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ADIS DRUG CLINICAL Q&A

Tiotropium Respimat® Soft Mist™ inhaler: a guide to its use in chronic obstructive pulmonary disease (COPD) in the EU

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Abstract Tiotropium Respimat® Soft Mist™ inhaler (Spiriva® Respimat®) is indicated as a maintenance bronchodilator to relieve the symptoms of patients with chronic obstructive pulmonary disease (COPD) in the EU. The delivered drug dose is independent of inspiratory effort and the prolonged duration of the aerosol cloud should make the co-ordination of actuation and inhalation easier. In patients with COPD, tiotropium Respimat® improved lung function, COPD exacerbations, health-related quality of life and dyspnoea, and was generally well tolerated. Relative to administration of tiotropium via the HandiHaler®, administration of the drug via the Respimat® Soft Mist™ inhaler improves lung deposition of the drug (allowing a lower nominal dose to be used), is at least as effective, and has a similar tolerability profile.

Adis evaluation of tiotropium Respimat® Soft Mist™ inhaler in chronic obstructive pulmonary disease
Improves lung function, disease exacerbations, health-related quality of life and dyspnoea
Inspiratory effort does not affect the dose of the drug delivered by the inhaler
Prolonged duration of the aerosol cloud should make the co-ordination of actuation and inhalation easier
Generally well tolerated
Is at least as effective and well tolerated as tiotropium HandiHaler®

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What is the rationale for using tiotropium bromide in COPD?

Chronic obstructive pulmonary disease (COPD) is characterized by chronic airflow limitation [1]. Bronchodilators are central to the symptomatic management of COPD, with long-acting bronchodilators generally preferred over short-acting bronchodilators and inhaled therapy generally preferred over oral therapy [1]. In the EU, inhaled long-acting bronchodilators include anticholinergics that are administered once daily (e.g. tiotropium bromide, glycopyrronium bromide and umeclidinium bromide) or twice daily (e.g. aclidinium bromide), and long-acting β_2-agonists that are administered once daily [e.g. indacaterol, olodaterol and vilanterol (latter is not available as monotherapy)] or twice daily [e.g. formoterol and salmeterol (given in combination with inhaled corticosteroids)] [1, 2].

Anticholinergic agents represent a rational approach to the management of COPD, as muscarinic M_1, M_2 and M_3 receptors are found in human airways, with M_3 receptors mediating bronchoconstriction and mucus secretion [3]. Tiotropium bromide binds with high affinity to M_1, M_2 and M_3 receptors in the human airways [3]. The competitive and reversible inhibition of M_3 receptors by tiotropium bromide results in relaxation of the bronchial smooth muscle [4]. Inhaled tiotropium bromide is topically selective, with its rapid (within 30 min) and prolonged (lasting for 24 h) bronchodilation resulting from local airway, rather than systemic, effects [5, 6].

There is a large body of data supporting the efficacy of tiotropium bromide administered via the dry-powder HandiHaler® (Spiriva® HandiHaler®) in patients with COPD [6]. This review focuses on the use of the more recently developed formulation of tiotropium bromide solution for inhalation administered via the Respimat® Soft

Mist™ inhaler [5] (Spiriva® Respimat®; hereafter referred to as tiotropium Respimat®).

What are the characteristics of delivery via the Respimat® Soft Mist™ inhaler?

The Respimat® Soft Mist™ inhaler is a multi-dose inhaler that uses mechanical power from a spring to generate a fine aerosol cloud suitable for inhalation [7, 8]; the inhaler is free of propellants, thereby avoiding potential harm to the climate. The aerosol cloud is generated from an aqueous solution, rather than from a powder [7]. The majority of the aerosol particle mass is 1–5 μm in diameter, with a high proportion of the droplets in the aerosol cloud falling into the fine particle fraction (i.e. <5.8 μm in diameter) [7, 8]. The particle size and the delivered drug dose is not dependent on the patient's inspiratory effort [8]; however, it is recommended that patient use a deep, relaxed inhalation [5].

The aerosol cloud produced by the Respimat® Soft Mist™ inhaler moved more slowly and had a prolonged duration relative to aerosols generated by pressurized metered-dose inhalers (pMDIs) [9]. This has the potential to reduce the extent of oropharyngeal deposition and facilitate the co-ordination of actuation and inhalation [9].

The Respimat® Soft Mist™ inhaler deposited drug in the lungs more efficiently than a dry powder inhaler (DPI) or pMDI [10, 11], which allows a lower nominal dose of tiotropium bromide to be used; ≈40 % of the inhaled tiotropium bromide dose was deposited in the lungs, with the remainder being deposited in the gastrointestinal tract [5]. In patients with COPD, systemic exposure to tiotropium bromide after administration of a 5 μg dose via the Respimat® Soft Mist™ inhaler was lower than that seen after administration of an 18 μg dose via the HandiHaler® [12]. Firing the Respimat® Soft Mist™ inhaler externally to the body should be avoided [5]; however, if this occurs, it is anticipated that drug deposition on the face and in the eyes will be low [13].

For whom is tiotropium Respimat® indicated in the EU?

In the EU, once-daily tiotropium Respimat® 5 μg is approved as a maintenance bronchodilator treatment to relieve symptoms in patients with COPD [5]. Table 1 presents a summary of the EU prescribing information for tiotropium Respimat® in patients with COPD. Tiotropium Respimat® is also indicated as an add-on maintenance bronchodilator in adults with asthma; however, a discussion of its use in this indication is beyond the scope of this article.

What is the therapeutic efficacy of tiotropium Respimat® in COPD?

Clinical trials have demonstrated the efficacy of tiotropium bromide administered via the Respimat® Soft Mist™ inhaler in patients with COPD, with improvements seen in lung function, COPD exacerbations, health-related quality of life (HR-QOL) and dyspnoea [12, 14–20]. In short-term dose-ranging [14] and other controlled trials [15, 16], once-daily tiotropium Respimat® 5 μg was more effective than placebo [14–16], noninferior to once-daily tiotropium HandiHaler® 18 μg [15, 17] and generally more effective than ipratropium bromide pMDI 36 μg four times daily [16] with regard to improvements in lung function and other COPD-related parameters.

The recommended dosage of tiotropium Respimat® 5 μg once daily was based on the results of trials that evaluated a range of dosages [14] or that included a tiotropium Respimat® 10 μg treatment arm [15, 16, 18], This section focuses on the results in treatment arms receiving once-daily tiotropium Respimat® 5 μg in longer-term trials [18–20]. In these trials, key inclusion criteria included age ≥40 years [18–20], a diagnosis of COPD [18–20], a prebronchodilator forced expiratory volume in 1 sec (FEV_1) of ≤60 [18, 19] or ≤70 % [20] predicted, a FEV_1: forced vital capacity ratio of ≤0.70 [18–20] and a smoking history of ≥10 pack-years [18–20]. The use of all other COPD medications (with the exception of other inhaled anticholinergics) was permitted.

Compared with placebo in 1-year trials

The efficacy of tiotropium Respimat® 5 μg once daily in the treatment of COPD has been shown in three randomized, double-blind 1-year trials [18, 19]. Two of these trials, which were of identical design, were reported as a prespecified pooled analysis [18]. In the pooled trials, 670 patients received tiotropium Respimat® 5 μg and 653 received placebo [18]; the corresponding patient numbers in the other trial were 1,939 and 1,953 (the number of patients evaluable for each endpoint varied).

Tiotropium Respimat® 5 μg once daily was more effective than placebo with regard to the following endpoints:

- *Trough FEV_1 response* Improvements from baseline in trough FEV_1 were significantly ($p < 0.0001$) greater with tiotropium Respimat® 5 μg than with placebo [between-group difference (BGD) 0.127 [18] and

Table 1 Prescribing summary of tiotropium Respimat® Soft Mist™ inhaler (Spiriva Respimat®) in chronic obstructive pulmonary disease (COPD) in the EU [5]. Consult local prescribing information for further details

What is its approved indication in patients with COPD?	
Maintenance bronchodilator treatment to relieve symptoms	
How should it be administered?	
Dosage	5 µg tiotropium (given as two puffs of tiotropium 2.5 µg) once daily
Administration	Instruct patients on the proper use and care of the inhaler
	Advise patients to avoid getting the spray into their eyes[a]
How is it available?	
Cartridges containing 60 puffs (30 medicinal doses) of tiotropium 2.5 µg solution for inhalation	
Cartridges can only be inserted and used in the Respimat® inhaler (supplied with the cartridges)	
How should it be used in patients with renal impairment?	
Mild (CL_{CR} >50 mL/min)	No dosage adjustment is necessary
Moderate to severe (CL_{CR} ≤50 mL/min)	Use only if the expected benefit outweighs the potential risk (tiotropium bromide is renally excreted, therefore, plasma concentrations of the drug increase with decreased renal function)
	Risk of overall, serious or fatal adverse events did not increase vs. placebo in patients with mild or moderate renal impairment (pooled analysis of seven trials [21])
	Long-term experience in patients with severe renal impairment is lacking
How should it be used in other selected special populations?	
Patients with hepatic impairment	No dosage adjustment is necessary
Patients with recent (<6 months) MI, any unstable or life threatening cardiac arrhythmia or cardiac arrhythmia requiring intervention or a change in drug therapy in the past year, or hospitalization for heart failure (NYHA Class III or IV) within the past year	Use with caution (patients with these cardiovascular conditions were excluded from clinical trials and these conditions may be be affected by the anticholinergic mechanism of action of tiotropium bromide)
Patients with narrow-angle glaucoma, prostatic hyperplasia or bladder-neck obstruction	Use with caution (these conditions may be affected by the anticholinergic activity of tiotropium bromide)
Women who are pregnant	Preferable to avoid use as a precautionary measure (data are limited)
Women who breastfeeding	Use is not recommended (unknown whether the drug is excreted in human breast milk)
What are the contraindications to its use?	
Hypersensitivity to tiotropium bromide, atropine or its derivatives (e.g. ipratropium or oxitropium) or any of the excipients of the formulation	
Can it be used with other drugs?	
Other anticholinergic-containing drugs	Concomitant use is not recommended (co-administration has not been studied)
Other drugs commonly used in the treatment of COPD	No clinical evidence of drug interactions with concomitant sympathomimetic bronchodilators, methylxanthines, oral and inhaled steroids, antihistamines, mucolytics, leukotriene modifiers, cromones and anti-IgE treatment (formal drug interaction studies have not been performed)

CL_{CR} creatinine clearance, *MI* myocardial infarction, *NYHA* New York Heart Association

[a] Although inadvertent ocular exposure to tiotropium is unlikely to result in ocular adverse effects [22], advise patients that such exposure may result in eye symptoms (e.g. precipitation or worsening of narrow-angle glaucoma, eye pain or discomfort, temporary blurring of vision, visual halos or coloured images in associated with red eyes from conjunctival congestion and corneal oedema). If any combination of these symptoms develops, patients should stop the use of the inhaler immediately and consult a specialist

0.102 L [19]] at week 48. There was no evidence of tachyphylaxis, in that the improvement in trough FEV_1 seen at week 48 was similar to that seen on day 1 [18].

- *COPD exacerbations* The time to the first COPD exacerbation was significantly longer in patients receiving tiotropium Respimat® 5 µg than in those receiving placebo [lower quartile 160 vs. 178 days ($p < 0.01$) in the pooled analysis [18] and 169 vs. 119 days ($p < 0.0001$); hazard ratio (HR) 0.693 (95 % CI 0.625–0769) in the other trials [19]]. In addition, the

number of COPD exacerbations per patient-year was significantly smaller with tiotropium Respimat® 5 μg than with placebo in the pooled analysis [0.93 vs. 1.91; $p < 0.01$; odds ratio 0.75 (95 % CI 0.60–0.93)] [18] and the other trial [0.69 vs. 0.87; $p < 0.0001$; relative rate 0.79 (95 % CI 0.72–0.87)] [19]. At least one COPD exacerbation was experienced by significantly lower proportions of tiotropium Respimat® 5 μg than placebo recipients [37.2 vs. 44.1 % ($p < 0.01$) [18] and 35.3 vs. 43.1 % ($p < 0.0001$) [19]].

- *HR-QOL* As assessed by St George's Respiratory Questionnaire (SGRQ) total score, improvements from baseline to week 48 in HR-QOL were significantly ($p < 0.0001$) greater with tiotropium Respimat® 5 μg than with placebo (mean BGD in SGRQ total score −3.5 [18] and −2.9 [19]), with significantly ($p < 0.05$) higher proportions of tiotropium Respimat® 5 μg than placebo recipients having an improvement that exceeded the minimal clinically important difference (MCID) of ≥4 units (50.5 vs. 40.7 % [18] and 49.5 vs. 41.4 % [19]).
- *Dyspnoea* At week 48 in the pooled analysis, tiotropium Respimat® 5 μg was significantly ($p < 0.0001$) more effective than placebo with regard to improvements from baseline in Mahler Transition Dyspnoea Index (TDI) focal scores (mean BGD 1.08), and the proportion of patients showing an improvement in the Mahler TDI focal score exceeding the MCID of ≥1 unit (56 vs. 44 %) [18].

Compared with tiotropium HandiHaler® in the TIOSPIR trial

The overall efficacy of once-daily tiotropium Respimat® 5 μg ($n = 5,705$) was similar to that of once-daily tiotropium HandiHaler® 18 μg ($n = 5,687$) in the large, randomized, double-blind TIOSPIR trial in patients with COPD [20]. The mean duration of follow-up was 2.3 years, with a median treatment duration of 835 days [20].

The incidence of COPD exacerbations of any severity did not significantly differ between patients receiving tiotropium Respimat® 5 μg and those receiving tiotropium HandiHaler® 18 μg [47.9 vs. 48.9 % of patients; HR 0.98 (95 % CI 0.93–1.03)], with an adjusted event rate of 0.59 per patient-year in both groups, and a median time to first COPD exacerbation of 756 and 719 days in the tiotropium Respimat® and tiotropium HandiHaler® groups [20]. Likewise, there were no significant BGDs in the incidence of moderate or severe COPD exacerbations [47.2 vs. 48.0 % of patients; HR 0.98 (95 % CI 0.93–1.04); adjusted event rate 0.58 per patient-years in both groups] or severe COPD exacerbations [14.5 vs. 14.3 %; HR 1.02 (95 % CI 0.93–1.13); adjusted event rate 0.12 vs. 0.11 per patient-year] [20].

In a spirometry substudy [20, 23], tiotropium Respimat® 5 μg was noninferior to tiotropium HandiHaler® with regard to the adjusted mean trough FEV_1 [BGD in average for weeks 24 to 120 was −0.01 L (95 % CI −0.038 to 0.018); noninferiority margin −0.05 L] [20, 23].

In the clinical practice setting

Tiotropium Respimat® 5 μg once daily for 6 weeks was effective in the treatment of COPD in a real-life setting, according to the results of a German, multicentre, observational study in 1,230 patients with COPD [24]. At week 6, 61.5 % of participants achieved therapeutic success [defined as an improvement in the physical function domain (PF-10) of the Short Form-36 questionnaire of ≥10 points from baseline], the mean PF-10 score significantly ($p < 0.001$) improved from 49.0 points at baseline to 62.3 points, and 76.9 % of patients were 'satisfied' or 'very satisfied' with tiotropium Respimat® Soft Mist™ inhaler [24].

What is the tolerability and safety of tiotropium Respimat® in COPD?

General tolerability profile

Tiotropium Respimat® was generally well tolerated in patients with COPD, with a tolerability profile that was generally similar to that of tiotropium bromide administered via the HandiHaler® [14, 15, 17].

As expected, anticholinergic adverse events were among the most commonly reported adverse events in patients receiving inhaled tiotropium bromide [14–19]. For example, the dry mouth incidence rate was 3.41 per 100 patient-years with tiotropium Respimat® 5 μg and 1.54 per 100 patient-years with placebo in a 1-year trial [rate ratio (RR) 2.21 (95 % CI 1.41–3.49)] [19]. In addition, among patients receiving tiotropium Respimat® 5 μg or placebo in a pooled analysis of two 1-year trials, dry mouth was reported in 7.2 and 2.1 % of patients, respectively, constipation in 2.1 and 1.5 %, and urinary tract infection in 2.5 and 1.1 % [18]. Treatment was discontinued because of adverse events in 10 vs. 18.7 % [18] and 7.2 vs. 7.8 % [19] of tiotropium Respimat® 5 μg and placebo recipients, respectively.

According to a retrospective analysis [25] of the pooled 1-year trials [18], no patients receiving tiotropium Respimat® 5 μg or placebo reported paradoxical bronchospasm occurring after inhalation, and 0.3 and 0.2 % of patients in the respective groups had at least two events suggestive of bronchoconstriction (i.e. rescue medication use, administration-related bronchoconstriction indicators,

asymptomatic fall in FEV_1 of ≥15 % from test-day pre-bronchodilator value) [25].

Tiotropium Respimat® was not associated with clinically relevant changes in vital signs [14–17, 19], ECG recordings [14, 16–19], Holter monitoring [18], physical examination findings [16, 19] or laboratory values [14, 15, 17].

Mortality and cardiovascular safety

The safety of inhaled tiotropium bromide has been a recent subject of debate [26]. However, a pooled analysis of randomized, double-blind, placebo-controlled trials did not indicate that the use of tiotropium HandiHaler® or Respimat® significantly increased the risk of fatal adverse events or fatal or nonfatal major adverse cardiovascular events relative to the use of placebo [27]. According to a retrospective pooled analysis of four placebo-controlled trials (one 6-month and three 1-year trials) that included 6,096 patients with COPD, the rate of all-cause mortality for the planned treatment period was numerically (but not statistically) higher with tiotropium Respimat® 5 μg than with placebo [2.64 vs. 1.98 cases per 100 patient-years; RR 1.33 (95 % CI 0.93–1.92)]. Patients with known cardiac rhythm disorders accounted for this excess in mortality [5].

In the overall populations of the three 1-year trials, rates of all-cause and cardiac-related mortality did not significantly differ between tiotropium Respimat® 5 μg and placebo recipients [18, 19]. The incidence of a composite cardiovascular endpoint (fatal and nonfatal myocardial infarction and stroke, fatal events in the organ classes cardiac disorders and vascular disorders, and the terms sudden death, cardiac death and sudden cardiac death) also did not differ significantly between tiotropium Respimat® 5 μg and placebo recipients (1.77 vs. 1.58 per 100 patient-years) [RR 1.12 (95 % CI 0.67–1.86)] [19].

In contrast with the findings that tiotropium Respimat® 5 μg did not have an effect on all-cause mortality relative to placebo [18, 19], tiotropium HandiHaler® reduced the risk of death by 13 % relative to placebo [HR 0.87 (95 % CI 0.76–0.99)] in the 4-year randomized UPLIFT trial in 5,993 patients with COPD that included vital status follow-up [28].

The large (>17,000 patients) TIOSPIR trial, therefore, was conducted to evaluate differences between tiotropium HandiHaler® and Respimat® with regard to mortality-related outcomes [20]. TIOSPIR demonstrated that tiotropium Respimat® 5 μg was noninferior to tiotropium HandiHaler® 18 μg in terms of the primary safety outcome of the incidence of all-cause mortality [7.4 vs. 7.7 % of patients; HR 0.96 (95 % CI 0.84–1.09)] [20]. Moreover, the proportion of patients with cardiovascular mortality [2.0 vs. 1.8 %; HR 1.11 (95 % CI 0.85–1.45)] and major adverse cardiovascular events [3.9 vs. 3.6 %; HR 1.10 (95 % CI 0.91–1.33)] did not significantly differ between the two treatment groups [20]. In TIOSPIR, ≈10 % of patients had prior cardiac arrhythmias and ≈20 % had prior myocardial infarction (MI), ischaemic heart disease or coronary artery disease [20]. Further analysis revealed no increased risk of all-cause mortality or fatal cardiac events in the subgroup of patients with stable cardiac disorders or arrhythmias at baseline [29]. TIOSPIR excluded patients with MI in the previous 6 months, hospitalization for New York Heart Association class III or IV heart failure in the previous year, or any unstable or life-threating arrhythmia requiring treatment in the previous year.

What is the current positioning of tiotropium Respimat® in COPD?

Tiotropium Respimat® is a useful option for the treatment of patients with COPD, as it improves lung function, COPD exacerbations, HR-QOL and dyspnoea in this patient population, and is at least as effective as tiotropium HandiHaler®. The improved lung deposition of drug seen with the Respimat® Soft Mist™ inhaler allows a lower nominal tiotropium bromide dose to be used when the drug is administered via this inhaler than when administered via the HandiHaler®.

Tiotropium Respimat® was generally well tolerated in patients with COPD, with anticholinergic adverse events being the most commonly reported. The overall and cardiovascular safety profile of tiotropium Respimat® 5 μg once daily is similar to that of tiotropium HandiHaler® 18 μg once daily.

An important consideration when selecting a treatment option in COPD is that the response to treatment may be affected by factors such as inhaler technique and patient adherence [16, 30]. The dose of tiotropium bromide delivered via Respimat® Soft Mist™ inhaler is independent of inspiratory effort. In addition, the prolonged duration of the aerosol cloud should make it easier for patients to co-ordinate actuation and inhalation [31, 32]. In a study examining the ease of switching from tiotropium HandiHaler® 18 μg to tiotropium Respimat® 5 μg in 34 patients with COPD [33], both devices were considered easy to use, with 21 patients reporting that tiotropium Respimat® was easier or much easier than tiotropium HandiHaler® [33].

Studies comparing the clinical efficacy and safety of Tiotropium Respimat® with that or the long-acting cholinergerics glycopyrronium bromide and umeclidinium bromide would be of value in establishing the relative place of these agents in the treatment of COPD.

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