UMECLIDINIUM BROMIDE/ VILANTEROL

Anoro® for COPD

No additions to efficacy, just to price

dtbn
DRUG ASSESSMENT REPORT
www.dtb.navarra.es
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ABSTRACT

Umeclidinium/vilanterol is a combination of a muscarinic antagonist and a long acting β2 adrenergic agonist.

No reduction in the risk of exacerbations has been shown.

It does not improve clinical results compared to tiotropium.

The role and contribution of vilanterol to the combination is not clear.

There are no comparative data available with respect to other LAMA+LABA combinations.

Its cardiovascular safety profile is still a concern.

CLASSIFICATION

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

Indications[3]

It is indicated as bronchodilator maintenance treatment to relieve the symptoms of chronic obstructive pulmonary disease (COPD) in adults.

Mechanism of action3

Umeclidinium is a long acting muscarinic receptor antagonist (LAMA) that blocks the action of acetylcholine in smooth muscle cells producing bronchodilation. Vilanterol is a selective long acting β2 adrenoceptor agonist (LABA) that produces relaxation of bronchial smooth muscle and the inhibition of the release of immediate hypersensitivity mediators.

Posology and form of adminstration3

The recommended dose is one inhalation per day using the dry powder inhaler (Ellipta®), for an inspiratory flow of 60ml/min for 4 seconds, providing a release dose of 55mcg of umeclidinium and 22mcg of vilanterol which correspond to pre-dispensed doses of 62.5mcg and 25mcg respectively. It should be applied at the same time every day.

Comparators

LABA and LAMA individually or in combination.

Clinical efficacy[4,5]

The clinical development program included trials which compared the authorized doses to placebo or monotherapy. The primary endpoint was change with respect to initial values in Forced Expiratory Volume in 1 second (FEV1). The minimum value considered clinically relevant is a difference of 100ml. The main trial compared umeclidinium/vilanterol with individual components separately (ie: umeclidinium alone and vilanterol alone) and with placebo. COPD patients included adults with ≥ 40 years (the average age was 63 years) with a history of smoking of 10 or more packets/year, a post-bronchodilator FEV1 of 70% or less the predicted value, and a score of ≥2 on the dyspnea mMRC scale. Patients with uncontrolled cardiovascular disease were excluded.

The differences with umeclidinium were not clinically relevant while in the case of vilanterol the clinical relevance of the differences observed is doubtful. No statistically significant differences were found when comparing umeclidinium/vilanterol and its individual components in the secondary variable,the Transition Dyspnea Index (TDI) which measures the impact of dyspnea on daily life of patients and where 1 point is considered as the minimum difference of clinical relevance. Nor were there statistically significant differences found when compared to placebo or the individual components with regard to either quality of life evaluated through the St. George Respiratory Questionnaire (SGRQ) or the risk of exacerbations.

Vilanterol has not shown to improve efficacy

Three trials comparing umeclidinium/vilanterol with tiotropium, one of them also compares vilanterol.

In the DB2113360 y DB2113374 studies comparing the umeclidinium/vilanterol combination with tiotropium did not show statistically significant differences in regard to TDI, SGRQ or in the use of rescue medication.

In the ZEP117115 study, when comparing the combination to tiotropium statistically significant differences were observed though they were not clinically relevant in terms of SGRQ (-2.10; 95%CI -3.61 to -0.59; the minimum difference for clinical relevance is 4) and the use of rescue treatment (0.5 inhalations less per day; 95% CI 0.2 – 0.7).

Two small cross over studies whose main objective was to evaluate the effect on resistance to exercise and lung function after 12 weeks showed inconsistent results. In one of them, neither statistically significant results nor clinical relevance were found when comparing the combination to placebo or to the individual components. In the other, there was a statistically significant improvement of 69.4 seconds in walking time with respect to placebo.

There are no studies lasting longer than 24 weeks.

No studies are available comparing other LABA/LAMA or combinations of LABA and corticoids.

Safety

Adverse reactions

Nasopharyngitis was the most frequently reported adverse effect. Other frequent adverse effects

Comparative treatments	Primary endpoint: FEV1 after 24 weeks Difference between treatments (95% CI) Limit for clinical relevance: 100 ml	Secundary endpoints: TDI Difference between treatments (95% CI) Limit for clinical relevance: 1 point
UMEC/VI 62.5/25 versus placebo	167 ml (128 a 207 ml)	1.2 (0.7; 1.7)
UMEC/VI 62.5/25 versus VI 25	95 ml (60 a 130 ml)	0.4 (-0.1; 0.8)
UMEC/VI 62.5/25 versus UMEC 62.5	52 ml (17 a 87 ml)	0.3 (-0.2; 0.7)

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.

Comparative treatments	Principal endpoint: FEV1 after 24 weeks		
UMEC/VI 62.5/25 vs TIO 18	DB2113360 study	DB2113374 study	ZEP117115 study
	90 ml (39 - 141 ml)	60 ml No statistical significance can be inferred	112 ml (81 - 154 ml)
UMEC/VI 62.5/25 versus VI 25	90 ml (39 - 142 ml)		

(incidence ≥1%) include cough, pharyngitis, upper respiratory tract infections sinusitis, oropharyngeal pain, dry mouth, urinary infection, cefalea and constipation. Less frequent adverse effects (incidence <1%) included atrial fibrillation, supraventricular tachycardia, ideoventricular rhythm, tachycardia, extrasystoles, and skin eruptions. Patients with known uncontrolled cardiovascular disease were excluded form the clinical studies.[3,4,11]

Contraindications[3]

Hypersensitivity to the drug or its excipients.

Warnings and precautions[3]

- Precaution is necessary in patients with narrow angle glaucoma
- Precaution should also be taken in patients with severe cardiovascular disorders, especially heart arrhythms.
- β2 agonists can produce hypokaliemia, which can lead to cardiovascular adverse effects. It should not be administered concomitantly with other drugs producing hypokaliemia.
- β2 agonist can also produce transitory hyperglycemia. Plasma levels of glucose should be monitored in diabetes patients before starting treatment.

Use in special situations[3]

Pregnancy and lactation: There are no data available in pregnant women and its excretion in breast milk is unknown. **Renal failure:** No dose adjustments are necessary. **Liver failure:** no dose adjustments are required in case of mild and moderate liver dysfunction. There are no studies in patients with severe liver failure and therefore it should be used with precaution. **Children.** There are no specific recommendations in patients under 18 years.

Interactions[1]

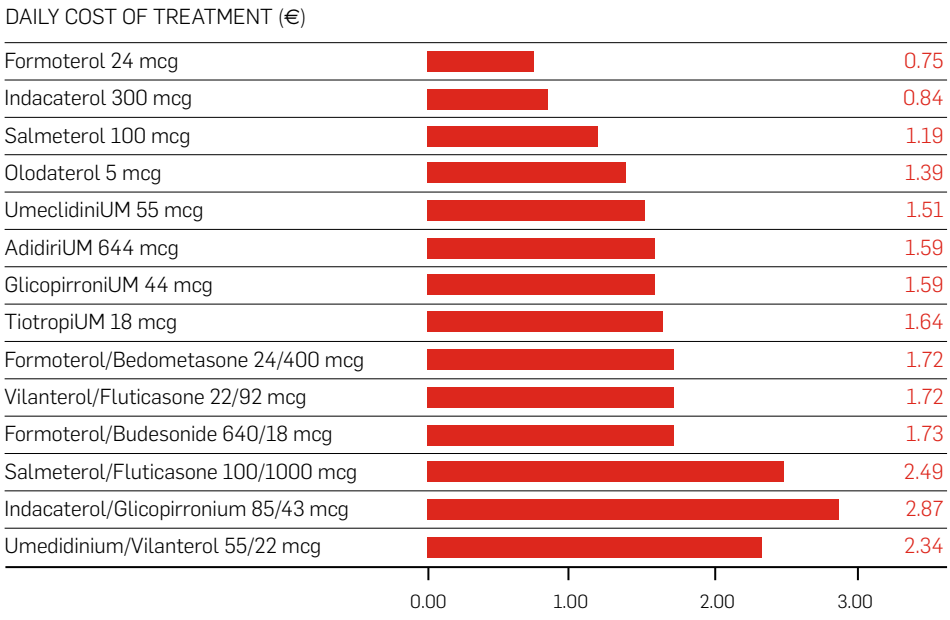
The concomitant use of non-selective or selective β-adrenergic blockers should be avoided, unless there is sufficient reason to employ them.

Concomitant use with other anticholinergic agents or long acting β2 adrenergic agents is not recommended.

EMA´s Risk Management Plan[4]

The potential important risks identified include cardiovascular and cerebrovascular disorders, paradoxical bronchospasm, narrow angle glaucoma, urinary retention and the use in asthma patients.

The EMA considers that there is a need for research on cardiovascular and cerebrovascular events and pneumonia in comparison with tiotropium through a post-approval observational study. There is also information lacking on patients with liver failure and on long term safety.



Place in therapeutics

Inhaled bronchodilators such as long acting beta-2 adrenergic agonists (LABA) and long acting anti-muscarinic antagonists (LAMA) constitute the basis of symptomatic treatment of patients with COPD and permanent symptoms. The GOLD guidelines do not include the LAMA/LABA combination without corticoid as a recommended first choice for the management in any of the patient groups.[1]

Umeclidinium/vilanterol is a LAMA/LABA combination that has only shown statistically significant differences in variables that evaluate lung function compared to placebo. No reductions in exacerbations have been shown.

With regard to symptom related variables (dyspnea, quality of life), the minimum differences considered clinically relevant were not reached in the majority of the studies.

This combination has not shown any improvement in either quality of life or a reduction in the use of rescue medication after 24 weeks. Neither has it shown a reduction in exacerbations nor has it been compared to other bronchodilators.

When comparing individual components the clinical relevance of the results obtained in lung function were dubious, especially in the case of umeclidinium alone. From a clinical point of view the contribution afforded by vilanterol (not authorized in monotherapy) is questionable. Although the combination of individual drugs in one device can be associated with better patient therapeutic compliance than the individual drugs taken separately, this situation is not possible in this case because vilanterol is not authorized as an individual treatment option.

When compared to tiotropium the differences in lung function were of uncertain clinical relevance and of no clinical relevance when evaluating symptom relief and quality of life.

The main concern on safety is the cardiovascular effects. More data is required to compare its safety profile to that of tiotropium.

Given the available evidence, umeclidinium/vilanterol does not provide additional advantages compared to other LABA/LAMA combinations and there is a lack of adequately designed studies that support the possible efficacy in the reduction of exacerbations, an aspect already shown in studies on other existing alternatives. Therefore, given the poor evidence available on efficacy and safety, it is not clear whether this drug has a role in the management of COPD.

Presentations

Anoro® (GlaxoSmithKline) 55/22 mcg 30 doses (70.25 €)

References

This information is based on the therapeutic positioning report of the AEMPS.

Servicio Navarro de Salud
Osasunbidea

INTERNATIONAL SOCIETY OF DRUG BULLETINS

Information: Servicio de Prestaciones Farmacéuticas Plaza de la Paz s/n, 4ª planta 31002 Pamplona Teléfono 848429047 Fax 848429010
New Drugs Assessment Committee: Iñaki Abad, Mª José Ariz, Ana Azparren, Mª Concepción Celaya, Juan Erviti, Javier Garjón, Isabel García, Isabel Aranguren, Rodolfo Montoya, Mikel Moreno, Lourdes Muruzábal