endpoints in the included studies.
- In addition, the included primary studies provide little data on the efficacy of adalimumab after previous iTNF treatment and, given the indication in question, such a clinical situation may occur in practice.
- Some of the data included in the report were analysed in publications included in the analysis within the framework of post-hoc analysis, characterised by lower reliability than the analyses planned in the study protocol.
- The criteria for inclusion in the OPAL Broaden study include a requirement for no prior iTNF treatment. The indication in question does not contain this restriction, so the identified study does not fully cover the assessed population.
- Patients after the failure of DMARD treatment participated in Atteno 2010, but the authors do not specify how many DRMARD treatment lines had been applied prior to their participation in the study. Population B is a group defined using the inclusion criteria for the B.35 drug programme, i.e. patients after ineffective treatment with at least two conventional synthetic DMARDs. At the same time, Atteno 2010 excluded all patients who had been treated with iTNF. Such an exclusion criterion does not exist in the current drug programme. Therefore, it

is not possible to determine to what extent the population in Atteno 2010 corresponds to the population in the application in question.

- The studies included in the clinical analysis did not assess patient survival.
- There are no long-term data on the effectiveness of the assessed technology.

The uncertainty of the clinical analysis results is affected by the following limitations:

- In Genovese 2007, the definition of the ITT (intention-to-treat) population is different from the standard one according to the guidelines (i.e. all patients randomised for the study) – in the study, the ITT population was defined as all patients who received at least 1 dose of the drug in question.
- Some of the data from the studies included in the analysis were interpreted from diagrams, which involves the risk of uncertainty as to the precision of interpretation.

Proposals of risk-sharing schemes

No risk-sharing scheme was proposed.

Economic analysis, including a cost-effectiveness estimation

An economic analysis consists in estimating and comparing the costs and health effects which may be associated with the use of a new therapy in an individual patient instead of therapies which are currently reimbursed.

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

The comparison of values concerning the costs and effects related to the use of a new therapy and comparing them to the costs and effects of currently reimbursed therapies allow for obtaining an answer to the question on whether the health effect achieved as a result of the new therapy is associated with higher costs in comparison to the currently reimbursed therapies.

The achieved cost-effectiveness ratios are compared with the so-called cost-effectiveness threshold, i.e. which indicates that taking into account the means at the disposal of Poland (expressed in its GDP), the maximum cost of a new therapy necessary to obtain a unit of health effect (1 LYG or 1 QALY), compared to the currently available treatments, should not exceed three times the amount of per capita GDP.

Currently the cost-effectiveness threshold in Poland amounts to PLN 147,024 (3 x PLN 49,008).

The cost-effectiveness ratio does not estimate or determine the value of life, it only allows to assess and, among other things, select, a therapy associated with the potentially best use of the currently available resources.

The applicant carried out an economic analysis using a cost-utility analysis (CUA) comparing Hyrimoz (adalimumab, ADA) with comparators selected for three subpopulations:

- Population 1 – adult patients with active and progressive severe psoriatic arthritis, in whom the response to previously used disease-modifying drugs has proved insufficient, eligible for treatment under the current drug programme for psoriatic arthritis treatment (after the failure of treatment with at least two conventional synthetic disease-modifying drugs (conventional synthetic DMARDs).
- Population 2 – adults with active and progressive severe psoriatic arthritis, in whom the response to previously used disease-modifying drugs proved to be insufficient, ineligible for treatment under the current drug programme for psoriatic arthritis treatment (after the failure of treatment with one conventional synthetic DMARD).

- Population 3 – adult patients with active and progressive, non-severe psoriatic arthritis, in whom the response to previously used disease-modifying drugs has proved insufficient, ineligible for treatment under the current drug programme for psoriatic arthritis treatment.

The estimates include the perspective of the public payer (the National Health Fund, NHF) and common perspective (the NHF and the patient). The analysis was conducted in a lifelong time horizon (51.9 years). As part of the analysis, the existing scenario, in which adalimumab is reimbursed under the drug programme for the treatment of psoriatic arthritis, was compared with the new scenario, in which ADA would be reimbursed under the following reimbursement availability category: "Reimbursed drugs available in a pharmacy on prescription for the entire range of registered indications and uses or in the indication of a particular clinical condition".

Only direct medical costs were taken into account in the applicant's analysis, which include the costs of: drugs and their administration, qualification for the drug programme and diagnostics as well as therapy monitoring. The costs of treating adverse effects were considered to be non-differentiating.

In line with the applicant's estimations, the introduction of adalimumab in pharmacy reimbursement, instead of drug programme reimbursement, entails higher costs but also more beneficial health effects. The applicant's analysis reveals that the technology in question is *[information protected as a trade secret]* in each of the included comparisons. *[information protected as a trade secret]* referred to in the Act on reimbursement (PLN 147,024/QALY).

With the ICUR values estimated in the basic analysis, the applicant's calculated threshold values of net selling prices of individual drug packaging, at which the cost of obtaining an additional quality adjusted year of life is equal to the cost-effectiveness threshold, from the public payer's perspective amount to:

- *[information protected as a trade secret]*

However, from the common perspective:

- *[information protected as a trade secret]*

The threshold prices estimated in the basic analysis are *[information protected as a trade secret]* than the net ex-factory price regardless of the adopted analysis perspective (NHF or common).

The results of the conducted one-way sensitivity analysis demonstrate that the inclusion of alternative analysis scenarios and changes in the values of individual parameters do not change the conclusion on cost-effectiveness, i.e. the technology in question *[information protected as a trade secret]*. Therefore, no probabilistic analysis was carried out by the applicant. The greatest impact on the increase of ICUR is due to *[information protected as a trade secret]*

Limitations of the analysis

All limitations of reliability and uncertainty of estimates concerning the efficacy and safety of the technology in question also apply to the economic assessment of the technology in question.

Furthermore, the uncertainty of estimates in the economic analysis is affected by the following issues:

- Adopting only conventional synthetic DMARDs as a treatment for patients who should discontinue effective adalimumab treatment may be questionable *[information protected as a trade secret]*
- The assumption that Hyrimoz is determining the basis of the limit within the new pharmacy reimbursement limit group is characterised by uncertainty. It seems to be highly probable that if Hyrimoz is excluded from the psoriatic arthritis treatment drug programme, other drugs containing adalimumab will most probably also be reimbursed within pharmacy reimbursement. This may result in a situation where the share structure in the new limit group will be the same as in the current limit group, where the basis of the limit is determined

by Imraldi, a solution for injection in a pre-filled syringe, 40 mg, 2 pre-filled syringes 0.8 ml + 2 gauze pads.

- The applicant's model assumes no cost of qualification for the ADA treatment, provided it is subject to pharmacy reimbursement. According to the expert interviewed by the AOTMiT, when qualifying patients, *"the necessary step is to exclude the risk of tuberculosis reactivation, which will be difficult in outpatient settings, and qualification should be carried out in facilities with appropriate experience"*. Taking the additional costs into account in the intervention arm could increase the ICUR.
- In the model, for bDMARD treatment under the drug programme, one of the following substances was used: etanercept, infliximab, golimumab or certolizumab pegol, whereas secukinumab (SEK), the market share of which was considered negligible, was not included. The small share of SEK is due to the fact that it was included in the reimbursement at the end of 2018. It is difficult to estimate what impact SEK would have on the outcome of the analysis.
- *[information protected as a trade secret]* and on the basis of Araujo 2013. It should be noted that in Araujo 2013, only 5 out of 26 patients were previously treated with bDMARD monotherapy and no information was given whether any of these patients were treated with adalimumab. Therefore, the adopted values are characterised by high uncertainty.
- The choice of a lifelong time horizon should be considered appropriate because, according to the identified clinical guidelines, the treatment of psoriatic arthritis should be carried out on a long-term basis. However, due to the lack of long-term data, estimates in the lifetime time horizon are subject to uncertainty. The applicant has carried out a sensitivity analysis in which it has made estimations for a 10- and 20-year time horizon *[information protected as a trade secret]*.
- The value (0.535) of utility in patients not responding to bDMARD treatment adopted in the basic analysis of the model is questionable for the analysts as it is much higher than the utility in patients entering the model (0.482) or the utility for patients not responding to conventional synthetic DMARD and BSC treatment (0.482). The applicant has tested utility values in a sensitivity analysis, where the adoption of alternative values resulted in *[information protected as a trade secret]*.

Indication whether the circumstances referred to in Article 13, paragraph 3 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional uses and medical devices (Journal of laws No. 2016, item. 1536, as amended) occur

In case the applicant's clinical analysis does not include randomised clinical trials which prove the superiority of the drug over the medical technologies which are currently reimbursed in the particular indication, it is the ex-factory price of the drug which must be calculated in such a way that the cost of using the drug applying for reimbursement is not higher than the cost of the health technology with the most favourable ratio of health effects to the cost of obtaining them.

Given the fact that the advantage of the intervention in question over its comparators has not been demonstrated, circumstances referred to in Article 13 paragraph 3 of the Act on reimbursement occur.

The value of the net ex-factory price at which the cost of using Hyrimoz is not higher than the cost of therapy with biological DMARD reimbursed under the drug programme for the treatment of psoriatic arthritis, with the greatest cost-effectiveness ratio (the lowest cost of use), i.e. ADA therapy under the drug programme, *[information protected as a trade secret]* than the cost of the comparator adopted in the applicant's basic analysis option.

Thus, the net ex-factory price of Hyrimoz, at which the cost of using the drug in question will not exceed the cost of the comparator is *[information protected as a trade secret]* in the analysis variant which is in accordance with Article 13(3) of the Act on reimbursement.

Analysis of the effects on the healthcare system, including budget impact analyses (BIA)

The analysis of the effects on the healthcare system consists of two important parts.

Firstly, the analysis of the impact on the payer's budget allows for estimating potential expenditure related to the financing of a new therapy from public funds.

The estimated expenditure related to the new therapy (the "tomorrow" scenario) is compared with how much currently is spent on the treatment of a particular health problem (the "today" scenario). On that basis it is possible to assess whether the new therapy will require a higher level of funding for the treatment of a particular health problem or whether it will involve savings in the payer's budget.

The budget impact assessment makes it possible to determine whether the payer possesses the necessary resources to finance a particular technology.

The second part of the analysis of the effects on the healthcare system raises the question on how the decision to finance a new therapy can affect the organisation of the provision of services (especially in the context of adjustments necessary for the new therapy to be used) and the availability of other healthcare services.

The analysis of the effects on the healthcare system, in the event that Hyrimoz (adalimumab), used in the treatment of active and progressive psoriatic arthritis in adult patients whose response to previously used disease-modifying drugs was insufficient, is reimbursed under pharmacy reimbursement, was carried out from the perspective of the public payer (National Health Fund, NHF) and the common perspective. The estimations were carried out in a 2-year time horizon. The costs were included in a similar way as in the economic analysis. The number of patients eligible for the technology in question was estimated to be *[information protected as a trade secret]* in the first year and *[information protected as a trade secret]* persons in the second year of reimbursement.

In line with the estimations, the introduction of Hyrimoz in the pharmacy reimbursement, instead of the reimbursement of the drug programme for the treatment of psoriatic arthritis, *[information protected as a trade secret]*

As part of the sensitivity analysis, the applicant tested the change of analogous parameters as those used in the economic analysis. In addition, two new scenarios were tested, which assume *[information protected as a trade secret]*

The sensitivity analysis of the key parameters of the model demonstrated that population assumptions have the greatest impact on the results of the analysis. In the maximum target population scenario carried out by the applicant, the NHF's expenditure *[information protected as a trade secret]*, and total expenditure of NHF and the patient *[information protected as a trade secret]* in the first and second year of the analysis, respectively.

Limitations of the analysis

The uncertainty of drawing conclusions based on the budget impact analysis depends i.a. on the following aspects:

- The uncertainty associated with the applicant's estimation of the target population constitutes the main limitation of the analysis. The applicant adopted the assumption that starting to finance Hyrimoz under the open list would result in the discontinuation of reimbursement of the other drugs containing ADA under the B.35 drug programme, but did not explain how patients who have hitherto used adalimumab under this programme would be treated. According to the AOTMiT, a large part of these patients will in the end continue to be treated with ADA within the pharmacy reimbursement, therefore the population size assumed by the

applicant is underestimated. Since calculating the scale of the underestimation is difficult (as patients are likely to switch to ADA under pharmacy reimbursement gradually and some may remain with a different bDMARD under the drug programme), the decision was taken not to perform the calculation.

According to the NHF data (included in the Agency's Verification Analysis for Xeljantz) in 2018, 925 patients were treated with adalimumab under the B.35 "Treatment of aggressive psoriatic arthritis" drug programme. They represented more than half of the total population treated under this programme (1,622 patients). Given that the number of patients treated with adalimumab in the drug programme for the treatment of psoriatic arthritis increases by about 100 each year, it can be assumed that in the analysed years, the population will amount to over 1,100-1,200 patients. It will be further increased by patients with an indication in line with the indication included in the application, who do not meet the eligibility criteria for the drug programme for the treatment of psoriatic arthritis (i.e. after treatment with only 1 conventional synthetic DMARD and with a non-severe form of psoriatic arthritis), *[information protected as a trade secret]* However, when estimating the size of this population, one should take into account the fact that not all patients will be able to immediately switch to treatment outside the drug programme and that some patients may switch to another biological drug used under the drug programme.

- Due to the fact that the cost assumptions adopted by the applicant in the budget impact analysis are analogous to those indicated in the economic analysis, the limitations of the economic analysis apply also in this case. The Agency has doubts concerning the assumptions relating to the adoption of minimum qualification costs and treatment monitoring costs in the case that adalimumab is included in the pharmacy reimbursement and the assumption that Hyrimoz will determine the basis of the limit in the new limit group.
- Failure to include secukinumab in the optional bDMARD (the small market share of this drug is due to its recent introduction into reimbursement). Secukinumab is one of the cheapest bDMARDs, so including the drug in the analysis would reduce the average cost of treatment with bDMARDs, while its small share will not change the conclusions of the analysis.

Remarks on the proposed risk-sharing instrument

Not applicable.

Remarks on the drug programme records

Not applicable.

Review of the solutions proposed in the rationalisation analysis

The objective of the rationalisation analysis is to identify a mechanism which, if introduced, will result in a release of public funds in an amount at least corresponding to the increase in costs resulting from a positive decision to reimburse the intervention in question.

A rationalisation analysis is submitted if the budget impact analysis of the public payer demonstrated that the cost of reimbursement would increase.

[information protected as a trade secret]

Review of recommendations issued in other countries in relation to the technology in question

The search resulted in the identification of 9 clinical guidelines regarding treatment of multiple sclerosis, including Polish guidelines:

- Tłustochowicz 2016 (Polish);
- American College of Rheumatology/National Psoriasis Foundation Guideline for the Treatment of Psoriatic Arthritis, ACR/NPF 2018 (American);
- National Institute for Health and Care Excellence, NICE 2018a, NICE 2018b; NICE 2017b, NICE 2017 (British);
- Sociedad Española de Reumatología SER 2018 (Spanish);
- European League Against Rheumatism, EULAR 2015 (European);
- Group for Research and Assessment of Psoriasis and Psoriatic Arthritis, GRAPPA 2015 (international).

All identified clinical guidelines recommend biological treatment in patients with active psoriatic arthritis after the failure of previous treatment with conventional DMARDs or NSAIDs, depending on the type of disease. All recommendations propose TNFα inhibitors as first-line biological drugs in patients with psoriatic arthritis, when the response to previously used disease-modifying drugs has been insufficient. Some guidelines condition the use of TNFα inhibitors to the use of at least two standard DMARDs (e.g. NICE 2017).

In patients with active psoriatic arthritis despite the monotherapy with TNFα inhibitor, the guidelines recommend to start by switching to another TNFα inhibitor. If the use of TNF-α inhibitors is not suitable, biological DMARD IL 12/23 (e.g. ustekinumab), IL-17 (e.g. secukinumab) or synthetic DMARD – PDE-4 inhibitor (EULAR 2015) may be considered. According to the 2018 ACR/NPF Guideline, if the use of TNF-α inhibitors is not suitable, the change to IL-17 inhibitor is preferable instead of IL-12/23, abatacept and tofacitinib.

According to the Polish 2016 recommendations, the treatment of psoriatic arthritis should be comprehensive and based on EULAR guidelines.

The search also identified 9 reimbursement recommendations for adalimumab in the indication of psoriatic arthritis, including 1 for Hyrimoz and 8 for Humira, its reference drug. All the identified recommendations were positive:

- Haute Autorité de Santé (HAS 2018; HAS 2010), France;
- National Institute for Health and Care Excellence (NICE 2010), the UK;
- All Wales Medicines Strategy Group (AWMSG 2007) Wales;
- Gemeinsame Bundesausschuss, Institute for Quality and Efficiency in Health Care (GBA, IQWIG 2006), Germany;
- Canadian Agency for Drugs and Technologies in Health (CADTH 2006), Canada;
- Pharmaceutical Benefits Advisory Committee (PBAC 2006) Australia;
- Pharmacology and Therapeutics Advisory Committee (PTAC 2006) New Zealand;
- Scottish Medicines Consortium (SMC 2005), Scotland.

According to the information provided by the applicant, both Hyrimoz (in the form of pens and in the form of pre-filled syringes with protection) is financed in 12 EU and EFTA countries (out of 31 countries indicated), including 3 countries with a GDP similar to Poland (Latvia, Slovakia, Hungary). The applicant has not provided data on the reimbursement levels in those countries. No risk-sharing scheme has been applied in any of those countries.

Legal basis for the recommendation

The recommendation was prepared on the basis of an order of the Minister of Health of 23/09/2019 (reference number: PLR.4600.1611.2019, PLR.4600.1620.2019), with regard to preparation of the recommendation of the President of the AOTMiT on whether to reimburse Hyrimoz (adalimumab), solution for injection in pre-filled syringe, 40 mg, 2 pre-filled syringes, EAN: 07613421020880; Hyrimoz (adalimumab), solution for injection in pre-filled syringe, 40 mg, 2 pre-filled syringes with protection, EAN: 07613421020897, in the indication: treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate pursuant to Article 35 paragraph 1 of the Act of 12 May 2011 on the reimbursement of drugs, foodstuffs for particular nutritional purposes and medical devices (Journal of Laws of 2019, item 784, as amended), after having read the Position of the Transparency Council No. 111/2019 of 9 December 2019 on the evaluation of Hyrimoz (adalimumab) in the indication: treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.

References

1. Position of the Transparency Council No. 111/2019 of 9 December 2019 on the evaluation of Hyrimoz (adalimumab) in the indication: treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate.
2. Reimbursement application for Hyrimoz (adalimumab) in the indication: treatment of active and progressive psoriatic arthritis in adults when the response to previous disease-modifying anti-rheumatic drug therapy has been inadequate. Verification analysis No. OT.4330.15.2019; completion date: 29/11/2019.