IQWiG Reports – Commission No. A21-85

Beclometasone/formoterol/ glycopyrronium (asthma) –

Addendum to Commission A21-18[1]

Addendum

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[1] Translation of addendum A21-85 *Beclometason/Formoterol/Glycopyrronium (Asthma) – Addendum zum Auftrag A21-18* (Version 1.0; Status: 15 July 2021). Please note: This translation 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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Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
Im Mediapark 8
50670 Köln
Germany

Phone: +49 221 35685-0
Fax: +49 221 35685-1
E-mail: berichte@iqwig.de
Internet: www.iqwig.de

IQWiG employees involved in the addendum

- Ulrike Mikulić
- Matthias Maiworm
- Beate Wieseler

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List of abbreviations

Abbreviation	Meaning
BDP	beclometasone
FORM	formoterol
G-BA	Gemeinsamer Bundesausschuss (Federal Joint Committee)
GLY	glycopyrronium
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care)
PT	Preferred Term
SAE	serious adverse event

1 Background

On 22 June 2021, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to conduct supplementary assessments for Commission A21-18 (Beclometasone/formoterol/glycopyrronium – Benefit assessment according to §35a Social Code Book V) [1].

The TRIGGER study [2] was used for the assessment of the added benefit of beclometasone/formoterol/glycopyrronium (BDP/FORM/GLY) in adult patients with asthma whose disease is not adequately controlled with a combination of a high-dose inhaled corticosteroid and a long-acting beta-2 agonist, and who experienced one or more asthma exacerbations in the previous year (research question 2 of the benefit assessment). This is a randomized controlled trial comparing BDP/FORM/GLY with BDP/FORM + tiotropium. The analyses for the outcome "serious adverse events (SAEs)" presented by the pharmaceutical company (hereinafter referred to as "the company") in the dossier [3] were not usable for the benefit assessment, as they contained a relevant proportion of events of the Preferred Term (PT) "asthma", which is to be allocated to the underlying disease.

The G-BA commissioned IQWiG with the assessment of the following data subsequently submitted by the company with its written comments [4] under consideration of the information provided in the dossier [3]:

- SAEs minus the severe asthma exacerbations

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

2.1 Results subsequently submitted on SAEs

In its comments, the company subsequently submitted data on SAEs without severe asthma exacerbations. However, events of the PT "asthma" were still included in the analysis. These events are also attributable to the underlying disease. The company stated that it did not consider an analysis without the PT "asthma" to be meaningful. According to the company, the analysis of this PT had shown that there was no difference between the treatment groups for the PT "asthma". The approach of the company is not appropriate. Regardless of whether group differences exist for an individual PT, consideration of individual PTs may influence group differences at the level of the overall rate of patients with SAEs because one or more different events may have occurred in each case for individual patients (double entries).

An analysis without any events of the underlying disease would be an adequate operationalization of the outcome "SAEs". The company did not present such an analysis. Therefore, the results on the SAEs subsequently submitted by the company are not usable.

Appendix A of the present addendum shows the analyses subsequently submitted by the company for the SAEs minus the severe asthma exacerbations.

2.2 Summary

The data subsequently submitted by the company in the commenting procedure have not changed the conclusion on the added benefit of BDP/FORM/GLY from dossier assessment A21-18.

The following Table 1 shows the result of the benefit assessment of BDP/FORM/GLY under consideration of dossier assessment A21-18 and the present addendum.

Table 1: BDP/FORM/GLY – probability and extent of added benefit

Research question	Subindication	ACT[a]	Probability and extent of added benefit
1	Adult patients whose asthma is not adequately controlled with medium-dose ICS/LABA therapy, and who experienced one or more asthma exacerbations in the previous year	Patient-specific treatment escalation taking into account the prior therapy, the severity of the disease and the symptoms, choosing from: ▪ medium-dose ICS and LABA and LAMA or ▪ high-dose ICS and LABA	Added benefit not proven
2	Adult patients whose asthma is not adequately controlled with high-dose ICS/LABA therapy, and who experienced one or more asthma exacerbations in the previous year	High-dose ICS and LABA and LAMA	Added benefit not proven

a. Presentation of the respective ACT specified by the G-BA.

ACT: appropriate comparator therapy; BDP: beclometasone; FORM: formoterol; G-BA: Federal Joint Committee; GLY: glycopyrronium; ICS: inhaled corticosteroid; LABA: long-acting beta-2 agonist; LAMA: long-acting muscarinic antagonist

The G-BA decides on the added benefit.

3 References

1. Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen. Beclometason/Formoterol/Glycopyrronium (Asthma) – Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung [online]. 2021 [Accessed: 17.05.2021]. URL: https://www.iqwig.de/download/a21-18_beclometason-formoterol-glycopyrronium_nutzenbewertung-35a-sgb-v_v1-0.pdf.

2. Chiesi Farmaceutici. TRIple in Asthma hiGh strenGth vErsus Ics/Laba hs and tiotRopium (TRIGGER) [online]. 2020 [Accessed: 05.03.2021]. URL: https://ClinicalTrials.gov/show/NCT02676089.

3. Chiesi Farmaceutici. Beclometason/Formoterol/Glycopyrronium (Trimbow); Dossier zur Nutzenbewertung gemäß § 35a SGB V [online]. 2021 [Accessed: 01.07.2021]. URL: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/653/#dossier.

4. Chiesi Farmaceutici. Stellungnahme zum IQWiG-Bericht Nr. 1110 Beclometason/Formoterol/Glycopyrronium (Asthma); Nutzenbewertung gemäß § 35a SGB V; Dossierbewertung. [Soon available under: https://www.g-ba.de/bewertungsverfahren/nutzenbewertung/653/#beschluesse in the document "Zusammenfassende Dokumentation"].

Appendix A – Supplementary presentation on SAEs

Table 2: Results (side effects, dichotomous) – RCT, direct comparison: BDP/FORM/GLY vs. BDP/FORM + TIO – data subsequently submitted with the comments (SAEs without severe asthma exacerbations)

Study Outcome category Outcome	BDP/FORM/GLY		BDP/FORM + TIO		BDP/FORM/GLY vs. BDP/FORM + TIO
	N	Patients with event n (%)	N	Patients with event n (%)	RR [95% CI]; p-value
TRIGGER					
Side effects					
SAEs without severe asthma exacerbations[a]	571	20 (3.5)	287	12 (4.2)	0.84 [0.42; 1.69]; 0.703

a. Supplementary presentation, data not usable.

BDP: beclometasone, CI: confidence interval; FORM: formoterol; GLY: glycopyrronium; n: number of patients with (at least one) event, N: number of analysed patients; RCT: randomized controlled trial; RR: relative risk; SAE: serious adverse event; TIO: tiotropium