Justification

to the Resolution of the Federal Joint Committee (G-BA) on an Amendment of the Pharmaceuticals Directive (AM-RL): Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a SGB V Belimumab (New Therapeutic Indication: Systemic Lupus Erythematosus, ≥ 5 Years)

of 14 May 2020

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1. Legal basis

According to Section 35a, paragraph 1 German Social Code, Book Five (SGB V), the Federal Joint Committee (G-BA) assesses the benefit of reimbursable medicinal products with new active ingredients. This includes in particular the assessment of the additional benefit and its therapeutic significance. The benefit assessment is carried out on the basis of evidence provided by the pharmaceutical company, which must be submitted to the G-BA electronically, including all clinical trials the pharmaceutical company has conducted or commissioned, at the latest at the time of the first placing on the market as well as the marketing authorisation of new therapeutic indications of the medicinal product, and which must contain the following information in particular:

1. Approved therapeutic indications,
2. Medical benefit,
3. Additional medical benefit in relation to the appropriate comparator therapy,
4. Number of patients and patient groups for whom there is a therapeutically significant additional benefit,
5. Treatment costs for statutory health insurance funds,
6. Requirements for a quality-assured application.

The G-BA may commission the Institute for Quality and Efficiency in Health Care (IQWiG) to carry out the benefit assessment. According to Section 35a, paragraph 2 SGB V, the assessment must be completed within three months of the relevant date for submission of the evidence and published on the internet.

According to Section 35a, paragraph 3 SGB V, the G-BA decides on the benefit assessment within three months of its publication. The resolution is to be published on the internet and forms part of the Pharmaceuticals Directive.

2. Key points of the resolution

The active ingredient belimumab (Benlysta®) was listed for the first time on 15 August 2011 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 21 October 2019, Benlysta® received the marketing authorisation for a new therapeutic indication classified as a major variation of type 2 according to Annex 2 No. 2a to Regulation (EC) number 1234/2008 of the Commission from 24 November 2008 concerning the examination of variations to the terms of marketing authorisations for medicinal products for human use and veterinary medicinal products (OJ L 334, 12 December 2008, p. 7).

On 14 November 2019, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 2 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 1, number 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient belimumab with the new therapeutic indication (add-on therapy in patients 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy)) in due time (i.e. at the latest within four weeks after informing the pharmaceutical company about the approval for a new therapeutic indication (treatment of acute lymphatic leukaemia in SLE-positive patients).

The G-BA commissioned the IQWiG to carry out the assessment of the dossier. The benefit assessment was published on the website of the G-BA (www.g-ba.de) on 17 February 2020, thus initiating the written statement procedure. In addition, an oral hearing was held.

The G-BA came to a resolution on whether an additional benefit of belimumab compared with the appropriate comparator therapy could be determined on the basis of the dossier of the pharmaceutical company, the dossier assessment prepared by the IQWiG, the statements submitted in the written statement and oral hearing procedure, and the addenda to the benefit assessment prepared by the IQWiG. In order to determine the extent of the additional benefit, the G-BA has assessed the data justifying the finding of an additional benefit on the basis of their therapeutic relevance (qualitative), in accordance with the criteria laid down in Chapter 5, Section 5, paragraph 7 VerfO. The methodology proposed by the IQWiG in accordance with the General Methods [1] was not used in the benefit assessment of belimumab.

In the light of the above and taking into account the statements received and the oral hearing, the G-BA has arrived at the following assessment:

2.1 Additional benefit of the medicinal product in relation to the appropriate comparator therapy

2.1.1 Approved therapeutic indication of belimumab (Belimumab®) in accordance with the product information

Benlysta is indicated as add-on therapy in patients 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy (see section 5.1).

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

Children and adolescents from 5 to 17 years with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity despite standard therapy

A patient-individual therapy, taking into account the respective organ attack, the previous therapy, and the disease activity and selecting amongst the following therapies:

- Hydroxychloroquine, chloroquine
- Non-steroidal anti-inflammatory drugs (NSAIDs)
- Glucocorticoids
- Azathioprine

Criteria according to Chapter 5, Section 6 of the Rules of Procedure of the G-BA:

The appropriate comparator therapy must be an appropriate therapy in the therapeutic indication according to the generally recognised state of medical knowledge (Section 12 SGB V), preferably a therapy for which endpoint studies are available and which has proven its worth in practical application unless contradicted by the guidelines under Section 92, paragraph 1 SGB V or the principle of economic efficiency.

[1] General Methods, Version 5.0 dated 10 July 2017. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen [Institute for Quality and Efficiency in Health Care], Cologne.

In determining the appropriate comparator therapy, the following criteria, in particular, must be taken into account as specified in Chapter 5, Section 6, paragraph 3 VerfO:

1. To be considered as a comparator therapy, the medicinal product must, principally, have a marketing authorisation for the therapeutic indication.
2. If a non-medicinal treatment is considered as a comparator therapy, this must be available within the framework of the SHI system.
3. As comparator therapy, medicinal products or non-medicinal treatments for which the patient-relevant benefit has already been determined by the Federal Joint Committee shall be preferred.
4. According to the generally recognised state of medical knowledge, the comparator therapy should be part of the appropriate therapy in the therapeutic indication.

Justification based on the criteria set out in Chapter 5, Section 6, paragraph 3 VerfO:

On 1. For the treatment of systemic lupus erythematosus, non-steroidal anti-inflammatory drugs (NSAIDs; including ibuprofen), systemic glucocorticoids (including prednisolone), azathioprine, antimalarial active ingredients (chloroquine, hydroxychloroquine), and belimumab are generally approved active ingredients for the treatment of systemic lupus erythematosus. For the treatment of lupus nephritis, cyclophosphamide is also considered an approved medicinal product.

On 2. A non-medicinal treatment is not indicated in this therapeutic indication.

On 3. The following resolutions of the G-BA are available in the therapeutic indication considered here:

- Belimumab (Resolution according to Section 35a SGB V of 2 August 2012)
- Resolution on an amendment of the Pharmaceuticals Directive (AM-RL): Annex VI – off-label-use
  Mycophenolate mofetil /mycophenolenic acid for lupus nephritis (Resolution of 21 September 2017)

On 4. The general accepted state of medical knowledge on which the decision of the G-BA are based was illustrated by systematic research for guidelines and reviews of clinical studies in this indication. For the treatment of systemic lupus erythematosus, the aforementioned active ingredients are available.

The systematic search revealed that for the therapeutic indication “treatment of juvenile SLE”, there is currently no uniform therapy algorithm. Patients with juvenile SLE are treated individually taking into account the respective organ attack, the potential previous therapy, and the predominant disease activity. The superiority of individual approved active ingredients is not conclusively evident within the framework of the evidence available.

Patients are usually first fine-tuned to optimised treatment with glucocorticoids, antimalarials (hydroxychloroquine or chloroquine) and to NSAID for symptomatic treatment.

Immunosuppressive agents (e.g. azathioprine) are used if the response is inadequate. In the case of sustained high disease activity (e.g. positive test for anti- dsDNA antibodies and low complement) despite standard therapy, belimumab was previously approved as an adjunctive therapy for adults only.In accordance with Section 6, paragraph 3, No. 1, Chapter 5 of the VerfO of the G-BA, medicinal products designated as appropriate comparator therapy must in principle have a marketing authorisation for the therapeutic indication. Deviations from this principle are possible if the G-BA allows the prescribability of an off-label medicinal product in accordance with Section 30, paragraph 1 of Section K of the AM-RL in the therapeutic indication concerned. By the resolution of 21 September 2017 on an amendment to the Pharmaceutical Directive (AM-RL) of Annex VI – Off-label use of mycophenolate mofetil/mycophenolenic acid for lupus nephritis (concerning Class III–V), a corresponding regulation was made for the use of mycophenolate mofetil/mycophenolenic acid for lupus nephritis.

Cyclophosphamide is approved only for severe, progressive forms of lupus nephritis.Lupus nephritis (LN) is a progressive form or organ manifestation of lupus erythematosus, which can be associated with serious complications. The treatment of patients with a severe LN (class III–V) is currently not recommended in accordance with the product information of belimumab. Cyclophosphamide and mycophenolate mofetil/mycophenolenic acid are thus not indicated and therefore not part of the underlying appropriate comparator therapy.

Within the framework of a patient-individual therapy, taking into account the respective organ attack, possibly the previous therapy, and the disease activity, the following active ingredients are therefore suitable for juvenile SLE patients from 5 years of age: Hydroxychloroquine, chloroquine, non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and azathioprine. It is assumed that the standard therapy within the framework of a study is used in both arms.
For the implementation of the patient-individual therapy in a direct comparative study, it is expected that the investigator will have a choice of several treatment options available. This will allow a patient-individual therapy decision to be made taking into account the criteria mentioned above.
A further differentiation of the patient population in the sense of patients who have not responded to standard therapy is not carried out at this time because of the lack of delimiting criteria and uniform therapy recommendations.

The findings in Annex XII do not restrict the scope of treatment required to fulfil the medical treatment contract.

2.1.3 Extent and probability of the additional benefit

In summary, the additional benefit of belimumab is assessed as follows.

Children and adolescents from 5 to 17 years with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity despite standard therapy

Hint for a non-quantifiable additional benefit

Justification:

To assess the additional benefit of belimumab in patients from 5 years of age with active, autoantibody-positive systemic lupus erythematosus (SLE) who show high disease activity despite standard therapy, the pharmaceutical company presented the pivotal, multi-centre, randomised, double-blind, placebo-controlled Phase III PLUTO study.

The PLUTO study is a double-blind RCT comparing belimumab + patient-individual concomitant medication vs placebo + patient-individual concomitant medication. The PLUTO study consists of 3 parts: the randomised part of the study (Part A; 52 weeks), the extension phase with the administration of belimumab (Part B) for all patients who completed Part A, and the follow-up without administration of belimumab or placebo (Part C) for patients whose participation in Part A or B was terminated. The dosage of belimumab followed the specifications in the product information.

The patients in the PLUTO study received patient-individual concomitant therapy for the treatment of SLE.

The concomitant medication administered in the PLUTO study also included active ingredients not authorised in Germany for the treatment of SLE (e.g. tacrolimus) or which are prescribable only in accordance with Annex VI to section K of the Pharmaceuticals Directive (off-label use) (mycophenolate mofetil/mycophenolenic acid for lupus nephritis). In order to take this into account, the pharmaceutical company also presents the results of the total population (ITT population; 53 vs 40 patients) and uses the results of sub-populations ITT-ZVT1 (32 vs 25 patients) and ITT-ZVT2 (21 vs 14 patients) to derive the additional benefit. The ITT-ZVT1 population corresponds to the ITT population without the patients who had received active

ingredients that are not approved in Germany (methotrexate, tacrolimus, leflunomide) as concomitant medication. The ITT-ZVT2 population corresponds to the ITT-ZVT1 population without the patients who received mycophenolate as concomitant medication at least once during the course of the study.

In the populations evaluated by the pharmaceutical company, the appropriate comparator therapy is best represented in the ITT-ZVT2 population. Hence, only sub-population ITT-ZVT2 is used for the benefit assessment.

The PLUTO study included 93 children and adolescents aged 5 to 18 years with active SLE who were undergoing pre-treatment. In the ITT-ZVT2 population, 21 children and adolescents were included in the verum arm and 14 in the comparator arm. Of the ITT-ZVT2 population included in the PLUTO study, about 90% were aged 12 to 18 years and about 10% were aged 5 to 12 years. The characteristics of the patients in the ITT-ZVT2 population of the PLUTO study are largely comparable between the two treatment arms. The average duration of the disease was about 2.5 years, and the average disease activity in accordance with the SELENA-SLEDAI score was about 9.5 points. SLE was diagnosed according to the American College of Rheumatology criteria. According to the inclusion criteria, the disease activity of SLE upon inclusion in the study had to be ≥ 8 in accordance with the Safety of Estrogens in Lupus Erythematosus – National Assessment (SELENA)-Systemic Lupus Erythematosus Disease Activity Index (SLEDAI). This was reduced to ≥ 6 with Amendment 4 to speed up recruitment, whereby ≥ 50% of patients had to show disease activity ≥ 8 points on the SELENA-SLEDAI. There had to be a positive test for anti-dsDNA antibodies or a low complement. Patients with lupus nephritis were not included in the ITT-ZVT2 population.

Belimumab is indicated as “add-on therapy in patients 5 years and older with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity despite standard therapy”. In accordance with the information provided in the product information, a high disease activity is defined as a positive test for anti-dsDNA antibodies and a low complement.

Overall, however, the proportion of patients with high disease activity in the ITT or ITT-ZVT2 population of the PLUTO study can be estimated only to a limited extent. Based on the data available, it is still unclear whether a relevant proportion of the patients did not exhibit high disease activity at the time of study inclusion and are thus not part of the target population. However, following the written statement procedure and the oral hearing, it turns out that this does not call into question the fundamental suitability of the PLUTO study and thus of the ITT-ZVT2 population for the benefit assessment.
The patients of the PLUTO study were stratified by age (5 to 11 years vs 12 to 18 years) and SELENA-SLEDAI value (6 to 12 vs ≥ 13 points) randomised to the two treatment arms. The distribution of patients in the Intention to treat (ITT) population (53 vs 40) is explained by the fact that inclusion and randomisation took place in 3 cohorts; the randomisation ratio of belimumab vs placebo was 5:1 in 2 cohorts and 1:1 in 1 cohort.

The primary endpoint of the PLUTO study was the “SLE Responder Index Response Rate”. In addition, endpoints in the categories mortality, morbidity, quality of life, and side effects were surveyed.

Extent and probability of the additional benefit

Mortality

No deaths occurred in the PLUTO study.

Morbidity and quality of life

In the PLUTO study, the following patient-relevant endpoints in the morbidity category were surveyed, among others: the SLE Responder Index, physical functioning using PedsQL,

symptoms using PedsQL, and severe flares according to the SELENA-SLEDAI SLE Flare Index (SFI)

In the PLUTO study, the health-related quality of life was surveyed using PedsQL.

The patients in the PLUTO study received patient-individual concomitant therapy for the treatment of SLE. Patients in the randomised part of the PLUTO study were evaluated as patients with a therapy failure provided that an optimisation of the patient-individual therapy was necessary. These patients, who received therapy optimisation in terms of the appropriate comparator therapy, were evaluated as non-responders in the evaluations for dichotomous endpoints (except adverse events). For continuous endpoints, the values no longer surveyed were replaced by the last value observed before discontinuation of study participation. This type of evaluation is viewed critically for the benefit assessment because the appropriate comparator therapy provides for patient-individual therapy using different active ingredients. It may be necessary to optimise the existing therapy during the course of the study (e.g. by increasing the dose or adding an active ingredient from a new active ingredient category). The patients who received an adjustment of the therapy were treated according to the appropriate comparator therapy.

Due to the lack of adjunctive therapy in the comparator arm, it is also assumed that the patients in the ITT-ZVT2 population under consideration in the comparator arm were more likely to have their existing therapy optimised and be evaluated as therapy failures than the patients in the belimumab arm. In accordance with the information provided by the pharmaceutical company in the oral hearing, in the ITT-ZVT2 population, 5% in the belimumab arm vs 29% in the comparison arm received an optimisation of the existing therapy. It can therefore not be excluded that the evaluations carried out by the pharmaceutical company for endpoints of the morbidity and quality of life categories may be to the disadvantage of the comparator arm.

The results for the endpoints in the categories morbidity, SLE Responder Index, physical functioning using PedsQL, symptoms using PedsQL, and severe flares according to SFI as well as for the endpoint PedsQL in the health-related quality of life category cannot be conclusively interpreted because of the type of analysis performed by the pharmaceutical company.

Severe flares according to the SELENA-SLEDAI SLE Flare Index (SFI)

The prevention of flares in the treatment of SLE is patient-individual.

In the PLUTO study, the endpoint of the morbidity category “severe flares after SFI” was defined as the occurrence of one of several components, including components that lead to events through the implementation of the appropriate comparator therapy. This concerns the increase of the prednisone dose or the addition of new active ingredients such as antimalarials or NSAIDs. A required therapy optimisation as a possible implementation of the appropriate comparator therapy is thus counted as an unfavourable event (flare).
A further component consisted of increasing the SELENA-SLEDAI to > 12 points according to the original definition of the SFI. This procedure does not correspond to the classification according to the modified SFI in accordance with the protocol of the PLUTO study, according to which flares that exclusively fulfil the criterion of a change to more than 12 points in the SELENA-SLEDAI score are no longer categorised as severe flares in the modified SFI.
Following the oral hearing of belimumab, the pharmaceutical company listed the respective criteria for a severe flare according to SFI for patients of the ITT-ZVT2 population.
In a relevant proportion of patients, the increase in the prednisone dose alone was considered a flare.

As part of the patient-individual therapy of SLE, glucocorticoids are often used for induction and maintenance therapy as well as for the treatment of flares and severe attacks.

It is generally assumed that the increase of a prednisone dose, especially in children and adolescents, is usually due to clinical symptoms (e.g. a flare). Conversely, however, it cannot be assumed that any increase in prednisone dose is due to a *severe* flare.

The operationalisation chosen by the pharmaceutical company for the endpoint "severe flares according to SFI" is regarded as critical for the benefit assessment because a dose increase of antimalarials and the addition of NSAIDs were also evaluated as a severe flare.

The analysis chosen by the pharmaceutical company, which includes any therapy adjustment and the change in the SELENA-SLEDAI, shows a statistically significant difference in favour of belimumab.

On the basis of the data subsequently submitted by the pharmaceutical company, two sensitivity analyses were also performed for the endpoint severe flares according to SFI. In the sensitivity analyses, patients in whom an adjustment of the therapy alone was considered a flare as well as patients in whom an increase of the SELENA-SLEDAI to > 12 was evaluated as a flare were not taken into account. There is no statistically significant difference between the two analyses.

Against the background of these results and uncertainties, it remains questionable whether an advantage can be derived from this.

Side effects

For the endpoint serious adverse events (SAE), the PLUTO study found a statistically significant advantage of belimumab + patient-individual concomitant medication compared with placebo + patient-individual concomitant medication. This is assessed as considerable in extent.

In the PLUTO study, no patient discontinued therapy with belimumab + patient-individual concomitant medication. In the comparator arm, treatment with placebo + patient-individual concomitant medication was discontinued by one patient because of AE. No difference between the treatment groups can be derived from this.

In the specific AEs, a statistically significant advantage of belimumab + patient-individual concomitant medication compared with placebo + patient-individual concomitant medication was found for the endpoint infections and infestations (system organ class (SOC)).

In the side effects category, there is a statistically significant advantage of belimumab + patient-individual concomitant medication compared with placebo + patient-individual concomitant medication.

Overall assessment/conclusion

To assess the additional benefit of belimumab in patients from 5 years of age with active, autoantibody-positive systemic lupus erythematosus (SLE) who show high disease activity despite standard therapy, the pharmaceutical company presented the pivotal, multi-centre, randomised, double-blind, placebo-controlled Phase III PLUTO study.

The results on mortality, morbidity, quality of life as well as side effects were yielded from the PLUTO study. Only for the endpoints in the mortality and side effects categories were usable results presented. The results for the endpoints of the morbidity categories (severe flares) cannot be evaluated conclusively, and the health-related quality of life cannot be interpreted because of the type of evaluation performed by the pharmaceutical company.

No deaths occurred in the PLUTO study.

In the side effects category, there is a statistically significant advantage of belimumab + patient-individual concomitant medication compared with placebo + patient-individual concomitant medication. The positive effect of belimumab observed in the side effects category for SAEs is not entirely called into question by the data on the endpoints in the morbidity and health-related quality of life categories that cannot be conclusively used or interpreted. Because of the inconclusive assessability of the data on morbidity and the non-interpretability of data on health-related quality of life, the advantage of belimumab + patient-individual concomitant medication compared with placebo + patient-individual concomitant medication in the side effects category is non-quantifiable.

In the overall view, for belimumab as add-on therapy for children and adolescents from 5 to 17 years with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity despite standard therapy, there is a hint for a non-quantifiable additional benefit.

Reliability of data (probability of additional benefit)

Belimumab is approved for SLE patients with high disease activity. Based on the characteristics of the patients in the ITT-ZVT2 population under consideration, it cannot be conclusively assessed whether all patients showed high disease activity upon inclusion in the study.

From the originally submitted PLUTO study, only the ITT-ZVT-2 population can be used to derive the additional benefit. Because this population now consists of only n = 21 versus n = 14 patients, which is a significantly lower number of patients compared with the total population of the PLUTO study, it is justified to downgrade the reliability to a hint.

The differential exclusion of patients who received therapy optimisation does not result in an uninterpretable endpoint for the endpoints of the mortality and side effects categories. However, for the endpoints of the mortality and side effects categories of the PLUTO study, the risk of bias is considered high because it is unclear how high the proportion is in the relevant sub-population ITT-ZVT2 of patients evaluated as therapy drop-outs who were not fully followed up. The pharmaceutical company provided information on this only for the ITT population.

Because of the uncertainties, only a hint for a non-quantifiable additional benefit can be derived with regard to the reliability of data.

2.1.4 Summary of the assessment

This assessment concerns the benefit assessment of a new therapeutic indication for the active ingredient belimumab. The therapeutic indication assessed here is as follows:
Belimumab is indicated as add-on therapy for children and adolescents from 5 to 17 years with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity (e.g. positive anti-dsDNA and low complement) despite standard therapy.
The G-BA specified a patient-individual therapy to be an appropriate comparator therapy, taking into account the respective organ attack, previous therapy, and disease activity and selecting the following therapies: hydroxychloroquine, chloroquine, non-steroidal anti-inflammatory drugs (NSAIDs), glucocorticoids, and azathioprine.
To assess the additional benefit of belimumab in patients from 5 years of age with active, autoantibody-positive systemic lupus erythematosus (SLE) who show high disease activity despite standard therapy, the pharmaceutical company presented the pivotal, multi-centre, randomised, double-blind, placebo-controlled Phase III PLUTO study.

The results on mortality, morbidity, quality of life as well as side effects were yielded from the PLUTO study. Only for the endpoints in the mortality and side effects categories were usable

results presented. The results on morbidity and the data on health-related quality of life cannot be assessed/interpreted conclusively because of the type of evaluations carried out by the pharmaceutical company.

No deaths occurred in the PLUTO study.

In the side effects category, there is a statistically significant advantage of belimumab + patient-individual concomitant medication compared with placebo + patient-individual concomitant medication. The positive effect of belimumab observed in the side effects category is not entirely called into question by the non-usable data on endpoints in the morbidity and health-related quality of life categories.–Because of the inconclusive assessability of the data on morbidity and the non-interpretability of data on health-related quality of life, the advantage of belimumab + patient-individual concomitant medication compared with placebo + patient-individual concomitant medication in the SAEs endpoint of the side effects category is non-quantifiable.

In the overall view, for belimumab as add-on therapy for children and adolescents from 5 to 17 years with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity despite standard therapy, a hint for a non-quantifiable additional benefit compared with the patient-individual therapy is derived.

2.2 Number of patients or demarcation of patient groups eligible for treatment

Children and adolescents from 5 to 17 years with active, autoantibody-positive systemic lupus erythematosus (SLE) with a high degree of disease activity despite standard therapy

The number of patients is the target population in the statutory health insurance (SHI). These are based on the data from the pharmaceutical company's dossier.

Data on the number of paediatric patients with SLE may be overestimated because of non-gender and age-specific prevalence rates, especially for the upper limit. Furthermore, there are uncertainties in the extent to which patients with a flare-based course of SLE are included in the calculation. Furthermore, it is unclear how high the proportion of patients with severe LN for whom treatment is not recommended is. In addition, the operationalisation of the high disease activity based on the SLEDAI of ≥ 6 is subject to uncertainty. Overall, a broad range is given for the number of patients with juvenile SLE. It can be assumed that the number of patients in the SHI target population falls within this range and is thus in a plausible magnitude.

2.3 Requirements for a quality-assured application

The requirements in the product information are to be taken into account. The European Medicines Agency (EMA) provides the contents of the product information (summary of product characteristics, SmPC) for Benlysta® (active ingredient: belimumab) at the following publicly accessible link (last access: 25 March 2020):

https://www.ema.europa.eu/documents/product-information/benlysta-epar-product-information_de.pdf

Treatment with belimumab should only be initiated and monitored by specialists who are experienced in the treatment of patients with SLE.

2.4 Treatment costs

The treatment costs are based on the contents of the product information and the information listed in the LAUER-TAXE® (last revised: 1 May 2020).

In general, initial induction schemes are not taken into account for the cost representation because this indication is a chronic disease with a continuous need for therapy and, as a rule, no new titration or dose adjustment is required after initial titration.

If no maximum treatment duration is specified in the product information, the treatment duration is assumed to be one year (365 days), even if the actual treatment duration is patient-individual and/or is shorter on average. The time unit “days” is used to calculate the “number of treatments/patient/year”, time between individual treatments, and for maximum treatment duration if specified in the product information.

In principle, the G-BA does not base the calculation of the consumption of weight-dependent medicinal products to be dispensed on indication-specific average weights. Body weight (BW) is therefore based on the average weight of the German population from the official representative statistics “Mikrozensus 2017 - Körpermaße der Bevölkerung” [Microcensus 2017 - Body measurements of the population][2]. The average body weight of 5-year-old children is 20.8 kg; the average body weight of 17-year-old children is 67 kg.

A total cumulative dose of 50 g chloroquine per kg body weight in adults and 1 g per kg body weight in children should not be exceeded. Without taking a possible weight gain into account, this results in 250 treatment days for the currently available minimum daily dose of 125 mg at an assumed minimum body weight of 31.25 kg and 200 treatment days for the daily dose of 250 mg.

Treatment duration:

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Belimumab	every 4 weeks	13	1	13
patient-individual standard therapy				
Hydroxychloroquine	daily	365	1	365
Chloroquine	daily	365	1	365
Ibuprofen[3]	daily	patient-individual	1	patient-individual
Prednisone	daily	patient-individual	1	patient-individual
Prednisolone	daily	patient-individual	1	patient-individual

[2] German Federal Office For Statistics, Wiesbaden 2017: www.gbe-bund.de
[3] Exemplary for the NSAID class of active ingredients

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Azathioprine	daily	365	1	365
Appropriate comparator therapy				
Hydroxychloroquine	daily	365	1	365
Chloroquine	daily	365	1	365
Ibuprofen[3]	daily	patient-individual	1	patient-individual
Prednisone	daily	patient-individual	1	patient-individual
Prednisolone	daily	patient-individual	1	patient-individual
Azathioprine	daily	365	1	365

Usage and consumption:

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Belimumab					
5 years (20.8 kg BW)	10 mg/kg BW	208 mg	2 × 120 mg	13	26 × 120 mg
17 years (67.0 kg BW)	10 mg/kg BW	670 mg	1 × 400 mg 3 × 120 mg	13	13 × 400 mg 39 × 120 mg
patient-individual standard therapy					
Hydroxychloroquine[4]	6.5 mg/kg BW	200–400 mg	1 × 200 mg 2 × 200 mg	365	365 × 200 mg 730 × 200 mg
Chloroquine	4 mg/kg BW	125– 250 mg[5]	0.5 × 250 mg 1 × 250 mg	250– 200	250 × 125 mg – 200 × 250 mg
Ibuprofen	different for each individual patient				
Prednisone	different for each individual patient				
Prednisolone	different for each individual patient				

[4] According to product information of hydroxychloroquine, the 200 mg tablet is not suitable for children under 6 years of age (≤ 35 kg).
[5] Chloroquine is currently only available in the potency 250 mg tablets that can be divided into 2 halves with the same dose. Thus, a minimum daily dose of 125 mg can be achieved.

Designation of the therapy	Dosage/ application	Dose/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Azathioprine	< 1 mg – 3 mg/kg BW	different for each individual patient			
Appropriate comparator therapy					
Hydroxychloroquine[5]	6.5 mg/kg BW	200–400 mg	1 × 200 mg 2 × 200 mg	365	365 × 200 mg 730 × 200 mg
Chloroquine	4 mg/kg BW	125– 250 mg[6]	0.5 × 250 mg 1 × 250 mg	250– 200	250 × 125 mg – 200 × 250 mg
Ibuprofen	different for each individual patient				
Prednisone	different for each individual patient				
Prednisolone	different for each individual patient				
Azathioprine	< 1 mg – 3 mg/kg BW	different for each individual patient			

Costs of the medicinal product:

In order to improve comparability, the costs of the medicinal products were approximated both on the basis of the pharmacy sales price level and also deducting the statutory rebates in accordance with Sections 130 and 130a SGB V. To calculate the annual treatment costs, the required number of packs of a particular potency was first determined on the basis of consumption. Having determined the number of packs of a particular potency, the costs of the medicinal products were then calculated on the basis of the costs per pack after deduction of the statutory rebates.

Designation of the therapy		Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Medicinal product to be assessed						
Belimumab	120 mg	1 PIK	€ 175.64	€ 1.77	€ 0.00	€ 173.87
Belimumab	400 mg	1 PIK	€ 559.75	€ 1.77	€ 0.00	€ 557.98
patient-individual standard therapy						
Hydroxychloroquine[6]	200 mg	100 FCT	€ 27.97	€ 1.77	€ 1.34	€ 24.86
Chloroquine[6,7]	250 mg	100 FCT	€ 27.97	€ 1.77	€ 1.34	€ 24.86

[6] Fixed reimbursement rate

[7] Chloroquine is currently available only as an imported medicinal product on the German market.

Designation of the therapy		Package size	Costs (pharmacy sales price)	Rebate Section 130 SGB V	Rebate Section 130a SGB V	Costs after deduction of statutory rebates
Ibuprofen[6]	200 mg	50 FCT	€ 7.76	€ 1.77	€ 0.34	€ 5.65
Prednisone[6]	5 mg	100 TAB	€ 16.47	€ 1.77	€ 0.43	€ 14.27
	20 mg	100 TAB	€ 29.01	€ 1.77	€ 1.42	€ 25.82
Prednisolone[6]	5 mg	100 TAB	€ 15.16	€ 1.77	€ 0.33	€ 13.06
	20 mg	100 TAB	€ 21.35	€ 1.77	€ 0.82	€ 18.76
Azathioprine[6]	25 mg	100 FCT	€ 29.50	€ 1.77	€ 1.46	€ 26.27
	50 mg	100 FCT	€ 40.40	€ 1.77	€ 2.32	€ 36.31
	100 mg	100 FCT	€ 57.74	€ 1.77	€ 3.69	€ 52.28
Appropriate comparator therapy						
Hydroxychloroquine[6]	200 mg	100 FCT	€ 27.97	€ 1.77	€ 1.34	€ 24.86
Chloroquine[6,7]	250 mg	100 FCT	€ 27.97	€ 1.77	€ 1.34	€ 24.86
Ibuprofen[6]	200 mg	50 FCT	€ 7.76	€ 1.77	€ 0.34	€ 5.65
Prednisone[6]	5 mg	100 TAB	€ 16.47	€ 1.77	€ 0.43	€ 14.27
	20 mg	100 TAB	€ 29.01	€ 1.77	€ 1.42	€ 25.82
Prednisolone[6]	5 mg	100 TAB	€ 15.16	€ 1.77	€ 0.33	€ 13.06
	20 mg	100 TAB	€ 21.35	€ 1.77	€ 0.82	€ 18.76
Azathioprine[6]	25 mg	100 FCT	€ 29.50	€ 1.77	€ 1.46	€ 26.27
	50 mg	100 FCT	€ 40.40	€ 1.77	€ 2.32	€ 36.31
	100 mg	100 FCT	€ 57.74	€ 1.77	€ 3.69	€ 52.28
Abbreviations: PIK: powder for the preparation of an infusion solution; FCT film-coated tablets; HC: tablets						

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 May 2020

Costs for additionally required SHI services:

Only costs directly related to the use of the medicinal product are taken into account. If there are regular differences in the necessary use of medical treatment or in the prescription of other services in the use of the medicinal product to be assessed and the appropriate comparator therapy in accordance with the product information, the costs incurred for this must be taken into account as costs for additionally required SHI services.

Medical treatment costs, medical fee services, and costs incurred for routine examinations (e.g. regular laboratory services such as blood count tests) that do not exceed standard expenditure in the course of the treatment are not shown.

Because there are no regular differences in the necessary medical treatment or the prescription of other services when using the medicinal product to be assessed and the

appropriate comparator therapy according to the product information, no costs for additionally required SHI services had to be taken into account.

Other services covered by SHI funds:
The special agreement on contractual unit costs of retail pharmacist services (Hilfstaxe; contract on price formation for substances and preparations of substances) is not fully used to calculate costs. Alternatively, the pharmacy sales price publicly accessible in the directory services according to Section 131, paragraph 4 SGB V is a suitable basis for a standardised calculation.

According to the special agreement on contractual unit costs of retail pharmacist services [Hilfstaxe"] (last revised: 11. Supplementary Agreement of 1 March 2020 to the contract on price formation for substances and preparations of substances), surcharges for the preparation of parenteral preparations containing cytostatics of a maximum of € 81 per ready-to-use preparation and for the preparation of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall apply. These additional costs are not added to the pharmacy sales price but rather follow the rules for calculating the Hilfstaxe. The cost representation is based on the pharmacy retail price and the maximum surcharge for the preparation and is only an approximation of the treatment costs. This presentation does not take into account, for example, the rebates on the pharmacy purchase price of the active ingredients, the invoicing of discards, and the calculation of application containers and carrier solutions according to the regulations of Annex 3 of the Hilfstaxe.

3. Bureaucratic costs

The proposed resolution does not create any new or amended information obligations for care providers within the meaning of Annex II to Chapter 1 VerfO and, accordingly, no bureaucratic costs.

4. Process sequence

The Subcommittee on Medicinal Products determined the appropriate comparator therapy at its session on 25 September 2018.

On 14 November 2019, the pharmaceutical company submitted a dossier for the benefit assessment of belimumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 15 November 2019 in conjunction with the resolution of the G-BA of 1 August 2011 concerning the commissioning of the IQWiG to assess the benefits of medicinal products with new active ingredients in accordance with Section 35a SGB V, the G-BA commissioned the IQWiG to assess the dossier concerning the active ingredient belimumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 13 February 2020, and the written statement procedure was initiated with publication on the website of the G-BA on 17 February 2020. The deadline for submitting written statements was 9 March 2020.

The oral hearing was held on 24 March 2020.

By letter dated 24 March 2020, the IQWiG was commissioned with a supplementary assessment of data submitted in the written statement procedure. The addendum prepared by IQWiG was submitted to the G-BA on 24 April 2020.

In order to prepare a recommendation for a resolution, the Subcommittee on Medicinal Products commissioned a working group (Section 35a) consisting of the members nominated by the leading organisations of the care providers, the members nominated by the SHI

umbrella organisation, and representatives of the patient organisations. Representatives of the IQWiG also participate in the sessions.

The evaluation of the written statements received and the oral hearing were discussed at the session of the subcommittee on 5 May 2020, and the proposed resolution was approved.

At its session on 14 May 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	25 September 2018	Determination of the appropriate comparator therapy
Working group Section 35a	17 March 2020	Information on written statements received; preparation of the oral hearing
Subcommittee Medicinal Products	24 March 2020	Conduct of the oral hearing, Commissioning of the IQWiG with the supplementary assessment of documents
Working group Section 35a	31 March 2020 14 April 2020 28 April 2020	Consultation on the dossier assessment by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	5 May 2020	Concluding discussion of the draft resolution
Plenum	14 May 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 14 May 2020

Federal Joint Committee
in accordance with Section 91 SGB V
The Chair

Prof. Hecken