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Indacaterol acetate/ glycopyrronium bromide/ mometasone furoate (asthma) –

Addendum to Commission A20-69[1]

Addendum

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List of abbreviations

Abbreviation	Meaning
AQLQ-S	standardized Asthma Quality of Life Questionnaire
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLY	glycopyrronium bromide
ICS	inhaled corticosteroid
IND	indacaterol acetate
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
LABA	long-acting beta-2 agonist
LAMA	long-acting muscarinic antagonist
MF	mometasone furoate
SGRQ	St. George's Respiratory Questionnaire

1 Background

On 22 December 2020, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A20-69 (Indacaterol acetate/glycopyrronium bromide/mometasone furoate – Benefit assessment according to §35a Social Code Book V) [1].

The dossier assessment used the ARGON study [2], which included patients whose asthma was inadequately controlled with a combination of a medium or high-dose inhaled corticosteroid (ICS) and a long-acting beta-2 agonist (LABA). Of this study, the subpopulation of those patients who, in accordance with the approval [3], had previously been treated with a high dose of an ICS and a LABA is relevant to the benefit assessment on Commission A20-69.

To be able to decide on the added benefit, the G-BA needs further analyses in this procedure. The G-BA therefore commissioned IQWiG with the following assessment of the analyses submitted by the company in the dossier:

- For the outcomes on health-related quality of life, recorded with the Asthma Quality of Life Questionnaire (AQLQ-S) and the St. George's Respiratory Questionnaire (SGRQ), it has to be checked with regard to the analysis of the responder analysis for the proportion of patients with an improvement of at least 0.5 (AQLQ-S) or 4 points (SGRQ), whether the requirements are met for the testing with an increased significance level of 15% for the subpopulation relevant to the assessment ("target population")
- and the results are to be presented, provided that the requirements are met.

The responsibility for the present assessment and the assessment result lies exclusively with IQWiG. The assessment is forwarded to the G-BA. The G-BA decides on the added benefit.

2 Assessment

Results of the health-related quality of life outcomes (recorded by AQLQ-S and SGRQ)

For the outcome "health-related quality of life" recorded using the instruments AQLQ-S and SGRQ, the company presented analyses for the patients with an improvement by at least 0.5 (AQLQ-S) or 4 points (SGRQ) (responder analyses) in its dossier. For the assessment of the added benefit of indacaterol acetate/glycopyrronium bromide/mometasone furoate (hereinafter referred to as IND/GLY/MF), the company tested the treatment effect in the subpopulation from the ARGON study (pretreated with high-dose ICS) relevant to the benefit assessment at the increased significance level of 15% instead of 5%. The company justified this by stating that the formation of the subpopulation from the ARGON study for the benefit assessment is associated with a major loss of power. With its approach, the company intended to increase the power at the cost of an increased significance level. With reference to working paper GA18-01 [4], the company formulated in Module 4 A prerequisites for its approach that would have to be fulfilled for conducting a test with an increased significance level.

With reference to IQWiG's General Methods 6.0 [5], the analyses presented by the company on the threshold values of 0.5 and 4 points were not used for dossier assessment A20-69. According to these methods, for a response criterion to reflect with sufficient certainty a patient-noticeable change, it has to correspond to at least 15% of the scale range of an instrument if prespecified (exactly 15% of the scale range in post-hoc analyses).

The company did not provide any post-hoc analyses for the response criterion of 15% of the scale range of the instruments for the health-related quality of life outcomes (recorded using the instruments AQLQ-S and SGRQ) in the commenting procedure [6].

In its comments, the company compared asthma-specific patient characteristics of the relevant subpopulation of the ARGON study with those of the subpopulation not relevant to the assessment and considered them to be demographically and medically comparable. It also referred again to the statistical criteria – as already in Module 4 A.

Prerequisites for testing with an increased significance level are not completely fulfilled

Dossier assessment A20-69 [1] explained that, in addition to statistical, clinical/content requirements must also be met for a discussion of a test of the treatment effect at an increased significance level [4].

One prerequisite is the demonstration that, from a clinical/content perspective, the results of the subpopulation of the entire population of the ARGON study not relevant to the benefit assessment are sufficiently transferable to the subpopulation relevant to the benefit assessment.

In accordance with the G-BA's commission, it is examined whether these prerequisites are fulfilled for both health-related quality of life outcomes (recorded using the instruments AQLQ-S and SGRQ).

Transferability of results not shown

All patients in the ARGON study initially received a dual combination consisting of an ICS and a LABA during the 2-week run-in phase. The patients took the ICS component either in a high dosage (subpopulation relevant to the assessment) or in a medium dosage (subpopulation not relevant to the assessment) (detailed description of the ARGON study in dossier assessment A20-69 [1]).

In the course of randomization, the therapy was escalated equally for all patients: With the addition of a long-acting muscarinic antagonist (LAMA), both patient populations received a triple combination instead of the previous dual combination of ICS/LABA. Thus, with the addition of a LAMA (tiotropium), one component of the asthma therapy was escalated in the comparator arm for the subpopulation relevant to the assessment. For the patients in the subpopulation not relevant to the assessment, however, 2 components were escalated, i.e., besides the addition of the LAMA, the ICS component was increased from the medium to a high dosage.

The simultaneous increase of 2 components does not comply with the recommendations of the guideline group of the German National Care Guideline Asthma [7]. According to this guideline, all available therapy components should be gradually exhausted before further treatment escalation. In the case of a pre-existing medication consisting of medium-dose ICS plus LABA, for example, the doctor should decide individually with the patient whether the ICS dose should first be increased or whether treatment should be switched to a triple combination (addition of a LAMA). Such a gradual exhaustion of the available therapy components was not conducted in the comparator group due to the simultaneous dose increase of the ICS component and the addition of a LAMA for the patients in the subpopulation of the ARGON study that is not relevant to the assessment.

The aspect that the simultaneous escalation of 2 components conducted in the comparator arm of the ARGON study for the subpopulation not relevant to the assessment does not comply with the current recommendations for care was not addressed by the company either in the dossier or in the commenting procedure [6]. The company also did not investigate to what extent, despite the different treatment approaches (increase of 1 component versus simultaneous increase of 2 components), the results of the subpopulation not relevant to the assessment can nevertheless be transferred to the subpopulation relevant to the assessment and thus also to the German health care context.

Statistical requirements fulfilled

The statistical requirements described in working paper GA18-01 [4] for testing the treatment effect in the relevant subpopulation at a significance level of 15% were examined for both health-related quality of life outcomes (AQLQ-S, SGRQ) and were considered to be met.

3 Summary

Overall, the requirements for testing an increased significance level are not fulfilled for the present benefit assessment for the health-related quality of life outcomes. Taking into account the data submitted with the comments of the company, the statistical requirements are fulfilled, but not the requirements for clinical transferability of the results.

The results of the relevant subpopulation of the ARGON study for the analyses of patients with an improvement by at least 0.5 (AQLQ-S) or 4 points (SGRQ), for which the company tested the treatment effect in the relevant subpopulation at a significance level of 15% (instead of 5%), can already be found in dossier assessment A20-69 (see Table 24 there).

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of IND/GLY/MF from dossier assessment A20-69.

The following Table 1 shows the result of the benefit assessment of IND/GLY/MF under consideration of dossier assessment A20-69 and the present addendum.

Table 1: IND/GLY/MF – probability and extent of added benefit

Therapeutic indication	**ACT[a]**	**Probability and extent of added benefit**
Adult patients with asthma not adequately controlled with a maintenance combination of a LABA and a high dose of an ICS who experienced one or more asthma exacerbations in the previous year	High-dose ICS and LABA and LAMA[b, c]	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.
b. According to G-BA, the graded scheme of the German National Care Guideline for Asthma (NVL Asthma 2018, 3rd edition, Version 1 [8]) must be taken into account. Based on the drug properties of the combination of mometasone furoate, indacaterol acetate and glycopyrronium bromide, the G-BA determined the ACT for patients who are candidates for a therapy according to step 4 of the NVL Asthma 2018. Accordingly, it is assumed that the patients in the therapeutic indication received at least a dual combination (of high-dose ICS and LABA) as prior therapy without achieving adequate control. In addition, according to the G-BA, it is assumed that the patients are not yet eligible for the administration of antibodies.
c. According to the G-BA, the unchanged continuation of an inadequate asthma treatment does not comply with an ACT in uncontrolled asthma if the option for treatment escalation is still available.

ACT: appropriate comparator therapy; G-BA: Federal Joint Committee; GLY: glycopyrronium bromide; ICS: inhaled corticosteroid; IND: indacaterol acetate; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist; MF: mometasone furoate; NVL: National Care Guideline

The G-BA decides on the added benefit.

4 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Indacaterolacetat/ Glycopyrroniumbromid/ Mometasonfuroat (Asthma): Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A20-69 [online]. 2020 [Accessed: 16.11.2020]. URL: https://www.iqwig.de/download/A20-69_Indacaterolacetat-Glycopyrroniumbromid-Mometasonfuroat_Nutzenbewertung-35a-SGB-V_1-0.pdf.

2. Gessner C, Kornmann O, Maspero J et al. Fixed-dose combination of indacaterol/glycopyrronium/mometasone furoate once-daily versus salmeterol/fluticasone twice-daily plus tiotropium once-daily in patients with uncontrolled asthma: a randomised, phase IIIb, non-inferiority study (ARGON). Respir Med 2020; 170: 106021. https://dx.doi.org/https://doi.org/10.1016/j.rmed.2020.106021.

3. Novartis Pharma Gmb H. Enerzair® Breezhaler®; Fachinformation. Stand: Juli 2020 [online]. 2020 [Accessed: 23.07.2020]. URL: https://www.fachinfo.de/.

4. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Untersuchung der statistischen Eigenschaften von Verfahren zur Übertragbarkeit von Studienergebnissen auf Teilpopulationen: Arbeitspapier; Auftrag GA18-01 [online]. 2018 [Accessed: 18.07.2018]. URL: https://www.iqwig.de/download/GA18-01_Uebertragbarkeit-von-Studienergebnissen-auf-Teilpopulationen_Arbeitspapier_V1-0.pdf.

5. Institute for Quality and Efficiency in Health Care. General Methods; Version 6.0 [online]. 2020 [Accessed: 22.03.2021]. URL: https://www.iqwig.de/methoden/general-methods_version-6-0.pdf.

6. Novartis Pharma GmbH. Stellungnahme zum IQWiG-Bericht Nr. 996: Indacaterolacetat/Glycopyrroniumbromid/Mometasonfuroat (Asthma); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung; Auftrag A20-69. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/577/#beschluesse in the document "Zusammenfassende Dokumentation"].

7. Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. Nationale VersorgungsLeitlinie Asthma: Langfassung; 4. Auflage; Version 1 [online]. 2020 [Accessed: 13.10.2020]. URL: https://www.leitlinien.de/mdb/downloads/nvl/asthma/asthma-4aufl-vers1-lang.pdf.

8. Bundesärztekammer, Kassenärztliche Bundesvereinigung, Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften. Nationale VersorgungsLeitlinie Asthma: Langfassung; 3. Auflage; Version 1 [online]. 2018 [Accessed: 13.10.2020]. URL: https://www.leitlinien.de/mdb/downloads/nvl/asthma/archiv/asthma-3aufl-vers1-lang.pdf.