IQWiG Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen

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# Tiotropium bromide for COPD[1]

## Executive Summary

[1] Translation of the executive summary of the final report "Tiotropiumbromid bei COPD" (Version 1.0; Status: 26.06.2012). 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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This report was prepared in collaboration with external experts. According to § 139b (3) No. 2 of Social Code Book (SGB) V, Statutory Health Insurance, external experts who are involved in the Institute's research commissions must disclose "all connections to interest groups and contract organizations, particularly in the pharmaceutical and medical devices industries, including details on the type and amount of any remuneration received." The Institute received the completed form "Disclosure of conflicts of interest" from each external expert. The information provided was reviewed by a Committee of the Institute specifically established to assess conflicts of interests. The information on conflicts of interest provided by the external experts and external reviewers is presented in Appendix G of the full report. No conflicts of interest were detected that could endanger professional independence with regard to the work on the present commission.

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## Background

On 22.02.2005, the Federal Joint Committee (G-BA) commissioned the Institute for Quality and Efficiency in Health Care (IQWiG) to assess the benefit of tiotropium bromide in the treatment of chronic obstructive pulmonary disease (COPD) and specified the details of this commission on 25.08.2009.

## Research question

The aims of this report were

- to assess the benefit of tiotropium bromide compared to placebo or other pharmacological treatment options, alone or in combination, and
- the comparative benefit assessment of the two forms of application of tiotropium bromide, namely the HandiHaler and the Respimat,

in each case for the long-term inhalation treatment of patients with COPD with respect to patient-relevant outcomes.

## Methods

The assessment was conducted on the basis of randomized controlled trials (RCTs) on the above-named research question. For this purpose, a systematic literature search was performed in the following databases: MEDLINE, EMBASE, and the Cochrane Central Register of Controlled Trials (Clinical Trials). In addition, a search for relevant systematic reviews was carried out in the databases MEDLINE, EMBASE, Cochrane Database of Systematic Reviews (Cochrane Reviews), Database of Abstracts of Reviews of Effects (Other Reviews) and Health Technology Assessment Database (Technology Assessments). The systematic reviews were screened for further relevant studies. The literature search covered the period up to 26.10.2011. Trial registries and publicly accessible approval documents were also screened and the manufacturers of the tiotropium bromide product (Spiriva) approved in Germany, Boehringer Ingelheim Pharma GmbH & Co. KG and Pfizer Deutschland GmbH, were requested to submit relevant published or unpublished studies. In addition, the companies, Novartis Pharma GmbH and GlaxoSmithKline GmbH & Co. KG, were asked to send study reports on studies in which their products were used as comparator to tiotropium bromide.

The literature screening was performed by 2 reviewers independently of each other. Following an assessment of the risk of bias, the results of the individual studies, arranged according to outcomes and treatment comparisons, were described.

## Results

A total of 27 studies were identified as relevant for the research question of this benefit assessment. Of these studies, some of which were multi-arm, 21 were placebo-controlled. In 10 studies tiotropium bromide (hereinafter referred to in brief as tiotropium) was in each case

compared with an active control – namely the drugs formoterol fumarate, indacaterol maleate, ipratropium bromide, salmeterol xinafoate and the combination of salmeterol xinafoate / fluticasone propionate (hereinafter referred to in brief as formoterol, indacaterol, ipratropium, salmeterol and salmeterol / fluticasone respectively). In 2 studies, tiotropium added to a medication (formoterol or salmeterol / fluticasone) was compared to this medication without tiotropium. In none of the studies were both tiotropium inhalers used. In 4 – exclusively placebo-controlled – studies the Respimat was used, whilst all other studies were conducted with the HandiHaler.

The most important results from the assessment of the 27 included studies are summarized in Table 1. For ease of reading, the presentation was focussed on outcomes for which effects were shown. The results on individual symptoms of COPD are listed separately in the following Table 2. In most cases (24 studies), the risk of bias at study level was low. At outcome level, the risk of bias was sometimes rated as high, especially due to a lack of implementation of the intention-to-treat (ITT) principle.

Table 1: Summary of the most important results of the assessed studies on tiotropium in COPD

| | Result of the meta-analyses or individual studies: group difference [95 % CI] | | |
|---|---|---|---|
| **Outcome / inhaler** | **HandiHaler / Respimat** | **HandiHaler** | |
| | **Tiotropium vs. placebo** | **Tiotropium vs. LABA** | **Tiotropium vs. ipratropium** |
| **COPD symptoms** | | | |
| TDI | 0.90 [0.74; 1.07] p < 0.001 | -0.07 [-0.54; 0.41] p = 0.778 | 0.80 [0.31; 1.29] p = 0.001 |
| Mean focal score at end of study[a] | **0.31 [0.25; 0.37][b]** | | |
| Responder analyses[c] | **1.59 [1.39; 1.82] p < 0.001** | Heterogeneous results, therefore individual results and dosages considered<br>Tio vs. 150 µg indacaterol<br>0.78 [0.56; 1.09] p = 0.141<br>**Tio vs. 300 µg indacaterol**<br>**0.60 [0.43; 0.83] p = 0.002**<br>Tio vs. salmeterol<br>heterogeneous results | **1.96 [1.22; 3.13] p = 0.005** |
| **Exacerbations** | | | |
| Patients with at least one exacerbation | **0.76 [0.70; 0.82][c] p < 0.001** | **0.87 [0.80; 0.94][c] p = 0.001** | **0.73 [0.55; 0.97][d] p = 0.032** |
| Subgroup analysis according to COPD severity at start of study | **4-year study: interaction p < 0.001** | **Interaction p = 0.060** | |
| GOLD II | **0.79 [0.68; 0.92][c]** | 0.87 [0.76; 1.00][c] | |
| GOLD III | 1.08 [0.91; 1.28][c] | 0.86 [0.74; 0.99][c] | |
| GOLD IV | **1.77 [1.18; 2.64][c,e]** | 0.57 [0.42; 0.79][c] | |

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Table 1: Summary of the most important results of the assessed studies on tiotropium in COPD (continued)

| | Result of the meta-analyses or individual studies: group difference [95 % CI] | | |
|---|---|---|---|
| **Outcome / inhaler** | **HandiHaler / Respimat** | **HandiHaler** | |
| | **Tiotropium vs. placebo** | **Tiotropium vs. LABA** | **Tiotropium vs. ipratropium** |
| Patients with at least one hospitalization due to exacerbations | **0.81 [0.70; 0.93][c] p = 0.003** | **0.76 [0.65; 0.89][c] p < 0.001** | 0.59 [0.31; 1.13][c] p = 0.109 |
| Subgroup analysis according to COPD severity at start of study | **4-year study: interaction p = 0.018** | | |
| GOLD II | **0.74 [0.61; 0.91][c]** | | |
| GOLD III/IV | 1.06 [ 0.92;1.23][c] | | |
| Number of hospitalizations due to exacerbations: subgroup analysis according to gender | **4-year study: interaction p = 0.06** | | |
| Women | **-0.05 [-0.09; -0.01][f]** | | |
| Men | **0.00 [-0.03; 0.03][f]** | | |

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Table 1: Summary of the most important results of the assessed studies on tiotropium in COPD (continued)

| | Result of the meta-analyses or individual studies: group difference [95 % CI] | | |
|---|---|---|---|
| **Outcome / inhaler** | **HandiHaler / Respimat** | **HandiHaler** | |
| | **Tiotropium vs. placebo** | **Tiotropium vs. LABA** | **Tiotropium vs. ipratropium** |
| **Health-related quality of life** | | | |
| SGRQ | -2.97 [-3.47; -2.48] p < 0.001 | Heterogeneous results, therefore individual drugs considered: | Heterogeneous results |
| Mean total score[g] | -0. 23 [-0.27; -0.19][b] | Tio vs. formoterol<br>1.0 [-1.6; 3.5] p = 0.450<br>Tio vs. indacaterol<br>**1.85 [0.01; 3.68] p = 0.048**<br>**0.13 [0.00; 0.26][b]**<br>Tio vs. salmeterol<br>-1.44 [-3.23; 0.36] p = 0.117 | |
| Responders[c] | **1.41 [1.28; 1.52] p < 0.001** | Heterogeneous results, therefore individual drugs considered<br>Tio vs. indacaterol<br>**0.73 [0.56; 0.94] p < 0.016**<br>Tio vs. salmeterol<br>heterogeneous results | |
| SF-36[a] | 2.13 [1.50; 2.77] p < 0.001 | | 1.63 [0.28; 2.98] p = 0.018 |
| Mean sum score “physical health” | **0.33 [0.23; 0.43][b]** | | 0.23 [0.04; 0.42][b] |
| Mean sum score “mental health” | 0.61 [-0.15; 1.37] p = 0.117 | | Heterogeneous results |

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Table 1: Summary of the most important results of the assessed studies on tiotropium in COPD (continued)

| | Result of the meta-analyses or individual studies: group difference [95 % CI] | | |
|---|---|---|---|
| **Outcome / inhaler** | **HandiHaler / Respimat** | **HandiHaler** | |
| | **Tiotropium vs. placebo** | **Tiotropium vs. LABA** | **Tiotropium vs. ipratropium** |
| **Deaths** | | | |
| All-cause mortality | 6 to 12-month studies: 0.002 [-0.002; 0.005][h] p = 0.385<br>2- and 4[i]-year study: p > 0.05[h] | -0.002 [-0.006; 0.003][h] p = 0.457 | 1.23 [0.30; 5-08][c] p = 0.777 |
| All-cause mortality subgroup analysis[k] | 4[i]-year study: | | |
| Ex-smokers | **0.82 [0.71; 0.95][f] p = 0.009** | 0.65 [0.41; 1.04] | |
| Smokers | 1.08 [0.86; 1.36][f] p = 0.527 | 1.03 [0.64; 1.66] | |
| **Adverse drug reactions** | | | |
| Patients with at least one SAE | 0.98 [0.89; 1.07][c] p = 0.645 | 0.87 [0.78; 0.98][c,j] | Heterogeneous results |
| Study discontinuation due to AE | 6 to 12-month studies: heterogeneous results<br>2- and 4-year study: p < 0.05[f,j] in favour of tiotropium | Heterogeneous results[j] | 0.77 [0.44; 1.37][d] p = 0.379 |
| Patients with at least one AE | 0.98 [0.91; 1.06][c] p = 0.601 | 1.02 [0.85; 1.22][c] p = 0.828 | 0.88 [0.48; 1.61][c] p = 0.681 |

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Table 1: Summary of the most important results of the assessed studies on tiotropium in COPD (continued)

Results in bold: result produces hint, indication or proof. Empty cells: no data available.

a: Mean difference, positive effect estimators signify better values of the patients under tiotropium.
b: SMD in the form of Hedges' g to assess the relevance of the statistically significant group difference. If the 95 % confidence interval for the SMD was not fully below the irrelevance threshold of -0.2 or above the irrelevance threshold of 0.2, the effect was not considered relevant.
c: Odds ratio.
d: Relative risk.
e: In terms of the number of exacerbations, there was no proof of an effect modification with respect to severity. The result of the total population applies accordingly (statistically significant difference in favour of tiotropium).
f: Result from the study / studies with HandiHaler.
g: Mean difference, negative effect estimators signify better values of the patients under tiotropium.
h: Risk difference.
i: Analysis of deaths with start of the event leading to death during the planned treatment period plus 30 days.
j: The result could not be interpreted because characteristics of the underlying disease COPD were also taken into account in the analysis of adverse events.
k: Hazard ratio.

AE: adverse event; CI: confidence interval; GOLD: Global Initiative for Chronic Obstructive Lung Disease; LABA: long-acting $beta_2$-agonist; SAE: serious adverse event; SF-36: Short Form-36; SMD: standardized mean difference; SGRQ: St. George's Respiratory Questionnaire; TDI: Transitional Dyspnoea Index; Tio: tiotropium; vs: versus.

***Tiotropium in comparison with placebo***

The Respimat was only used in 4 studies, all of which were placebo-controlled and exclusively used this type of inhaler. Therefore the influence of the inhaler could only be investigated for the comparison tiotropium vs. placebo, namely in the form of interaction tests from meta-regressions of the studies grouped according to inhaler and combined in meta-analyses.

Data on the effects on **COPD symptoms** were collected in a total of 12 placebo-controlled studies. Because meta-analyses of scores for the symptoms of wheeze, cough and chest discomfort showed, in each case, an indication of an effect modification by the type of inhaler used, the studies were assessed separately according to inhaler type. In respect of individual symptoms scores, a statistically significant difference and definitely not irrelevant effect was shown only in the meta-analysis of the studies comparing placebo and tiotropium (applied with the Respimat) for the symptom of wheeze, and this was in favour of tiotropium. As regards the days without COPD symptoms, there was also a statistically significant difference in favour of tiotropium (see Table 2).

Table 2: Summary of the results on individual symptoms, tiotropium vs. placebo

| | **Results of the meta-analyses or individual studies group difference [95 % CI]** | |
|---|---|---|
| **Outcome** | **Tiotropium vs. placebo from HandiHaler** | **Tiotropium vs. placebo from Respimat** |
| Symptom score wheeze[a] | Heterogeneous results | -0.22 [-0.28; -0.15] p < 0.001<br>-0.34 [-0.46; -0.23][b] |
| Symptom score dyspnoea[a] | Heterogeneous results[c] | |
| Symptom score cough[a] | -0.06 [-0.10; -0.02] p = 0.002<br>-0.10 [-0.16; -0.04][b] | -0.13 [-0.21; -0.05] p = 0.002<br>-0.17 [-0.28; -0.06][b] |
| Symptom score chest discomfort[a] | -0.07 [-0.13; -0.01] p = 0.023<br>-0.11 [-0.20; -0.01][b] | -0.15 [-0.21; -0.08] p < 0.001<br>-0.23 [-0.34; -0.12][b] |
| Symptom score amount of sputum[a] | -0.07 [-0.14; -0.003] p = 0.039<br>Heterogeneous results | |
| Symptom sum score[a] | p = 0.108[d] | |
| Proportion of days with marked COPD symptoms [%] | Heterogeneous results | |
| Proportion of days without COPD symptoms [%] | 2.21 [0.57; 3.85] p = 0.008 | |

Empty cells: no data available.

a: Mean difference, negative effect estimators signify better values of the patients under tiotropium.
b: SMD in the form of Hedges' g to assess the relevance of the statistically significant group difference. If the 95 % confidence interval for the SMD was not fully below the irrelevance threshold of -0.2, the effect was regarded as non-relevant.
c: Heterogeneous results with a clear direction of effect, however there was no sense in calculating an overall estimator. In 10 of the 11 studies, the 95 % confidence interval for the SMD in the form of Hedges' g was not fully below the irrelevance threshold of -0.2.
d: Only reported in one study, group difference not stated.

CI: confidence interval; SMD: standardized mean difference; vs.: versus

In respect of the mean transitional dyspnoea index (TDI) focal score, the effect in favour of tiotropium from the meta-analysis of the 11 studies that investigated this outcome was assessed as relevant. The meta-analysis of the available 8 TDI responder analyses also showed a statistically significant difference in favour of tiotropium (see Table 1). In both analyses, the interaction test showed no effect modification by the type of inhaler. The majority of studies had an outcome-related high risk of bias. From the results on the individual symptom scores, the days without COPD symptoms and the TDI, there was overall an indication of a benefit of tiotropium for COPD symptoms (irrespective of inhaler type, period investigated: 6 to 12 months).

Data on the frequency of **exacerbations** were collected in all 22 studies that compared tiotropium with placebo (21 studies) or no treatment (1 study). The results of studies lasting 6 to 12 months showed a statistically significant difference in favour of tiotropium for the comparison tiotropium versus placebo in the meta-analysis for the outcome "patients with at least one exacerbation" (for result, see Table 1). The results for the outcome "number of exacerbations/year" were heterogeneous, but all 6 studies of this meta-analysis showed a statistically significant difference in favour of tiotropium. The results of other studies that were not included in the meta-analyses on the number of exacerbations because of differing methods of analysis pointed in the same direction. In the 2 long-term studies, there was a statistically significant difference only in terms of the number of exacerbations in the 4-year UPLIFT study, and this was in favour of tiotropium (Wilcoxon test $p < 0.001$). The results from the 5 studies (duration 6 to 12 months) that, by recording the number of unplanned outpatient visits to a doctor due to exacerbations, investigated the need for outpatient medical treatments due to exacerbations pointed in the same direction and therefore supported this assessment. The interaction test never showed an effect modification by the inhaler type used. A **subgroup analysis on the proportion of patients with at least one exacerbation according to COPD severity at baseline** of the 4-year UPLIFT study produced proof of an effect modification. In this study, which represents about 90 % of all the patients observed regarding this outcome over a long period, the patients with the highest severity (Global Initiative for Chronic Obstructive Lung Disease (GOLD IV)) showed discrepant results in comparison with the outcome "number of exacerbations" (statistically significantly higher proportion of patients with at least one exacerbation under tiotropium, see Table 1). There is thus no proof for these patients of an effect in respect of the frequency of exacerbations in the period of more than one year. This discrepancy was not seen for patients with lower grades of severity (GOLD II and III). Therefore, in summary there is proof of a benefit of tiotropium regarding the frequency of exacerbations (irrespective of inhaler type) for the period of up to one year and for patients with moderate or severe COPD (GOLD II and III) beyond this period.

Data on the **need for hospitalizations due to exacerbations** were reported in 18 placebo-controlled studies. The results of studies of 6 to 12 months duration for the comparison tiotropium versus placebo showed a statistically significant difference in favour of tiotropium

in the meta-analyses for the outcomes "patients with at least one hospitalization due to exacerbations" (for result, see Table 1) and "number of hospitalizations due to exacerbations/year" (mean difference [95 % CI]: -0.03 [-0.05; -0.01]; p = 0.002). The results of other studies that, because of differing methods of analysis, were not to be included in the meta-analyses on the number of hospitalizations due to exacerbations pointed in the same direction. The interaction test never showed an effect modification by the inhaler type used. The 2 long-term studies demonstrated no statistically significant difference for either of the two outcomes relating to the need for hospitalizations due to exacerbations. The corresponding **subgroup analysis on the number of hospitalizations due to exacerbations according to gender** of the 4-year UPLIFT study produced an indication of an effect modification. In this study, which represents about 90 % of all the patients observed regarding this outcome over a long period, a significant difference between the treatment groups was only shown in women (see Table 1). Another **subgroup analysis on the number of hospitalizations due to exacerbations according to severity at baseline** of the UPLIFT study produced proof of an effect modification. In contrast to the overall population, there was a statistically significant difference in favour of tiotropium in patients with disease of moderate severity (GOLD II). Therefore, in summary, in respect of the need for hospitalizations due to exacerbations, there is proof of a benefit of tiotropium (irrespective of inhaler type) for the period of up to one year. For the period beyond one year, for this outcome there is an indication of a benefit of tiotropium in women, and proof in patients with disease of moderate severity.

Data on **health-related quality of life** were recorded in a total of 18 placebo-controlled studies using the St George's Respiratory Questionnaire (SGRQ). The generic scales SF-36 (3 studies) and EQ-5D (1 study) were also used. Meta-analysis of the results of the SGRQ responder analyses for the comparison tiotropium vs. placebo in the studies of 6 to 12 months duration showed a statistically significant difference in favour of tiotropium (see Table 1). From long-term studies, there were evaluable data on only 2 study outcomes concerning health-related quality of life, in each case recorded with the SGRQ. In the 2-year EXACTT study, although there was a statistically significant effect (mean difference [95 % CI]: -4.03 [-6.97; -1.10]; p = 0.007) for the mean SGRQ total score in favour of tiotropium, the 95 % confidence interval of the related SMD was not fully below the irrelevance threshold of -0.2 (SMD in the form of Hedges' g [95 % CI]: -0.26 [-0.45; -0.07]). For the change in SGRQ total score with time during the 4-year UPLIFT study, there was no statistically significant difference between tiotropium and placebo. In contrast to the sum score "mental health" of the SF-36, the meta-analysis on the sum score "physical health" showed a statistically significant and relevant difference in favour of tiotropium (see Table 1). There was no statistically significant difference between tiotropium and placebo in the EQ-5D in the INHANCE study.

The interaction test showed no effect modification by the type of inhaler in any analysis. Although the majority of studies showed an outcome-related high risk of bias, the influence of this risk on the result in these studies was rated as low. Therefore, in summary, there is proof

of a benefit of tiotropium for the period of up to one year in respect of health-related quality of life measured with the disease-specific SGRQ, irrespective of the type of inhaler. In terms of the sum score "physical health" of the generic SF-36, there is proof of a benefit of tiotropium in respect of health-related quality of life (period investigated: 6 to 12 months).

Data on **exercise capacity** were collected in a total of 12 placebo-controlled studies. A variety of recording methods were used and, in some cases, no evaluable data were available, so that all results are based only on 1 or 2 – in one case on 3 (6-minute walk test) – studies. The constant work rate treadmill protocol was used in 2 studies, where a statistically significant difference in favour of tiotropium was shown only in the smaller, 6-month study 205.230, but not in the far larger 2-year EXACTT study. There was no statistically significant difference between tiotropium and placebo for the outcomes "daily step count", "shuttle walk test", "6-minute walk test", "retirement due to COPD", "loss of employment due to COPD" and "incapacity for work due to COPD". In the 205.365 study, only in 1 of the 4 subscales of the Work, Productivity and Activity Impairment (WPAI) questionnaire was there a statistically significant difference in favour of tiotropium, but this was not assessed as relevant. From these outcomes, there is therefore overall no proof of a benefit of tiotropium in terms of exercise capacity. A meta-analysis of 2 studies showed a statistically significant difference in favour of tiotropium for various individual outcomes used to record limitations in activities of daily living. Although this difference could not be confirmed in the other studies, the two studies represented a majority of the patients. Overall, there is a hint of a benefit of tiotropium in respect of the ability to perform activities of daily living.

Outcomes of **COPD-associated cardiovascular morbidity and mortality** and of **COPD-related mortality** were recorded in 1 and 2 studies respectively and in neither comparison was there a statistically significant difference between tiotropium and placebo.

There was no statistically significant difference between tiotropium and placebo in terms of **all-cause mortality** in the studies of 6 to 12 months duration. This also applies to the two studies with a longer duration (2 and 4 years) if the more valid analyses including a follow-up of the study discontinuations in the UPLIFT study are considered. The corresponding **subgroup analysis of all-cause mortality according to smoker status** of the 4-year UPLIFT study produced an indication of effect modification. This study, which represents about 40 % of all patients investigated with respect to all-cause mortality and in which tiotropium was applied with the HandiHaler, showed no significant difference between the groups for smokers. There was, however, a statistically significant difference in favour of tiotropium in those who, at the time of start of the study, had stopped smoking (see Table 1). There is therefore an indication of a benefit of tiotropium in ex-smokers in terms of all-cause mortality (period investigated: 4 years, inhaler investigated: HandiHaler).

In respect of the outcomes relating to **adverse drug reactions** – which were reported in almost all studies – there was no statistically significant difference in the proportion of patients with at least one AE and in the proportion of patients with at least one SAE. In

respect of the outcome "study discontinuation due to AE", the meta-analysis of the studies of 6 to 12 months duration showed considerable heterogeneity without a clear direction of effect. In the two long-term EXACTT and UPLIFT studies, there was a statistically significant difference in favour of tiotropium here. Adverse events recorded in the studies also took account of events that represented a characteristic of the underlying disease (e.g. exacerbations). Inspection of the AE documentation showed an unequal distribution of such COPD-related reasons for discontinuation in favour of tiotropium. Through this type of analysis, the outcome illustrated a lack of benefit of placebo, but not harm from tiotropium through adverse drug reactions. In this benefit assessment, characteristics of the underlying disease, e.g. exacerbations, were considered as an independent outcome, so the effect described above is already taken into account. In summary, there is no proof of harm from tiotropium compared to placebo.

***Tiotropium added to LABA in comparison with LABA***

One study (FOR258F2402) was available for the comparison of the combination of tiotropium and formoterol with a formoterol monotherapy, in which data on this comparison were collected for the following outcomes: "COPD symptoms", "exacerbations", "health-related quality of life", "exercise capacity", "COPD-related mortality", "all-cause mortality", and "adverse drug reactions". There was no significant difference between the treatment groups for any of the outcomes. Therefore, for none of the patient-relevant outcomes specified in the report plan is there proof of benefit or harm from tiotropium if it is given in addition to treatment with a drug from the class of LABA.

***Tiotropium added to salmeterol / fluticasone in comparison with salmeterol / fluticasone***

Only one study (Fang 2008) was available for assessment of the comparison of the combination of tiotropium, salmeterol and fluticasone with a combination of salmeterol and fluticasone. This study recorded and compared data on exacerbations and on health-related quality of life. There was no statistically significant difference between the treatment groups in terms of the frequency of exacerbations. The statistically significant result in respect of the mean SGRQ total score proved to be incomprehensible and hence an irrelevant effect cannot be ruled out with certainty. The study provided no evaluable data on all-cause mortality or on the adverse drug reactions. Therefore, for none of the patient-relevant outcomes specified in the report plan is there proof of benefit or harm from tiotropium if it is given in addition to treatment with a combination of salmeterol / fluticasone.

***Tiotropium in comparison with LABA***

In the 3 studies on the comparison tiotropium versus LABA, in which results on **COPD symptoms** were reported, the meta-analyses and/or the results of the individual studies for the symptom scores of wheeze, dyspnoea, cough and chest discomfort, the symptom sum score and the days with marked and without symptoms, showed no statistically significant difference between the treatment groups, or there was considerable heterogeneity without a clear direction of effect. The meta-analysis of all studies that compared tiotropium versus

LABA (indacaterol and salmeterol) in terms of TDI showed considerable heterogeneity. When the individual drugs were considered separately, there was a statistically significant difference to the disadvantage of tiotropium compared to indacaterol (dosage 300 µg). In the corresponding meta-analysis on the comparison tiotropium versus salmeterol, there was considerable heterogeneity without a clear direction of effect (see Table 1). There is therefore overall a hint of a lesser benefit of tiotropium compared to indacaterol (dosage 300 µg) in respect of COPD symptoms.

The 5 studies in which data on the frequency of **exacerbations** were collected for this comparison, showed a statistically significant difference in favour of tiotropium compared to the LABA class of drugs for the outcome "patients with at least one exacerbation" (for results, see Table 1). The corresponding results on the number of exacerbations pointed in the same direction. The results of one study regarding the need for outpatient medical treatments due to exacerbations revealed contradictory effects for different categories of doctors, i.e. they provided no additional findings. In summary, there is proof of an added benefit of tiotropium compared to the LABA class of drugs regarding the frequency of exacerbations (period investigated: 6 to 12 months, inhaler investigated: HandiHaler).

The 5 studies in which data on the **need for hospitalizations due to exacerbations** were collected for this comparison showed a statistically significant difference in favour of tiotropium compared to the LABA class of drugs for the outcome "patients with at least one hospitalization due to exacerbations" (for results, see Table 1). The corresponding results on the number of hospitalizations due to exacerbations pointed in the same direction. In summary, there is proof of an added benefit of tiotropium compared to the LABA class of drugs regarding the need for hospitalizations due to exacerbations (period investigated: 6 to 12 months, inhaler investigated: HandiHaler).

In the 4 studies in which data on **health-related quality of life** were collected for this comparison, both the meta-analysis on the mean SGRQ total score and also the responder analysis showed considerable heterogeneity that could be explained by the drug of the comparator group or by the lack of blinding of tiotropium respectively. In the subsequent separate analyses on the comparison with formoterol, indacaterol and salmeterol respectively (mean change in SGRQ), or with salmeterol (SGRQ responder analyses), there was either no statistically significant difference, or an irrelevant effect could not be ruled out with certainty, or considerable heterogeneity was present in the meta-analysis without a clear direction of effect. In the responder analysis of the comparison tiotropium versus indacaterol, there was a statistically significant difference to the disadvantage of tiotropium (see Table 1). There was no statistically significant difference in the comparison of tiotropium versus LABA for the EQ-5D. Overall, there is a hint of a lesser benefit of tiotropium compared to the LABA indacaterol in terms of health-related quality of life.

The 4 studies on this comparison showed no statistically significant difference between the treatment groups in the individual studies or meta-analyses regarding various outcomes

relating to **exercise capacity**, or considerable heterogeneity without a clear direction of effect was present. Therefore there is no proof of added benefit of tiotropium compared to the LABA class of drugs in respect of exercise capacity.

With respect to the outcomes of **COPD-associated cardiovascular morbidity and mortality,** in the POET study regarding this comparison no statistically significant difference between the treatment groups was shown. The meta-analyses on **COPD-related mortality** and on **all-cause mortality** of all 2 and 5 studies respectively, which had collected data on this comparison, also showed no statistically significant difference between the treatment groups. There is therefore no proof of a difference in benefit or harm from tiotropium compared to the LABA class of drugs for any of the above-named areas.

In terms of **adverse drug reactions** (for results, see Table 1), meta-analyses of the 5 studies of this comparison on the proportion of patients with at least one serious adverse event and on discontinuation due to adverse events, showed an effect in favour of tiotropium in each case. However, in all 5 studies patients were also included in whom an exacerbation was documented as SAE or as reason for discontinuation. In this benefit assessment, exacerbations were evaluated as an independent outcome. The effect of tiotropium in comparison with salmeterol in respect of exacerbations was thus already taken into account via this outcome. On the basis of the available data, it was only possible in a fraction of the patient data to exclude those patients from the analysis in whom an exacerbation was reported as a unique SAE or single cause for discontinuation. Since it was therefore not possible to undertake an adequate assessment of this outcome, no proof for lesser harm from tiotropium compared to salmeterol was derived from the two results. The meta-analysis found no statistically significant difference between tiotropium and LABA for the proportion of patients with at least one adverse event and for **all-cause mortality**. In summary, there is no proof of greater or lesser harm from tiotropium compared to the LABA class of drugs.

***Tiotropium in comparison with ipratropium***

The meta-analysis of the 2 studies that compared tiotropium versus ipratropium, in which results on **COPD symptoms** were reported, showed a statistically significant difference in favour of tiotropium for the responder analysis of the TDI focal score. Based on 2 studies with outcome-related high risk of bias, there is therefore an indication of an added benefit of tiotropium compared to ipratropium in respect of COPD symptoms.

The 2 studies in which data on **exacerbations** were collected showed a statistically significant difference in favour of tiotropium compared to ipratropium for the outcome “patients with at least one exacerbation” (for result, see Table 1) and “number of exacerbations” (Wilcoxon test $p = 0.006$). There was no statistically significant difference for the outcomes “patients with at least one hospitalization due to exacerbations” and “number of hospitalizations due to exacerbations”. In summary, there is proof of added benefit of tiotropium compared to ipratropium in respect of the frequency of exacerbations (period investigated: 1 year, inhaler investigated: HandiHaler).

In the 2 studies in which data on **health-related quality of life** were collected, there was considerable heterogeneity in the meta-analysis without a clear direction of effect for the outcomes "SGRQ total score" and also for SF-36 sum score "mental health". In respect of the outcome SF-36 sum score "physical health", the effect was assessed as not relevant. There is therefore no proof of added benefit of tiotropium compared to ipratropium in respect of health-related quality of life.

For the comparison tiotropium versus ipratropium, the 205.126A study showed a statistically significant difference to the disadvantage of tiotropium for the recorded outcomes in the area of **exercise capacity** in respect of the number of days with restriction of activities of daily living. No evaluable data were available from the 205.126B study on the outcomes in the area of exercise capacity. The Jia 2008 study showed a statistically significant difference between tiotropium and ipratropium in the 6-minute walk test in favour of tiotropium. In summary, due to these contradictory results, there is no proof of added benefit of tiotropium compared to ipratropium in respect of exercise capacity.

In respect of the outcome "proportion of patients with at least one serious adverse event", the meta-analysis of 2 studies showed a statistically significant difference in favour of tiotropium. The recording of adverse events in the studies also included events that represented a characteristic of the underlying disease (e.g. exacerbations). However, in this benefit assessment, exacerbations were evaluated as an independent outcome. The effect of tiotropium in comparison with ipratropium in respect of exacerbations was therefore already taken into account via this outcome. A meta-analysis with exclusion of patients in whom exacerbations were exclusively reported as SAE showed considerable heterogeneity without a clear direction of effect. In these studies there was no statistically significant difference between tiotropium and ipratropium in **all-cause mortality** and the other outcomes relating to **adverse drug reactions** (study discontinuation due to AE, patients with at least one AE) (see Table 1). There were no evaluable data in a third (not manufacturer-sponsored) study with these comparisons. In summary, there is no proof of greater or lesser harm from tiotropium compared to ipratropium.

***Tiotropium in comparison with salmeterol / fluticasone***

Two studies on the comparison of tiotropium with the combination of salmeterol and fluticasone were included in the assessment. There was no statistically significant difference between the treatment groups for the outcomes "COPD symptoms", "hospitalizations due to exacerbations", "health-related quality of life", "exercise capacity", "study discontinuation due to AE" and "patients with at least one AE", so that here there was no proof of added benefit of tiotropium. Although in one 2-year study there was a statistically significant difference to the disadvantage of tiotropium ($p = 0.033$) in terms of all-cause mortality, because of the increased uncertainty caused by the lack of follow-up of the study discontinuations, there was no proof of a difference in benefit or harm here between tiotropium and the combination of salmeterol and fluticasone. In respect of exacerbations, in the total group of the study there was no statistically significant difference between the

treatment groups. In the subgroup analysis on the number of exacerbations, the 2-year study showed a statistically significant difference to the disadvantage of tiotropium for women ($p = 0.004$) and for ex-smokers ($p = 0.008$). Due to the possibly systematic disadvantaging of the tiotropium group through the abrupt withdrawal of treatment with inhaled corticosteroids at the start of the study, here, too, no proof was derived of a difference in benefit between the treatment options. In respect of the proportion of patients with at least one SAE, there was a statistically significant difference in favour of tiotropium ($p = 0.022$). However, exacerbations were also documented as SAE in the study. In this benefit assessment, exacerbations were evaluated as an independent outcome. On the basis of the available data it was not possible to exclude patients from the analysis in whom an exacerbation was reported as the only SAE. This meant that the results on this outcome could not be adequately assessed. Therefore no proof was derived from the result of lesser harm from tiotropium in comparison with the combination of salmeterol and fluticasone.

Table 3 summarizes the results of the benefit assessment.

Table 3: Tiotropium in COPD – evidence map

| Outcome / inhaler | HandiHaler / Respimat | HandiHaler | | | | |
|---|---|---|---|---|---|---|
| | **Tiotropium vs. Placebo** | **Tiotropium / LABA vs. LABA** | **Tiotropium / salmeterol / fluticasone vs. salmeterol / fluticasone** | **Tiotropium vs. LABA** | **Tiotropium vs. ipratropium** | **Tiotropium vs. salmeterol / fluticasone** |
| **COPD symptoms** | ↑↑ | ⇔ | | ⇔ / ↓[a] | ↑↑ | ⇔ |
| **Exacerbations** | ↑↑↑[b] | ⇔ | ⇔ | ↑↑↑ | ↑↑↑ | ⇔ |
| **Hospitalizations due to exacerbations** | ↑↑↑[c] | ⇔ | | ↑↑↑ | ⇔ | ⇔ |
| **Health-related quality of life** | ↑↑↑[d] | ⇔ | ⇔ | ⇔ / ↓[e] | ⇔ | ⇔ |
| Sub-areas of physical health | ↑↑↑ | | | | ⇔ | |
| **Exercise capacity** | ↑[d,f] | ⇔ | | ⇔ | ⇔ | ⇔ |
| **COPD-associated cardiovascular morbidity and mortality** | ⇔ | | | ⇔ | | |
| **COPD-related mortality** | ⇔ | (⇔) | | ⇔ | | |
| **All-cause mortality** | ↑↑ in ex-smokers[g] | (⇔) | | ⇔ | (⇔) | ⇔ |
| **SAE** | ⇔ | ⇔ | | ⇔ | ⇔ | ⇔ |
| **Discontinuation due to AE** | ⇔ | ⇔ | | ⇔ | ⇔ | ⇔ |
| **AE** | ⇔ | ⇔ | | ⇔ | ⇔ | ⇔ |

(continued on next page)

Table 3: Tiotropium in COPD – evidence map (continued)

↑↑↑ = Proof of benefit/added benefit or lesser harm.
↑↑ = Indication of benefit/added benefit or lesser harm.
↑ = Hint of benefit/added benefit or lesser harm.
↓ = Hint of harm or lesser benefit.
⇔ = No proof of a difference.
( ) = Few data available.
Empty cells: No data or no evaluable data available.

a: Heterogeneous results compared to the LABA class of drugs. In comparison with the LABA indacaterol at the 300 µg dose, there is a hint of a lesser benefit of tiotropium for dyspnoea.
b: Proof for patients with very severe COPD (GOLD IV) only for the period of up to one year.
c: Proof only for the period of up to one year. For patients with moderate COPD (GOLD II) this proof also applies to the period of more than one year. In addition, there is an indication for women that this benefit persists beyond the period of one year.
d: Proof only for the period of up to one year.
e: Heterogeneous results compared to the LABA class of drugs. In comparison with the LABA indacaterol, there is a hint of a lesser benefit of tiotropium in respect of health-related quality of life.
f: The hint of a benefit relates solely to the ability to perform activities of daily living.
g: Result from the study with HandiHaler.

AE: adverse events; GOLD: Global initiative for Chronic Obstructive Lung Disease; LABA: long-acting $beta_2$-agonists; SAE: serious adverse events; vs: versus

## Conclusions

### *Benefit of tiotropium*

*Tiotropium versus placebo*

There is proof of a benefit of tiotropium for the period of up to one year in respect of the frequency of exacerbations. For patients with moderate and severe COPD (GOLD II and III) this proof also applies beyond this period of time.

There is proof of a benefit of tiotropium for the period of up to one year in respect of the need for hospitalizations due to exacerbations. For patients with COPD of moderate severity (GOLD II) this proof also applies beyond this period of time. In addition, for women there is an indication that this benefit also extends beyond this period of time.

There is proof of a benefit of tiotropium in respect of the sub-area "physical health" of health-related quality of life, and for the period of up to one year, proof of a benefit of tiotropium in respect of the entire health-related quality of life.

There is an indication of a benefit of tiotropium for COPD symptoms.

From a long-term study in which tiotropium was used with the HandiHaler, there is an indication of a benefit of tiotropium in respect of all-cause mortality in patients who have stopped smoking.

In terms of the ability to perform activities of daily living, there is a hint of a benefit of tiotropium.

In the areas of exercise capacity, COPD-associated cardiovascular morbidity and mortality, COPD-related mortality and adverse drug reactions, there is no proof of a benefit or harm from tiotropium.

Studies of 6 to 12 months duration were available for assessing the benefit of tiotropium and in addition – with the exception of the two outcomes "COPD symptoms" and "COPD-associated cardiovascular morbidity and mortality" – 2 long-term studies of 2 and 4 years duration.

*Tiotropium / LABA versus LABA*

There is no proof of a benefit or harm from tiotropium when given in addition to treatment with LABA.

*Tiotropium / salmeterol / fluticasone versus salmeterol / fluticasone*

There is no proof of benefit or harm from tiotropium, if it is added to treatment with a combination of salmeterol and fluticasone.

***Added benefit of tiotropium***

*Tiotropium versus LABA*

There is proof of added benefit of tiotropium compared to the LABA class of drugs in terms of the frequency of exacerbations and the need for hospitalizations due to exacerbations.

There is a hint of a lesser benefit of tiotropium compared to the LABA indacaterol (dose 300 µg) for COPD symptoms.

There is a hint of a lesser benefit of tiotropium compared to the LABA indacaterol in respect of health-related quality of life.

*Tiotropium versus ipratropium*

There is proof of added benefit of tiotropium compared to ipratropium in respect of the frequency of exacerbations.

There is an indication of an added benefit of tiotropium compared to ipratropium for COPD symptoms.

Studies of 6 to 12 months duration were available to assess the added benefit of tiotropium.

*Tiotropium versus salmeterol / fluticasone*

There is no proof of added benefit or lesser harm from tiotropium compared to the combination of salmeterol and fluticasone.

***Comparative benefit assessment of the two forms of application of tiotropium bromide, HandiHaler and Respimat***

There is no study of relevance to the assessment that compared the two tiotropium inhalers, HandiHaler and Respimat with each other.

Only placebo-controlled studies were available for the Respimat. No conclusion-relevant modification of the effect by the inhaler type could be demonstrated in placebo-controlled studies, relative to the total population. Therefore in these cases, the conclusions also apply to the Respimat. In contrast, the above-mentioned indication of a benefit of tiotropium in respect of the all-cause mortality in patients who had given up smoking refers only to application by the HandiHaler, because this assessment is based solely on a study carried out with this type of inhaler.

Since no studies were available that compared the Respimat with other treatment alternatives, all the conclusions regarding added benefit also refer only to application by the HandiHaler.

**Keywords:** tiotropium, cholinergic antagonists, pulmonary disease – chronic obstructive, systematic review, benefit assessment

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