Justification

Gemeinsamer Bundesausschuss

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 Dupilumab (New Therapeutic Indication: Bronchial Asthma)

of 20 February 2020

Contents

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 dupilumab (Dupixent®) was listed for the first time on 1 December 2017 in the “LAUER-TAXE®”, the extensive German registry of available drugs and their prices.

On 6 May 2019, dupilumab received marketing authorisation for a new therapeutic indication classified as a major variation of Type 2 according to Annex 2, number 2a to Regulation (EC) No. 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 20 December 2018, the pharmaceutical company filed an application to consolidate the evaluation procedures for dupilumab according to Section 35a, paragraph 5b SGB V. At its session on 7 February 2019, the G-BA approved the application for consolidation.

On 29 August 2019, the pharmaceutical company submitted a dossier in accordance with Section 4, paragraph 3, number 3 Ordinance on the Benefit Assessment of Pharmaceuticals (AM-NutzenV) in conjunction with Chapter 5, Section 8, paragraph 2 of the Rules of Procedure (VerfO) of the G-BA on the active ingredient dupilumab.

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 2 December 2019, 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 dupilumab 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, and the statements submitted in the written statement and oral hearing procedure. In order to determine the extent of the additional benefit, the G-BA has evaluated 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 dupilumab.

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 dupilumab (Dupixent®) in accordance with the product information

Dupixent is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO (see section 5.1), who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.

2.1.2 Appropriate comparator therapy

The appropriate comparator therapy was determined as follows:

a) Adolescents of 12–17 years as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.

Appropriate comparator therapy:

A patient-individual therapy escalation taking into account previous therapy of either:

- high-dose ICS and LABA and LAMA

  or

- high-dose ICS and LABA and, where appropriate, LAMA and omalizumab, provided that the criteria necessary for the use of omalizumab are met

b) Adults as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.

Appropriate comparator therapy:

A patient-individual therapy escalation taking into account previous therapy and the pathogenesis of the asthma of either:

- high-dose ICS and LABA and LAMA

[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.

or

- high-dose ICS and LABA and, where appropriate, LAMA and omalizumab, provided that the criteria necessary for the use of omalizumab are met

or

- high-dose ICS and LABA and, where appropriate, LAMA and mepolizumab or reslizumab or benralizumab, provided that the criteria necessary for the use of the respective antibodies are met

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.

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. Active ingredients generally approved to treat patients with severe asthma:

- Selective beta-2 agonists: fenoterol, reproterol, salmeterol, formoterol, terbutaline, salbutamol, bambuterol and clenbuterol
- Inhaled muscarinic antagonists: ipratropium bromide and tiotropium bromide
- Inhaled corticosteroids: beclometasone, budesonide, ciclesonide, fluticasone and mometasone
- Oral corticosteroids: e.g. prednisolone and prednisone
- Combination preparations: beclometasone / formoterol, budesonide / formoterol, salmeterol / fluticasone, formoterol / fluticasone, vilanterol / fluticasone and ipratropium bromide / fenoterol
- Others: theophylline, omalizumab, mepolizumab, reslizumab, benralizumab

On 2. To treat severe asthma, non-pharmaceutical measures alone cannot be considered as appropriate comparator therapy

On 3. The following resolutions on an amendment to the Pharmaceuticals Directive (AM-RL) have been adopted:

- Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a of the German Social Code Book V (SGB V) Mepolizumab (resolution of 22 March 2019)

- Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a of the German Social Code Book V (SGB V) Benralizumab (resolution of 2 August 2018)
- Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a of the German Social Code Book V (SGB V) Reslizumab – repeal of the limitation of the period of validity (resolution of 6 December 2018)
- Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a of the German Social Code Book V (SGB V) Mepolizumab – repeal of the limitation of the period of validity (resolution of 6 December 2018)
- Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a of the German Social Code Book V (SGB V) Resilizumab (resolution of 6 July 2017)
- Annex XII – Benefit Assessment of Medicinal Products with New Active Ingredients According to Section 35a of the German Social Code Book V (SGB V) Mepolizumab (resolution of 21 July 2016)
- Annex IV: Therapeutic information on omalizumab (resolution of 17 December 2015).
- Annex XII / Annex IX Fixed amount group formation of fluticasone furoroate/vilanterol (resolution of 30 March 2014)

On 4. The prescription ladder scheme for children, adolescents and adults specified in the National Service Guidelines for Asthma (NVL Asthma 2018, 3rd edition, version 1) must be taken into account. This is the basis for grouping the patients into adolescents (patient group a) and adults (patient group b).

It is assumed that the patients in patient group a) will be considered to be at levels 5 to 6 of the 2018 NVL Asthma 2018 prescription ladder scheme for children and adolescents and the patients in patient group b) will be considered to be at levels 4 to 5 of the 2018 NVL Asthma 2018 prescription ladder scheme for adults.

The guidelines recommend therapy with the long-acting inhaled muscarinic antagonist (LAMA) tiotropium in addition to high-dose ICS and LABA, both at level 5 for children and adolescents and at level 4 for adults. Concomitant administration of tiotropium alongside ICS and LABA has been shown to be beneficial to morbidity. Omalizumab represents a further potential escalation for children and adolescents (level 6) and for adults (level 5) alongside high-dose ICS and LABA and possibly LAMA. Omalizumab can only be administered as a potential appropriate comparator therapy in patients who fully meet the approval and therapeutic guidance criteria for omalizumab. According to the product information, treatment with omalizumab "should only be considered for patients with convincing IgE(immunoglobulin E)-mediated asthma (see section 4.2)." In adults and adolescents (12 years of age and older) omalizumab “is indicated as add-on therapy to improve asthma control in patients with severe persistent allergic asthma who have a positive skin test or *in vitro* reactivity to a perennial aeroallergen and who have reduced lung function (FEV1 <80%) as well as frequent daytime symptoms or night-time awakenings and who have had multiple documented severe asthma exacerbations despite daily high-dose inhaled corticosteroids, plus a long-acting inhaled beta2-agonist.” (product information Xolair®, Juni 2019). According to the therapeutic guidelines in Section 92 paragraph 2 sentence 7 SGB V together with Section 17 AM-RL on the cost-effective prescription of medicinal products, omalizumab should also only be prescribed as an add-on therapy for adolescents from the age of 12 years and adult patients if the patient's body weight is within the limits of the dosage table (≥ 20 kg and ≤ 150 kg) and if the patient is a non-smoker.

Taking into account the generally accepted state of medical knowledge as well as the current edition of NVL Asthma of September 2018, administration of OCS as a maintenance treatment should no longer be regarded as a regularly preferable escalation option for adolescents and adults with severe asthma but, rather, as a

secondary alternative in justified cases. Consequently, treatment with OCS was no longer identified as an appropriate escalation option in the context of reviewing the appropriate comparator therapy. Even before the review of the appropriate comparator therapy, escalation with OCS as an option in maintenance treatment was considered to be a suboptimal option.
In justified cases, OCS may also be administered to treat severe asthma. This should only be for short periods of time and at the lowest effective dose. When treating asthma with OCS, care must be taken to ensure that the OCS dose never permanently exceeds the Cushing's threshold. This must be distinguished from treatment of exacerbations.

For patient group a (adolescents between 12 and 17 years of age with severe, uncontrolled asthma) patient-individual therapy escalation, in summary, should be long-acting inhaled muscarinic antagonists (LAMA), omalizumab (if the criteria for use of omalizumab are met) or a combination of omalizumab and LAMA.

NVL Asthma recommends that adult patients with severe stage 5 eosinophilic asthma should be treated with mepolizumab, reslizumab or benralizumab. Likewise, as part of the benefit assessment in accordance with Section 35a SGB V, it has been found that the active ingredients mepolizumab, reslizumab and benralizumab each had a hint for a minor additional benefit in specific sub-populations.

For patient group b (adult patients with severe, uncontrolled asthma), in addition to long-acting inhaled muscarinic antagonists (LAMA), omalizumab and mepolizumab, reslizumab and benralizumab are also identified as active ingredients for patient-individual therapy escalation in the present therapeutic indication, provided that the criteria for administration of the respective antibodies are met. In such escalation, mepolizumab, reslizumab and benralizumab are equally appropriate therapy options.

Due to its narrow therapeutic range, theophylline is not a first-choice agent in asthma therapy and is therefore not considered to be an appropriate comparator therapy.

Patient-individual therapy is based on selection of active ingredient classes, not selection of individual active ingredient within an active ingredient class

The authorisations and product informations of the medicinal products used in appropriate comparator therapies must be complied with.

In severe uncontrolled asthma, unaltered continuation of inadequate therapy is not to be regarded as appropriate comparator therapy, if therapy escalation is still an option.

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 dupilumab is assessed as follows.

a) Adolescents of 12–17 years as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.

An additional benefit is not proven.

b) Adults as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.

An additional benefit is not proven.

Justification:

The pharmaceutical company draws on the results of the DRI12544, QUEST and VENTURE studies to demonstrate the additional benefit of dupilumab in the entire therapeutic indication. The patient populations a) and b) have not been considered separately.

DRI12544 is a randomised, double-blind, placebo-controlled phase IIb study that included 776 adult patients with uncontrolled moderate to severe asthma who were already receiving therapy with medium or high-dose ICS and LABA at stable doses. Patients receiving oral corticosteroid (OCS) maintenance treatment were excluded. Only patients whose asthma had worsened within the last year prior to the start of the study, defined as ≥ 1 treatment with systemic steroids, hospitalization or emergency admission due to worsening of symptoms, were included in the study. The study investigated administration of four different doses of dupilumab (300 mg every 2 weeks, 200 mg every 2 weeks, 300 mg every 4 weeks and 200 mg every 4 weeks at a 1:1:1:1 ratio, a total of 618 patients) compared to placebo (158 patients). The primary endpoint was the change in forced expiratory volume over one second (FEV1) at week 12. The treatment was administered for 24 weeks, with a follow-up period of 16 weeks. The study was conducted at 174 sites worldwide between June 2013 and April 2015.

In its benefit assessment, the pharmaceutical company only drew on the sub-population of patients who received the approval-compliant dose of dupilumab (maintenance treatment of 200mg every 2 weeks) and a high dose of ICS at the start of the study (corresponding to 75 patients in the intervention arm and 77 patients in the control arm).

The randomised, double-blind Phase III QUEST study included a total of 1902 patients aged 12 years and older with uncontrolled moderate to severe asthma who were already receiving an existing therapy with medium or high-dose ICS and 1 to 2 additional stable-dose controller medications. Patients receiving OCS maintenance treatment were excluded. Only patients whose asthma had worsened within the last year prior to the start of the study, defined as ≥ 1 treatment with systemic steroids, hospitalization or emergency admission due to worsening of symptoms, were included in the study. The study investigated administration of two different doses of dupilumab (300 mg every 2 weeks and 200 mg every 2 weeks) against two control arms with placebo at a 2:2:1:1 ratio. The study's primary endpoints were the annual rate of severe exacerbations and the change in FEV1 at week 12. The treatment duration lasted 52 weeks. The study was conducted at 331 sites worldwide between April 2015 and November 2017.

In its benefit assessment, the pharmaceutical company only drew on the sub-population of patients who received the approval-compliant dose of dupilumab (maintenance treatment of 200mg every 2 weeks) and a high dose of ICS at the start of the study. This corresponds to a total of 317 patients (including 6 adolescents aged ≥ 12 and < 18 years) in the intervention arm and 172 patients (including 6 adolescents aged ≥ 12 and < 18 years) in the control arm.

The VENTURE study is a randomised, double-blind phase III study comparing dupilumab with placebo in 210 patients aged 12 years and older with uncontrolled severe asthma receiving ongoing asthma therapy with high-dose ICS and 1 to 2 additional stable-dose

controller drugs, as well as regular OCS treatment. The study evaluated treatment with 300mg dupilumab every 2 weeks versus placebo. The primary endpoint was the dose reduction of regularly administered OCS. Prior to randomisation, the OCS dose was reduced weekly to the lowest effective dose in a 3 to 8 week optimization phase using a pre-specified titration scheme. If symptoms worsened the dose was not reduced. Only patients who could tolerate their lowest effective OCS dose for 2 weeks were randomised. During the 24-week treatment period, the lowest effective dose of OCS was reduced after 4 weeks every 4 weeks until week 20 according to a predetermined titration scheme, provided that asthma control was maintained. After the treatment phase, the patients were followed for 12 weeks. The study was conducted at 68 sites worldwide between October 2015 and November 2017.

In patients with severe asthma on oral corticosteroids, maintenance treatment of 300 mg every two weeks is consistent with the approved recommended dosage. As all patients of the VENTURE study also received a high dose of ICS at the start of the study, the pharmaceutical company decided to include all patients in the benefit assessment, i.e. a total of 103 patients (including 1 adolescent aged ≥ 12 and < 18 years) in the intervention arm and 107 patients (including 2 adolescents aged ≥ 12 and < 18 years) in the control arm.

Suitability of the studies for the benefit assessment

a) Adolescents of 12–17 years as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.

Overall, the data presented for the benefit assessment were very limited for adolescent patients with inadequately controlled severe asthma with type 2 inflammation. In the DRI12544 study, in accordance with the inclusion criteria, no adolescents were included. In the sub-population of the QUEST and VENTURE studies drawn on by the pharmaceutical company for the benefit assessment, a total of 12 adolescents (2.5%) and, respectively, 3 adolescents (approx. 1%) were examined. Hence, for the benefit assessment, no relevant data are available to evaluate the additional benefit of dupilumab as add-on maintenance treatment in adolescents aged 12 to 17 years with inadequately controlled severe asthma with type 2 inflammation who are already receiving high-dose ICS and at least one other medicinal product as maintenance treatment compared to the appropriate comparator therapy.

In addition, there are considerable uncertainties regarding the implementation of the appropriate comparator therapy for patient group a. The adolescent patients of the relevant sub-population in the QUEST and VENTURE studies are, as per the inclusion criterion, patients with severe asthma, insufficiently controlled despite therapy with high-dose ICS and at least one additional controller. The G-BA considers that continuation of treatment in cases where there the option of escalation of treatment still exists does not constitute appropriate comparator therapy. For patient group a, a patient-individual therapy escalation with a LAMA and/or omalizumab, provided that the criteria necessary for the use of omalizumab are met, was determined as an appropriate comparator therapy. Separate analyses for adolescents aged 12 to 17 years are only available in the dossier as subgroup analyses from the QUEST study. The pharmaceutical company does not draw on these analyses to determine additional benefit in this patient group. The uncertainties associated with exhaustion of specific escalation options are discussed below in the comments section on adult patients (patient group b).

In summary, an additional benefit for dupilumab compared to the appropriate comparator therapy for adolescents of 12–17 years as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who

are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment has not been proven, as no relevant data have been presented to evaluate the additional benefit of dupilumab as an add-on maintenance therapy.

b) Adults as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment

The patients of the DRI12544, QUEST and VENTURE studies considered by the pharmaceutical company for the benefit assessment had insufficiently-controlled asthma with approx. two exacerbations in the previous year and an ACQ-5 value of 2 to 3 (mean in each case) despite existing maintenance treatment consisting of high-dose ICS and at least one additional controller. Thus, the G-BA determined that, to adequately treat patients' symptoms and to provide a suitable comparison between dupilumab and the appropriate comparator therapy for the benefit assessment, the options for escalation of treatment for individual patients in the control arms of the studies should have been exhausted. In the respective control arms of the studies, however, no therapy escalation was planned at the start of the study, during which patients in the intervention arms received dupilumab as add-on therapy. The concomitant therapy during the study was to be maintained in all the study arms at the existing stable dose prior to the study (with the exception of the OCS reduction in the VENTURE study).

The option of escalation with a LAMA is a component of the appropriate comparator therapy as determined by the G-BA and represents a possible therapeutic escalation both for patients in the VENTURE study and for the patients in the sub-populations considered in the DRI12544 and QUEST studies who were not receiving tiotropium as maintenance treatment at the start of the study. Tiotropium was approved in September 2014 to treat asthma. However, as per the study documentation, patients were not permitted to start control medication with LAMA during the treatment phase in any of the studies. In DRI12544, 2.6 % of patients received tiotropium as concomitant medication. In the QUEST and VENTURE studies, approximately 10% and, respectively, 20% of the patients in the control arms considered for the benefit assessment maintained their existing LAMA treatment as a second or third controller medication. However, it remains unclear how many patients without existing or previous LAMA therapy would have been suitable to receive trial treatment with LAMA.

In the DRI12544, QUEST and VENTURE studies, omalizumab was not authorised either as concomitant medication or as a potential therapy escalation. No information is available for the DRI12544 and QUEST studies on how many patients had already received previous therapy with omalizumab, excluding this as a potential escalation therapy. The VENTURE study did not include patients previously treated with an anti-IgE antibody. Even taking into account the restrictive criteria specified by the authorisation and the therapeutic guidelines of the G-BA, it remains unclear how many patients in the control arms of the DRI12544, QUEST and VENTURE studies would have been eligible for treatment with omalizumab as an adequate escalation option.

Furthermore, for the relevant adult patient population of the DRI12544, QUEST and VENTURE studies, the escalation options determined as appropriate comparator therapies by the G-BA are the anti-IL-5-(R)-antibodies mepolizumab, reslizumab and benralizumab. In the DRI12544, QUEST and VENTURE studies, biological medications were not authorised either as concomitant medication or as a potential therapy escalation. Although mepolizumab, reslizumab and benralizumab were not approved and not commercially available when the DRI12544, QUEST and VENTURE trials were initiated, they are currently recommended and appropriate options for escalation therapy for patients with severe, uncontrolled eosinophilica asthma within the therapeutic indication. In the relevant sub-

populations of the DRI12544 and QUEST studies, 87% and 73%, respectively, and in the VENTURE study 65% of patients in the control arms suffered from eosinophilic asthma, as defined by a blood eosinophil count of > 150 eosinophils/µl. Taking into account the generally recognised current state of medical knowledge, a great deal of uncertainty therefore remains regarding implementation of the appropriate comparator therapy, as it can be assumed that a high proportion of patients in the control arms of the studies would have been eligible, in principle, for trial treatment with mepolizumab, reslizumab or benralizumab.

The pharmaceutical company outlines the possibility of indirectly comparing the additional benefit of dupilumab with the escalation options of mepolizumab, reslizumab and benralizumab as appropriate comparator therapies, but does not perform such comparisons due to insufficient similarity of the studies.

It is unclear whether the present therapeutic indication also includes patients for whom no further escalation of their existing therapy is possible. In the written statements procedure, the pharmaceutical company points out that, as per marketing authorisation, patients with elevated FeNO but not elevated eosinophil levels are not eligible for treatment with an anti-IL-5-(R) antibody. According to the pharmaceutical company, in the VENTURE study this corresponds to 14 patients in the control arm (13%) and 8 patients in the intervention arm (8%). However, for these patients no separate evaluations for the endpoints obtained in the study were presented. It also remains unclear whether these patients would have benefited from an escalation of their existing inadequate asthma therapy with a LAMA or with omalizumab, and to what extent these patients, in everyday care, represent a relevant patient population.

In summary, both the results of the VENTURE study and the results of the sub-population of the DRI12544 and QUEST studies relevant for the benefit assessment cannot be incorporated into the benefit assessment due to the high degree of uncertainty regarding implementation of the appropriate comparator therapy. An additional benefit of dupilumab over the appropriate comparator therapy has, therefore, not been proven for adults with severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.

2.1.4 Summary of the assessment

The present assessment concerns the benefit assessment of a new therapeutic indication for the active ingredient dupilumab. The therapeutic indication assessed here is as follows: Dupixent is indicated in adults and adolescents 12 years and older as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO (see section 5.1), who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.

In the therapeutic indication to be considered, two patient groups were distinguished:

a) Adolescents of 12–17 years as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.

and

b) Adults as add-on maintenance treatment for severe asthma with type 2 inflammation characterised by raised blood eosinophils and/or raised FeNO, who are inadequately controlled with high dose ICS plus another medicinal product for maintenance treatment.

About patient group a)

The G-BA determined the appropriate comparator therapy to be a patient-individual therapy escalation, taking into account the previous therapy, selecting from high-dose ICS and LABA and LAMA or high-dose ICS and LABA and, if necessary, LAMA and omalizumab, provided that the criteria necessary for the use of omalizumab are met.

The pharmaceutical company draws on the results of the randomised, double-blind, placebo-controlled DRI12544, QUEST and VENTURE studies to demonstrate the additional benefit of dupilumab in the entire therapeutic indication. The patient populations a) and b) have not been considered separately. Overall, the data presented for the benefit assessment were very limited for adolescent patients with inadequately controlled severe asthma with type 2 inflammation. As explained in more detail for patient group b, there is also great uncertainty regarding the implementation of the appropriate comparator therapy in all three studies. Hence, for patient group a, no relevant data are available to assess the additional benefit. In summary, an additional benefit is not proven.

About patient group b)

As an appropriate comparator therapy, the G-BA recommended a patient-individual escalation of therapy taking into account the previous therapy and the pathogenesis of asthma and selecting from high-dose ICS and LABA and LAMA; high-dose ICS and LABA and LAMA (where appropriate) and omalizumab (provided that the criteria necessary for the use of omalizumab are met); high-dose ICS and LABA and LAMA (where appropriate) and mepolizumab; reslizumab; or benralizumab, provided that the criteria necessary for the use of the respective antibodies are met.

The patients of the DRI12544, QUEST and VENTURE studies considered by the pharmaceutical company for the benefit assessment had insufficiently-controlled asthma despite existing maintenance treatment consisting of high-dose ICS and at least one additional controller. Thus, the G-BA determined that a suitable comparison between dupilumab and the appropriate comparator therapy for the benefit assessment would require exhaustion of the options for escalation of treatment for individual patients in the control arms of the studies. In the respective control arms of the studies, however, no therapy escalation was planned at the start of the study, during which patients in the intervention arms received dupilumab as add-on therapy. With the exception of the OCS dose in the VENTURE study, no alteration or dose adjustment of maintenance treatment was planned over the course of the studies. However, it can be assumed that a high proportion of patients in the three studies would, in principle, have been eligible for a trial therapy with one of the escalation options determined by the G-BA. Since great uncertainties exist in all three studies regarding implementation of the appropriate comparator therapy, the studies cannot be used for the benefit assessment for patient group b. Therefore, overall, an additional benefit is not proven.

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

The number of patients is the target population in the statutory health insurance (SHI). The G-BA bases the resolution on the estimate of the number of patients derived by the pharmaceutical company in the dossier. However, the reported patient numbers are subject to uncertainties, due to the severe asthma, type 2 inflammation and uncontrolled asthma operationalisations adopted for both patient populations by the pharmaceutical company. In determining the number of adolescents with asthma, a further uncertainty arises, as medical verification and/or validation of the KiGGS study (2nd wave) used by the pharmaceutical company could only be partially undertaken due to a lack of further studies.

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 Dupixent® (active ingredient: dupilumab) at the following publicly accessible link (last access: 18 November 2019):

https://www.ema.europa.eu/en/documents/product-information/dupixent-epar-product-information_en.pdf

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 February 2020).

The G-BA determined the costs for the appropriate comparator therapy based on the costs of the most cost-effective inhaled corticosteroids (ICS), long-acting beta-2 agonists (LABA), and ICS + LABA fixed combinations.

Treatment duration:

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 employed in calculating the "number of treatments/patient/year", time intervals between individual treatments and for the maximum treatment duration, if specified in the product information.

Patient population a)

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Dupilumab	continuously; 1 × every 14 days	26.1	1	26.1
Inhaled corticosteroids (ICS, high-dose)				
Fluticasone	continuously, 2 × daily	365	1	365
Long-acting beta-2-agonists (LABA)				
Clenbuterol	continuously, 2 × daily	365	1	365
ICS + LABA fixed combinations (high-dose)				
Fluticasone | formoterol	continuously, 2 × daily	365	1	365
Long-acting muscarinic antagonists (LAMA)				
Tiotropium	continuously, 1 × daily	365	1	365

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Appropriate comparator therapy				
Inhaled corticosteroids (ICS, high-dose)				
Fluticasone	continuously, 2 × daily	365	1	365
Long-acting beta-2 agonists (LABA)				
Clenbuterol	continuously, 2 × daily	365	1	365
ICS + LABA fixed combinations (high-dose)				
Fluticasone | formoterol	continuously, 2 × daily	365	1	365
Long-acting muscarinic antagonists (LAMA)				
Tiotropium	continuously, 1 × daily	365	1	365
Monoclonal antibodies				
Omalizumab	continuously; 1 × every 28 days or every 14 days	13 or 26.1	1	13 or 26.1

Patient population b)

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
Medicinal product to be assessed				
Dupilumab	continuously; 1 × every 14 days	26.1	1	26.1
Inhaled corticosteroids (ICS, high-dose)				
Budesonide	continuously, 2 × daily	365	1	365
Long-acting beta-2-agonists (LABA)				
Clenbuterol	continuously, 2 × daily	365	1	365

Designation of the therapy	Treatment mode	Number of treatments/patient/year	Treatment duration/treatment (days)	Treatment days/patient/ year
ICS + LABA fixed combinations (high-dose)				
Fluticasone | salmeterol	continuously, 2 × daily	365	1	365
Long-acting muscarinic antagonists (LAMA)				
Tiotropium	continuously, 1 × daily	365	1	365
Appropriate comparator therapy				
Inhaled corticosteroids (ICS, high-dose)				
Budesonide	continuously, 2 × daily	365	1	365
Long-acting beta-2 agonists (LABA)				
Clenbuterol	continuously, 2 × daily	365	1	365
ICS + LABA fixed combinations (high-dose)				
Fluticasone | salmeterol	continuously, 2 × daily	365	1	365
Long-acting muscarinic antagonists (LAMA)				
Tiotropium	continuously, 1 × daily	365	1	365
Monoclonal antibodies				
Mepolizumab	continuously; 1 × every 28 days	13	1	13
Omalizumab	continuously; 1 × every 28 days or every 14 days	13 or 26.1	1	13 or 26.1
Reslizumab	continuously; 1 × every 28 days	13	1	13
Benralizumab	continuously; 1 × every 56 days	6.5	1	6.5

Usage and consumption:

Patient population a)

Designation of the therapy	Dosage/ application	Dosage/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Dupilumab	200 mg – 300 mg	200 – 300 mg	1 × 200 mg – 1 × 300mg	26.1	26.1 × 200 mg – 26.1 × 300 mg
Inhaled corticosteroids (ICS, high-dose)					
Fluticasone	500 µg	1000 µg	4 x 250 µg	365	1460 x 250 µg
Long-acting beta-2-agonists (LABA)					
Clenbuterol	10–20 µg	20 µg – 40 µg	1 x 20 µg – 2 x 20 µg	365	365 x 20 µg – 730 x 20 µg
ICS + LABA fixed combinations (high-dose)					
Fluticasone | formoterol	250 µg/ 10 µg	500 µg/ 20 µg	4 × 125 µg/5 µg	365	1460 x 125 µg/5 µg
Long-acting muscarinic antagonists (LAMA)					
Tiotropium	5 µg	5 µg	2 x 2.5 µg	365	730 x 2.5 µg
Appropriate comparator therapy					
Inhaled corticosteroids (ICS, high-dose)					
Fluticasone	500 µg	1000 µg	4 x 250 µg	365	1460 x 250 µg
Long-acting beta-2 agonists (LABA)					
Clenbuterol	10–20 µg	20 µg – 40 µg	1 x 20 µg – 2 x 20 µg	365	365 x 20 µg – 730 x 20 µg
ICS + LABA fixed combinations (high-dose)					
Fluticasone | formoterol	250 µg/ 10 µg	500 µg/ 20 µg	4 × 125 µg/5 µg	365	1460 x 125 µg/5 µg

Designation of the therapy	Dosage/ application	Dosage/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Long-acting muscarinic antagonists (LAMA)					
Tiotropium	5 µg	5 µg	2 x 2.5 µg	365	730 x 2.5 µg
Monoclonal antibodies					
Omalizumab	150 mg – 600 mg	150 mg – 600 mg	1 × 150 mg – 4 × 150 mg	13 - 26.1	13 × 150 mg – 104.4 × 150 mg

Patient population b)

Designation of the therapy	Dosage/ application	Dosage/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Medicinal product to be assessed					
Dupilumab	200 mg – 300 mg	200 – 300 mg	1 × 200 mg – 1 × 300 mg	26.1	26.1 × 200 mg – 26.1 × 300 mg
Inhaled corticosteroids (ICS, high-dose)					
Budesonide	400 µg	800 µg	2 x 400 µg	365	730 x 400 µg
Long-acting beta-2 agonists (LABA)					
Clenbuterol	10–20 µg	20 µg – 40 µg	1 x 20 µg – 2 x 20 µg	365	365 x 20 µg – 730 x 20 µg
ICS + LABA fixed combinations (high-dose)					
Fluticasone | salmeterol	500 µg/ 50 µg	1,000 µg/ 100 µg	2 x 500 µg/50 µg	365	730 x 500 µg/50 µg
Long-acting muscarinic antagonists (LAMA)					
Tiotropium	5 µg	5 µg	2 x 2.5 µg	365	730 x 2.5 µg
Appropriate comparator therapy					
Inhaled corticosteroids (ICS, high-dose)					
Budesonide	400 µg	800 µg	2 x 400 µg	365	730 x 400 µg
Long-acting beta-2 agonists (LABA)					
Clenbuterol	10–20 µg	20 µg – 40 µg	1 x 20 µg – 2 x 20 µg	365	365 x 20 µg – 730 x 20 µg
ICS + LABA fixed combinations (high-dose)					
Fluticasone | salmeterol	500 µg/ 50 µg	1,000 µg/ 100 µg	2 x 500 µg/50 µg	365	730 x 500 µg/50 µg

Designation of the therapy	Dosage/ application	Dosage/patient/treatment days	Consumption by potency/treatment day	Treatment days/ patient/ year	Average annual consumption by potency
Long-acting muscarinic antagonists (LAMA)					
Tiotropium	5 µg	5 µg	2 x 2.5 µg	365	730 x 2.5 µg
Monoclonal antibodies					
Mepolizumab	100 mg	100 mg	1 × 100 mg	13	13 × 100 mg
Omalizumab	150 mg – 600 mg	150 mg – 600 mg	1 × 150 mg – 4 × 150 mg	13 – 26.1	13 × 150 mg – 104.4 × 150 mg
Reslizumab	225 mg	225 mg	2 × 100 mg + 1 × 25 mg	13	26 × 100 mg + 13 × 25 mg
Benralizumab	30 mg	30 mg	1 × 30 mg	6.5	6.5 × 30 mg

Costs:

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 130 a 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. For the long-acting beta-2 agonists (LABA), inhaled corticosteroids (ICS), and ICS + LABA fixed combinations, the respective fixed reimbursement rate was applied.

Costs of the medicinal product:

Patient population a)

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					
Dupilumab 200 mg	6 SFI	€ 4,645.00	€ 1.77	€ 262.00	€ 4,381.23

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
Dupilumab 300 mg	6 SFI	€ 4,645.00	€ 1.77	€ 262.00	€ 4,381.23
Clenbuterol 20 µg[2]	100 SD	€ 35.44	€ 1.77	€ 0.00	€ 33.67
Fluticasone 500 µg[2]	240 SD	€ 51.74	€ 1.77	€ 3.22	€ 46.75
Fluticasone / formoterol 125 µg/ 5 µg [2]	360 SD	€ 106.67	€ 1.77	€ 0.00	€ 104.90
Tiotropium 5 µg	180 SD	€ 191.27	€ 1.77	€ 9.98	€ 179.52
Appropriate comparator therapy					
Clenbuterol 20 µg[2]	100 SD	€ 35.44	€ 1.77	€ 0.00	€ 33.67
Fluticasone 500 µg[2]	240 SD	€ 51.74	€ 1.77	€ 3.22	€ 46.75
Fluticasone / formoterol 125 µg/ 5 µg [2]	360 SD	€ 106.67	€ 1.77	€ 0.00	€ 104.90
Omalizumab 150 mg	10 SFI	€ 4,926.15	€ 1.77	€ 278.06	€ 4,646.32
Tiotropium 5 µg	180 SD	€ 191.27	€ 1.77	€ 9.98	€ 179.52
Acronyms: SD = single doses; SFI = solution for injection; CIS = concentrate for infusion solution					

Patient population b)

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					
Dupilumab 200 mg	6 SFI	€ 4,645.00	€ 1.77	€ 262.00	€ 4,381.23
Dupilumab 300 mg	6 SFI	€ 4,645.00	€ 1.77	€ 262.00	€ 4,381.23
Budesonide 400 µg[2]	300 SD	€ 63.59	€ 1.77	€ 4.16	€ 57.66
Clenbuterol 20 µg[2]	100 SD	€ 35.44	€ 1.77	€ 0.00	€ 33.67
Fluticasone | Salmeterol 500 µg/50 µg[2]	180 SD	€ 133.65	€ 1.77	€ 9.70	€ 122.18
Tiotropium 5 µg	180 SD	€ 191.27	€ 1.77	€ 9.98	€ 179.52
Appropriate comparator therapy					
Benralizumab 30 mg	1 SFI	€ 2,605.98	€ 1.77	€ 145.55	€ 2,458.66

[2] Fixed reimbursement rate

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
Budesonide 400 µg[2]	300 SD	€ 63.59	€ 1.77	€ 4.16	€ 57.66
Clenbuterol 20 µg[2]	100 SD	€ 35.44	€ 1.77	€ 0.00	€ 33.67
Fluticasone | salmeterol 500 µg/50 µg[2]	180 SD	€ 133.65	€ 1.77	€ 9.70	€ 122.18
Mepolizumab 100 mg	3 SFI	€ 3,747.35	€ 1.77	€ 0.00	€ 3,745.58
Omalizumab 150 mg	10 SFI	€ 4,926.15	€ 1.77	€ 278.06	€ 4,646.32
Reslizumab 100 mg	2 CIS	€ 1,180.75	€ 1.77	€ 64.76	€ 1,114.22
Reslizumab 25 mg	2 CIS	€ 303.49	€ 1.77	€ 16.19	€ 285.53
Tiotropium 5 µg	180 SD	€ 191.27	€ 1.77	€ 9.98	€ 179.52
Acronyms: SD = single doses; SFI = solution for injection; CIS = concentrate for infusion solution					

Pharmaceutical retail price (LAUER-TAXE®) as last revised: 1 February 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 evaluated 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: arbitral award to determine the mg prices for parenteral preparations from proprietary medicinal products in oncology in the Hilfstaxe according to Section 129, paragraph 5c, sentences 2–5 SGB V of 19 January 2018), surcharges for the production of parenteral preparations containing cytostatic drugs of a maximum of € 81 per ready-to-use preparation and for the production of parenteral solutions containing monoclonal antibodies of a maximum of € 71 per ready-to-use unit shall be payable. 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 8 May 2018.

The appropriate comparator therapy established by the G-BA was reviewed. The Subcommittee on Medicinal Products redefined the appropriate comparator therapy at its session on 24 April 2019.

On 29 August 2019, the pharmaceutical company submitted a dossier for the benefit assessment of dupilumab to the G-BA in due time in accordance with Chapter 5, Section 8, paragraph 1, number 2 VerfO.

By letter dated 30 August 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 dupilumab.

The dossier assessment by the IQWiG was submitted to the G-BA on 28 November 2019, and the written statement procedure was initiated with publication on the website of the G-BA on 2 December 2019. The deadline for submitting written statements was 23 December 2019.

The oral hearing was held on 6 January 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 11 February 2020, and the proposed resolution was approved.

At its session on 20 February 2020, the plenum adopted a resolution to amend the Pharmaceuticals Directive.

Chronological course of consultation

Session	Date	Subject of consultation
Subcommittee Medicinal Products	8 May 2018	Determination of the appropriate comparator therapy
Subcommittee Medicinal Products	24 April 2019	Redefinition of the appropriate comparator therapy
Subcommittee Medicinal Products	6 January 2020	Conduct of the oral hearing,
Working group Section 35a	14 January 2020 4 February 2020	Consultation on the dossier evaluation by the IQWiG, evaluation of the written statement procedure
Subcommittee Medicinal Products	11 February 2020	Concluding discussion of the draft resolution
Plenum	20 February 2020	Adoption of the resolution on the amendment of Annex XII of the AM-RL

Berlin, 20 February 2020

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

Prof. Hecken