IQWiG Reports – Commission No. A18-58

Mepolizumab (asthma in adolescents and children aged 6 years and older) –

Benefit assessment according to §35a Social Code Book V[1]

Extract

[1] Translation of the executive summary of the dossier assessment *Mepolizumab (Asthma bei Jugendlichen und Kindern ab 6 Jahren) – Nutzenbewertung gemäß § 35a SGB V* (Version 1.0; Status: 20 December 2018). Please note: This document was translated by an external translator and is provided as a service by IQWiG to English-language readers. However, solely the German original text is absolutely authoritative and legally binding.

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Executive summary of the benefit assessment

Background

In accordance with §35a Social Code Book (SBG) V, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of the drug mepolizumab. The assessment is based on a dossier compiled by the pharmaceutical company (hereinafter referred to as the "company"). The dossier was sent to IQWiG on 24 September 2018.

Research question

The aim of this report is to assess the added benefit of add-on treatment with mepolizumab in comparison with the appropriate comparator therapy (ACT) in adolescents and children aged 6 years and older with severe refractory eosinophilic asthma.

For the benefit assessment, the G-BA's specification of the ACT results in the research question presented in Table 2.

Table 2[2]: Research question of the benefit assessment of mepolizumab

Indication	**ACT[a]**
Add-on treatment[b] in adolescents and children aged 6 years and older with severe refractory eosinophilic asthma	Individually optimized treatment escalation[c] ▪ of moderate-dose inhaled corticosteroids (ICS) and of long-acting bronchodilators (LABAs) to high-dose ICS and LABAs, or ▪ in IgE-mediated pathogenesis of asthma, omalizumab[d] in addition to high-dose ICS and LABAs and, if applicable, to oral corticosteroid (OCS)[e] treatment or ▪ if applicable, moderate to high-dose ICS and LABAs with OCS[e,f]
a: Presentation of the ACT specified by the G-BA. b: It is assumed that mepolizumab treatment is indicated only as an add-on to inhaled corticosteroids (ICS) and long-acting bronchodilators (LABAs). c: As specified by the G-BA, the Global Initiative for Asthma (GINA) graded scheme is to be taken into account. It is assumed that the therapeutic indication of mepolizumab is represented in steps 4 to 5. Placebo or the unchanged continuation of inadequate treatment of severe asthma does not comply with an ACT in severe refractory asthma, if the option for treatment escalation is still available. However, the therapeutic indication also includes patients for whom there is no further escalation option for their current treatment. d: Only in patients who completely fulfil the criteria of the approval and of the note on treatment for omalizumab. e: Oral corticosteroids (OCS) should be used only on a short-term basis and in their lowest effective dose. In the OCS treatment of asthma, it should be ensured that the OCS dosage does not permanently exceed the Cushing threshold, if possible. This rule should not be extended to the treatment of exacerbations. f: OCS therapy is not considered the preferred treatment option when compared to the other drugs mentioned, provided they are suitable. ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroids; IgE: immunoglobulin E; LABA: long-acting beta-2-sympathomimetic; OCS: oral corticosteroid	

[2] Table numbers start with "2" as numbering follows that of the full dossier assessment.

In the course of the dossier assessment, the G-BA changed the ACT for this assessment (discussion in the G-BA's Pharmaceuticals Subcommittee dated 11 December 2018). The following is the newly specified ACT:

- continuation of optimized therapy of severe asthma according to stage 5 of the National Disease Management Guideline for Asthma 2018 and additional escalation with omalizumab if the criteria for the use of omalizumab are fulfilled

The dossier presented by the company describes the added benefit in comparison with the ACT previously specified by the G-BA (see information in Table 2). These documents continue to be relevant for this assessment.

The assessment was conducted by means of patient-relevant outcomes on the basis of the data provided by the company in the dossier. RCTs with a minimum duration of 24 weeks were used for deriving an added benefit.

Results

To assess the added benefit, the company used 3 randomized controlled trials (RCTs: MENSA, MUSCA, and SIRIUS) as well as 4 single-arm mepolizumab studies (200363, COSMOS, COSMEX, and OSMO). The company pointed out that the patients included in these studies were mostly adults, and only a few were children and adolescents.

Therefore, the company presented data from the above-mentioned studies, which, in its view, show that the results of adults translate to adolescents and children (evidence transfer). For this purpose, the company merely provided a descriptive presentation of results (e.g. number of patients with an event for dichotomous outcomes or change from study start for continuous outcomes) for each study arm and study regarding the outcomes it considered relevant. The company did not perform an overall analysis including all studies. To quantify uncertainties in the determined results of dichotomous outcomes, the company calculated the associated 95% confidence intervals. In the company's view, the results of adults and children/adolescents were comparable if, for dichotomous outcomes, the confidence intervals of the two patient populations overlapped, or, for continuous outcomes, the changes from the study start were similar in adults and the paediatric target population. Since this was true for all data it examined, the company concluded that the results for adults and children/adolescents are comparable. Consequently, the company reasoned that the added benefit derived by the G-BA in a previous benefit assessment procedure on the basis of the SIRIUS mepolizumab study on adults translates to children and adolescents.

The company's methodology is not appropriate. Merely comparing the event rates or changes from the start of the study for adults with those for children and adolescents within the mepolizumab arms or within the placebo arms – if they exist in the studies – is not a suitable method for proving the comparability of effects (mepolizumab versus placebo) of mepolizumab between adults and children/adolescents. The objective of evidence transfer is to show that the treatment effects found in adults translate to children and adolescents. No data are available on

the effects of mepolizumab in comparison with the ACT for adults concerning patient-relevant outcomes. It must also be noted that the very small numbers of children and adolescents in the available studies cause the estimate to be of very low precision – not only for the comparison of event rates presented by the company, but also for a potential comparison of effects. The fact that in this constellation, the resulting very wide confidence intervals do overlap is not evidence for the comparability of the data of adults and children. For the same reason, given the low number of children and adolescents, comparing the means of the changes for continuous outcomes is not meaningful.

Overall, the approach chosen by the company is not suitable for justifying any evidence transfer of the results from adults to children and adolescents.

Overall, the company's presented evidence from the RCTs (MENSA, MUSCA, and SIRIUS) and 1-arm studies (200363, COSMOS, COSMEX [in Module 4 A named 201312], and OSMO) is insufficient for drawing conclusions on the added benefit of mepolizumab in children and adults for the reasons below.

- A prerequisite for evidence transfer of the results of adults to children/adolescents is the availability of relevant studies on adults which provide results on patient-relevant outcomes. However, this prerequisite is not met by the MENSA and MUSCA studies. The ACT specified by the G-BA was not implemented by either of them since they did not provide for sufficient individualized treatment escalation.
- In its decision dated 21 July 2016, the G-BA stated a hint of minor added benefit based on the SIRIUS study, particularly for the patient population of adults with severe refractory eosinophilic asthma who are regularly treated with OCS even beyond the treatment of acute exacerbations; overall, the studies presented by the company include data of no more than 2 adolescents and 1 child (all in the mepolizumab arm) who regularly receive OCS. This evidence is insufficient to assume transferability of results from adults to adolescents and children.
- Due to their single-arm study design, the studies 200363, COSMOS, COSMEX, and OSMO, which were presented by the company, are not suitable for deriving an added benefit in comparison with the ACT.

Overall, no suitable data are available to assess the added benefit of mepolizumab in comparison with the ACT in adolescents and children aged 6 years or older with severe refractory eosinophilic asthma.

Probability and extent of added benefit, patient groups with therapeutically important added benefit[3]

Table 3 presents a summary of the probability and extent of the added benefit of mepolizumab.

Table 3: Mepolizumab – probability and extent of added benefit

Indication	ACT[a]	Probability and extent of added benefit
Add-on treatment[b] in adolescents and children aged 6 years and older with severe refractory eosinophilic asthma	Individually optimized treatment escalation[c] ▪ of moderate-dose inhaled corticosteroids (ICS) and of long-acting bronchodilators (LABAs) to high-dose ICS and LABAs, or ▪ in IgE-mediated pathogenesis of asthma, omalizumab[d] in addition to high-dose ICS and LABAs and, if applicable, to oral corticosteroid (OCS)[e] treatment, or ▪ if applicable, moderate to high-dose ICS and LABAs with OCS[e, f]	Added benefit not proven

a: Presentation of the ACT specified by the G-BA.
b: It is assumed that mepolizumab treatment is indicated only as an add-on to inhaled corticosteroids (ICS) and long-acting bronchodilators (LABAs).
c: As specified by the G-BA, the Global Initiative for Asthma (GINA) graded scheme is to be taken into account. It is assumed that the therapeutic indication of mepolizumab is represented in steps 4 to 5. Placebo or the unchanged continuation of inadequate treatment of severe asthma does not comply with an ACT in severe refractory asthma, if the option for treatment escalation is still available. However, the therapeutic indication also includes patients for whom there is no further escalation option for their current treatment.
d: Only in patients who completely fulfil the criteria of the approval and of the note on treatment for omalizumab.
e: Oral corticosteroids (OCS) should be used only on a short-term basis and in their lowest effective dose. In the OCS treatment of asthma, it should be ensured that the OCS dosage does not permanently exceed the Cushing threshold, if possible. This rule should not be extended to the treatment of exacerbations.
f: OCS therapy is not considered the preferred treatment option when compared to the other drugs mentioned, provided they are suitable.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GINA: Global Initiative for Asthma; ICS: inhaled corticosteroids; IgE: immunoglobulin E; LABA: long-acting beta-2-sympathomimetic; OCS: oral corticosteroid

The G-BA decides on the added benefit.

[3] On the basis of the scientific data analysed, IQWiG draws conclusions on the (added) benefit or harm of an intervention for each patient-relevant outcome. Depending on the number of studies analysed, the certainty of their results, and the direction and statistical significance of treatment effects, conclusions on the probability of (added) benefit or harm are graded into 4 categories: (1) "proof", (2) "indication", (3) "hint", or (4) none of the first 3 categories applies (i.e., no data available or conclusions 1 to 3 cannot be drawn from the available data). The extent of added benefit or harm is graded into 3 categories: (1) major, (2) considerable, (3) minor (in addition, 3 further categories may apply: non-quantifiable extent of added benefit, added benefit not proven, or less benefit). For further details see [1,2].

References for English extract

Please see full dossier assessment for full reference list.

1. Institute for Quality and Efficiency in Health Care. General methods: version 5.0 [online]. 10 July 2017 [Accessed: 4 June 2018]. URL: https://www.iqwig.de/download/General-Methods_Version-5-0.pdf.

2. Skipka G, Wieseler B, Kaiser T, Thomas S, Bender R, Windeler J et al. Methodological approach to determine minor, considerable, and major treatment effects in the early benefit assessment of new drugs. Biom J 2015; 58(1): 43-58

The full report (German version) is published under https://www.iqwig.de/en/projects-results/projects/drug-assessment/a18-58-mepolizumab-asthma-benefit-assessment-according-to-35a-social-code-book-v.10618.html.