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OLODATEROL / TIOTROPIUM

▼SPIOLTO RESPIMAT®, YANIMO RESPIMAT® FOR COPD

dtbn
DRUG ASSESSMENT REPORT
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Indications[1]

It is indicated as a maintenance bronchodilator treatment in adult patients with chronic obstructive pulmonary disease (COPD).

Mechanism of action[1]

Tiotropium is a long-acting anticholinergic agent (LAMA) that inhibits the action of acetylcholine in smooth muscle cells, thereby triggering bronchodilation. Olodaterol is a long-acting selective ß2-adenergic receptor agonist (LABA) that induces bronchial smooth-muscle relaxation and inhibits the release of immediate-hypersensitivity mediators.

Posology and method of administation[1]

The recommended dose is two puffs once daily at the same time of the day, which corresponds to a dose of 5mg of tiotropium plus 5mg of olodaterol.

Comparators

LABA and LAMA alone or in combination.

Clinical efficacy[7-10]

The clinical development of tiotropium bromide involved two double-blind pivotal trials —TONADO 1 and 2— with a follow-up period of 52 weeks, (although the primary endpoints were assessed over 24 weeks). The TONADO trials were aimed to assess the efficacy and safety of olodaterol/tiotropium as compared to monotherapy with either component alone in patients with moderate-to-very severe COPD (GOLD 2-4) (n=3100 at authorized doses). The primary endpoints included: lung function as assessed by the forced expiratory volume in one second (FEV1), area under the curve from 0 to 3 h (FEV1 AUC0-3); and health-related quality of life, through St George's Respiratory Questionnaire (SGRQ). Trials were not primarily designed to detect differences in exacerbation, and COPD exacerbation was a secondary endpoint.

Statistically significant differences were observed in favor of olodaterol/tiotropium regarding lung function and health-related quality of life, as compared to monotherapy with its individual components. However, the clinical relevance of these differences is questionable in lung function, and irrelevant in health-related quality of life (minimal clinically important differences are 100 mL in FEV1 and a score of 4 points in the SGRQ scale).

The incidence of moderate-to-severe exacerbations was lower with olodaterol/tiotropium as compared to olodaterol alone (HR=0.81; p=0.0091), but no differences were observed as compared to tiotropium alone. No differences were found in severe exacerbations between olodaterol/tiotropium and any of the comparators.

No comparative studies have been performed of olodaterol/tiotropium vs. other LABA/LAMA combinations.

Safety

In general, the safety profile of olodaterol/tiotropium is similar to that observed in other authorized LABA/LAMA combinations.

Adverse Reactions[1]

The most common adverse effect (≥ 1%) is dry mouth, urinary infection, headache, and constipation. Less frequent adverse events (0.1%-1.0%) included dizziness, insomnia, headache, atrial fibrillation, palpitations, tachycardia, hypertension, cough and constipation. Patients with a clinically relevant cardiovascular disease were excluded from trials.

Contraindications[1]

Hypersensitivity to the active substance or any of its excipients.

Special warnings and precautions for use[1]

Caution in patients with narrow-angle glaucoma, prostatic hyperplasia, or obstruction of the bladder neck.

Caution in patients with severe cardiovascular alterations such as cardiac arrhythmias.

ß2 agonists can cause hypokalemia, which may result in adverse cardiovascular effects.

ß2 agonists can also cause transient hyperglycemia.

Oral dryness can cause dental caries in the long term.

Usage in special situations[1]

Pregnancy and lactation. No data are available on the use of olodaterol/tiotropium during pregnancy or whether it is excreted into breastmilk. Olodaterol/tiotropium should not be used during pregnancy. **Renal failure:** Dosage adjustment is not necessary. In patients with moderate-to-severe renal failure (CrCl ≤ 50 ml/min), olodaterol/tiotropium should only be used when the expected benefit outweighs

ABSTRACT

Olodaterol/tiotropium offers a long-acting ß2-agonist in combination with a long-acting anticholinergic.

It has not been demonstrated to reduce the risk for COPD exacerbation.

No clinically relevant differences have been observed versus tiotropium alone either in lung function or in health-related quality of life in patients with moderate-to-severe COPD.

No comparative data are available of tiotropium vs. other LAMA/LABA combinations.

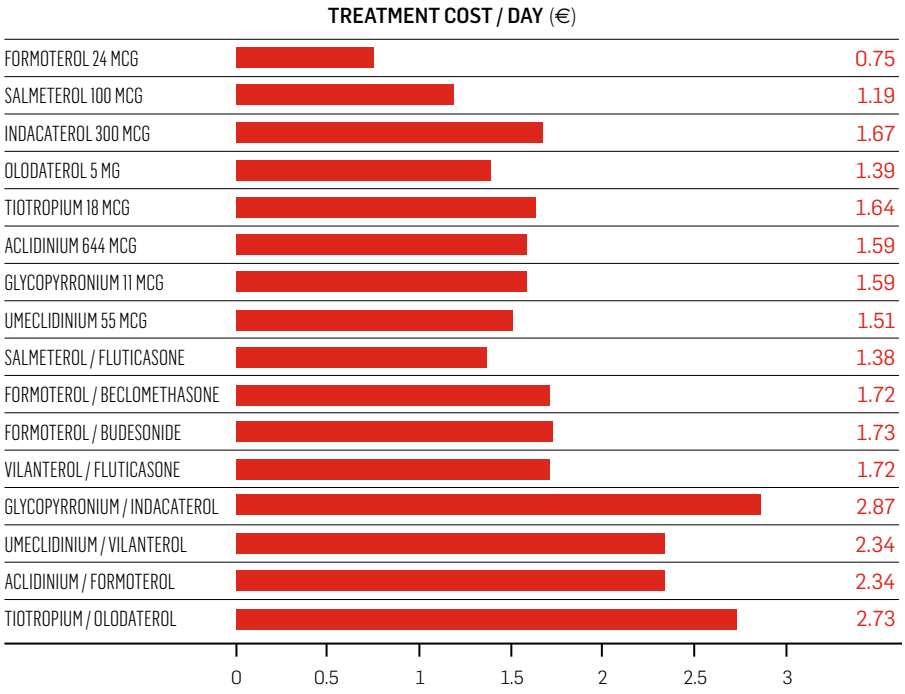
Concerns have arisen on the cardiovascular safety profile. Patients with a history of cardiovascular events were excluded from trials.

CLASSIFICATION

4	IMPORTANT THERAPEUTIC INNOVATION
3	MODEST THERAPEUTIC INNOVATION
2	SOME ADDED VALUE IN SPECIFIC SITUATIONS
1	**NO THERAPEUTIC INNOVATION**
0	INSUFFICIENT EVIDENCE

The qualification assigned to the drug was agreed by the Drug Assessment Committees of Andalusia, Basque Country, Catalonia Institute of Health, Aragon and Navarre. The current report is based on the available information and is susceptible to be updated according to the latest evidence. Let us remind the reader about the importance of notifying the Pharmacovigilance Centre when there are suspicions of adverse reactions to drugs.

		Olodaterol/Tiotropium vs Olodaterol	Olodaterol/Tiotropium vs Tiotropium
FEV_1	Tonado 1	82 ml (95%CI 59 to 106 ml)	71 ml (95%CI 47 to 94 ml)
	Tonado 2	88 ml (95%CI 63 to 113 ml)	50 ml (95%CI 24 to 75 ml)
SGRQ	Tonado 1 & 2	-1.69 (95%CI -2.77 to -0.61)	-1.23 (95%CI -2.31 to -0.15)



the potential risk. Long-term olodaterol/tiotropium therapy has not been tested in patients with severe renal failure. **Severe hepatic impairment.** Dose adjustment is not required in patients with mild or moderate hepatic impairment. Olodanerol should be administered with caution in patients with severe liver impairment. **Children.** No recommendations have been published on the use of olodanerol/tiotropium in patients aged < 18 years.

Drug interactions[1]

Beta-adrenergic blockers may attenuate or antagonize the effect of olodaterol/tiotropium. In this setting, the use of cardioselective beta-blockers could be considered, although they should be administered with caution.

Concomitant administration of other long-acting anticholinergics or ß2-adrenergic agonists is not recommended.

Monoamine oxidase inhibitors, tricyclic antidepressants or other drugs prolonging the QTc interval can potentiate cardiovascular adverse effects.

Xantine derivatives, steroids or non-potassium sparing diuretics can potentiate hypokalemic effects.

Risk Management Plan[7]

Relevant potential risks identified include: blood and lymphatic system disorders, hyperglycemia, psychiatric disorders, syncope, myocardial ischaemia, cardiac arrhythmia, cardiac failure, cardiac mortality, aneurysm, renal failure, overdose, hypokalemia, off-label use in asthma. No data are available on the use of olodaterol/tiotropium in patients with a history of cardiovascular events, hepatic impairment, severe renal impairment, pregnancy, lactation and long-term use.

Place in therapeutics

Drug therapy for COPD is aimed to reduce its symptoms and/or complications. After diagnosis, therapy must be progressive, based on the severity of the obstruction and symptoms, being bronchodilation the first step in the treatment for this condition. Inhaled bronchodilators —such as LABA and LAMA— are the base for treating COPD symptoms.

Clinical trials with olodaterol/tiotropium in patients with moderate-to-severe COPD (GOLD 2-4) report statistically significant improvements in lung function and health-related quality of life, compared to mono-components, although the clinical relevance of such differences is questionable in lung function and irrelevant in health-related quality of life. Olodaterol/tiotropium has not been compared to other fixed-dose LABA/LAMA combinations.

Olodaterol/tiotropium has not been proven to be superior to tiotropium alone or other LABA/LAMA combinations. No methodologically validated studies have been conducted that demonstrate its potential effectiveness in reducing COPD exacerbations.

Presentations

Spiolto Respimat®, Yanimo Respimat® (Boehringer) 2.5 mcg/ 2.5 mcg 60 puffs. 30 doses (€81.49)

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