

IQWiG Reports – Commission No. A12-13

**Aclidinium bromide –
Benefit assessment according
to § 35a Social Code Book V¹**

Extract

¹ Translation of Sections 2.1 to 2.6 of the dossier assessment (“Aclidiniumbromid – Nutzenbewertung gemäß § 35a SGB V” [Version 1.0; Status: 21.12.2012]). 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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List of abbreviations

| Abbreviation | Meaning |
|---------------------|---|
| ACT | appropriate comparator therapy |
| COPD | chronic obstructive pulmonary disease |
| G-BA | Gemeinsamer Bundesausschuss (Federal Joint Committee) |
| ICS | inhaled corticosteroids |
| IQWiG | Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen (Institute for Quality and Efficiency in Health Care) |
| SGB | Sozialgesetzbuch (Social Code Book) |

2 Benefit assessment

2.1. Executive summary of the benefit assessment

Background

In accordance with § 35a Social Code Book (SGB) 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 acclidinium bromide. The assessment was based on a dossier compiled by the pharmaceutical company (hereinafter abbreviated to “the company”). The dossier was sent to IQWiG on 01.10.2012.

Research question

The aim of this report is to assess the added benefit of acclidinium bromide (hereinafter abbreviated to “acclidinium”) according to the approval status for the following therapeutic indication: maintenance bronchodilator treatment to relieve symptoms in adult patients with chronic obstructive pulmonary disease (COPD).

The G-BA specified the following appropriate comparator therapy (ACT):

The graded scheme of the current German National Care Guideline COPD is to be taken into account:

- From Stage II, long-acting beta-2 sympathomimetics (formoterol, salmeterol) and/or long-acting anticholinergics (tiotropium bromide),
- From Stage III/IV with more than 2 exacerbations per year, inhaled corticosteroids (ICS) should be used in addition.

From the above-named drugs, the company chose tiotropium bromide (hereinafter abbreviated to “tiotropium”) as ACT and specified that account would be taken of the aforementioned graded scheme insofar as tiotropium plus ICS was the ACT for patients with Stage III or IV COPD with more than 2 exacerbations per year. The company’s approach with regard to the choice of ACT is appropriate. Accordingly, the dossier does not contain a comparison of acclidinium with long-acting beta-2 sympathomimetics.

Only studies with a minimum duration of 6 months were considered in this benefit assessment, because only such studies are capable of contributing reliable knowledge about the benefit or added benefit of acclidinium in the approved maintenance therapy. This deviates from the company’s approach, which also included studies of shorter duration.

The benefit assessment was undertaken with respect to patient-relevant outcomes.

Results

The company carried out a direct comparison and an indirect comparison between acclidinium and tiotropium.

No relevant study regarding a direct comparison was available for answering the research question. Due to their short duration of 2 and 6 weeks respectively, the studies submitted by the company were not suitable for demonstrating the added benefit of aclidinium over the ACT in the maintenance treatment of COPD.

Information retrieval by the company regarding the indirect comparison of aclidinium and tiotropium produced a study pool in the dossier of a total of 24 studies that compared aclidinium (3 studies) or tiotropium (21 studies) with placebo. Of these, 1 aclidinium study and 13 tiotropium studies were relevant for the assessment, because they had a corresponding duration of at least 6 months.

Comparison of the results of these studies presented in Module 4 of the dossier with the respective original sources revealed the existence of discrepancies in a relevant proportion of the data presented in Module 4 of the dossier compared to the corresponding data shown in the cited original sources. At the same time, Module 4 contained many details that could not be found in the original sources. There was no note in the dossier that these numbers had been calculated by the company itself, nor any information about how they had been derived. It was also not clear how most of the numbers reported in Module 4 could be derived from the data in the original sources.

This meant that for several of the outcomes presented by the company, in particular the outcomes regarding benefit, either the correct numbers were not entered in the resulting network meta-analysis or it was not possible to check these numbers. Therefore the result of the network meta-analysis could not be evaluated for most of these outcomes. Furthermore, in several cases the results of studies on different outcomes were not considered in the assessment, although corresponding results were available in the original source.

In summary, due to the deficiencies described above, a valid assessment of the added benefit of aclidinium on the basis of the indirect comparison with tiotropium presented in Module 4 of the dossier was not possible. Overall, the indirect comparison of aclidinium and tiotropium is regarded as non-evaluable.

Extent and probability of added benefit, patient groups with therapeutically important added benefit³

On the basis of the results presented, the extent and probability of the added benefit of the drug aclidinium is assessed as follows:

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 1-3 cannot be drawn from the available data), see [1]. 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, no added benefit, or less benefit), see [2].

The available data do not provide proof of an added benefit of aclidinium in comparison with the ACT specified by the G-BA. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

The decision regarding added benefit is made by the G-BA.

2.2 Research question

The benefit assessment of aclidinium was undertaken according to the approval status for the following therapeutic indication: maintenance bronchodilator treatment to relieve symptoms in adult patients with COPD [3,4].

The G-BA specified the following ACT:

“The graded scheme of the German National Care Guideline COPD, Version 1.9, January 2012 is to be taken into account:

- From Stage II, long-acting beta-2 sympathomimetics (formoterol, salmeterol) and/or long-acting anticholinergics (tiotropium bromide),
- From Stage III/IV with more than 2 exacerbations per year, ICS should be used in addition”.⁴

The company followed the specification of the G-BA and from the above-named drugs chose tiotropium as the ACT. The company also specified that account was to be taken of the aforementioned graded scheme as follows:

- Tiotropium for patients of Stage II and Stage III/IV with up to 2 exacerbations per year,
- Tiotropium and ICS for patients of Stage III/IV with more than 2 exacerbations per year.

The company’s approach with regard to the choice of ACT appears appropriate. Accordingly, the dossier does not contain a comparison of aclidinium with long-acting beta-2 sympathomimetics.

According to the summary of product characteristics of aclidinium, there is no restriction of patients in respect of COPD severity [3,4]. The company did not include patients with mild COPD (Stage I). This approach is understandable, bearing in mind the recommendations of the German National Care Guideline [5]. Moreover, the G-BA has not specified any ACT for this subpopulation (see Section 2.7.2.1 of the full dossier assessment).

Only studies with a minimum duration of 6 months were considered in this benefit assessment, because only such studies are capable of contributing reliable knowledge about the benefit or added benefit of aclidinium in the approved maintenance therapy (see Section 2.7.2.1 of the full dossier assessment). This deviates from the company’s approach, which set

⁴ Original quote in German.

a minimum duration of 12 weeks. If the company identified no studies of this duration for the comparison searched for in each case, then it also included studies with a shorter duration than 12 weeks.

The benefit assessment was carried out with respect to patient-relevant outcomes.

Further information about the research question can be found in Module 3, Section 3.1 and in Module 4, Section 4.2.1 of the dossier and in Sections 2.7.1 and 2.7.2.1 of the full dossier assessment.

2.3 Information retrieval and study pool

The study pool of the assessment was compiled on the basis of the following information:

- Studies on aclidinium completed by the company up to 09.07.2012 (study list of the company)
- Results of a search in bibliographical databases and in trial registries to identify studies for the direct comparison of aclidinium with the ACT tiotropium (last search on 28.08.2012 in bibliographical databases and on 29.08.2012 in trial registries, searches by the company)
- Results of a search in bibliographical databases and in trial registries to identify studies for the indirect comparison of aclidinium with the ACT tiotropium (last search on 05.07.2012 in bibliographical databases and on 06.07.2012 in trial registries, searches by the company)
- The Institute's own search in trial registries to identify studies on aclidinium to check the search results of the company up to 18.10.2012
- The Institute's own search in bibliographical databases and trial registries to identify studies on tiotropium to check the search results of the company up to 19.10.2012
- In addition, a supplementary screening of the contents of the entire information retrieval was undertaken using inclusion criteria relevant for the research question which differed considerably from those of the company, especially in relation to the minimum study duration (see Section 2.7.2.1 of the full dossier assessment). The results of checking and supplementary screening produced deviations from the study pool presented by the company in its dossier.

No relevant study for the direct comparison of aclidinium und tiotropium was identified from the above-named steps of information retrieval. The studies included by the company for the indirect comparison were basically suitable for the assessment. However, the processing of this study pool in the company's dossier shows such great deficiencies that the results are not evaluable. Reasons for these estimations are given below separately for the direct and the indirect comparison.

Study pool for the direct comparison

The company submitted 2 direct comparative randomized studies for the direct comparison of acclidinium und tiotropium [6,7]. However, these 2 studies are not relevant because, due to the study duration of 2 and 6 weeks respectively, they are unsuitable for addressing the research question of the added benefit of maintenance bronchodilator therapy of acclidinium compared with tiotropium (see Section 2.7.2.1 of the full dossier assessment). Only studies of at least 6 months' duration were relevant for the present research question.

Study pool for the indirect comparison

In addition to the direct comparison of acclidinium and tiotropium, the company submitted an indirect comparison with placebo as intermediate comparator. The information retrieval by the company for the indirect comparison of acclidinium and tiotropium produced a study pool in the dossier of a total of 24 studies that compared acclidinium (3 studies) or tiotropium (21 studies) with placebo. Of these, 1 acclidinium study and 13 tiotropium studies were relevant for the assessment, because they had a corresponding study duration of at least 6 months.

During a dossier assessment, a comparison is made between the data that the company submitted on the relevant studies in Module 4 of the dossier and the data in the original sources (publication and/or study report) of the respective studies. This comparison demonstrated that a relevant proportion of the data presented in Module 4 of the dossier revealed discrepancies compared to the corresponding information in the cited original sources.

At the same time, Module 4 of the dossier contains many details relating to results of relevant studies that could not be understood on the basis of information in the original sources. There was no note in the dossier that these numbers had been calculated by the company itself, nor any information about how they had been derived. It was also not clear how most of the numbers quoted in Module 4 could be derived from the data in the original sources.

This meant that for several of the outcomes shown by the company either the correct numbers were not entered in the resulting network meta-analysis or it was not possible to check these numbers. This affected almost all the relevant outcomes regarding benefit presented by the company. Therefore, the result of the network meta-analysis could not be evaluated for most of these outcomes. On the other hand, for the outcomes relating to harm (adverse events, serious adverse events, discontinuation due to adverse events) the respective correct values for all studies were entered in the analysis. Furthermore, in several cases the results of studies on different outcomes were not considered in the assessment, although corresponding results were available in the original source. A detailed commentary on the deficiencies in the underlying data and the effects on the assessment can be found in Section 2.7.2.3.2 of the full dossier assessment.

In summary, due to the deficiencies described above, a valid assessment of the added benefit of acclidinium on the basis of the indirect comparison with tiotropium presented in Module 4

of the dossier was not possible. Overall, the indirect comparison of acclidinium and tiotropium is regarded as non-evaluable.

Further information about the inclusion criteria for studies in this benefit assessment and on methods and results of the information retrieval can be found in Module 4, Sections 4.2.2 and 4.2.3 of the dossier and in Sections 2.7.2.1 and 2.7.2.3 of the full dossier assessment.

2.4 Results concerning added benefit

No relevant studies (direct comparison) or no evaluable data (indirect comparison) were available for the research question of the benefit assessment. Hence, there is no proof of an added benefit of acclidinium over the ACT specified by the G-BA.

Further information about the results on added benefit can be found in Module 4, Sections 4.3.1.3 and 4.3.2.1.3 of the dossier and in Section 2.7.2.4 of the full dossier assessment.

2.5 Extent and probability of added benefit

On the basis of the submitted data, there is no proof of an added benefit of acclidinium in comparison with the ACT specified by the G-BA. Hence, there are also no patient groups for whom a therapeutically important added benefit can be derived.

This deviates from the company's assessment, which overall, on the basis of the results of the direct comparison between acclidinium and its ACT tiotropium selected in accordance with the specifications of the G-BA, derived proof of a minor added benefit of acclidinium.

The decision regarding added benefit is made by the G-BA.

Further information about the extent and probability of the added benefit can be found in Module 4, Section 4.4 of the dossier and in Section 2.7.2.5 of the full dossier assessment

2.6 List of included studies

There is no list because the company did not present any study data in Module 4 of the dossier from which an added benefit of acclidinium over the ACT specified by the G-BA could be determined.

References for English extract

Please see full dossier assessment for full reference list.

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The full report (German version) is published under www.iqwig.de.