Umeclidinium (Incruse Ellipta)
National PBM Abbreviated Review
VA Pharmacy Benefits Management Services, Medical Advisory Panel, and VISN Pharmacist Executives

The PBM prepares abbreviated reviews to compile information relevant to making formulary decisions. VA clinical experts may provide input on the content. Wider field review is not sought. Documents no longer current will be placed in the Archive section.

Introduction
Umeclidinium has been available in a combination formulation with vilanterol, a long-acting beta-agonist. Umeclidinium is now available as a single agent. Like tiotropium, it has similar affinity to the subtypes of muscarinic receptors M1 to M5. The pharmacological effects occur through inhibition of M3 receptor in the smooth muscle of the airways.

FDA Approved Indication(s)
Umeclidinium is approved for long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
This product is NOT indicated for the relief of acute bronchospasm or for the treatment of asthma.

Potential Off-Label Uses
This section is not intended to promote any off-label uses. Off-label use should be evidence-based. See VA PBM-MAP and Center for Medication Safety's Guidance on "Off-label" Prescribing (available on the VA PBM Intranet site only).

- Treatment of asthma

Current VA Formulary Alternatives
Anticholinergics: tiotropium, ipratropium, ipratropium/albuterol

Dosing/Administration
One oral inhalation of 62.5mcg once daily and should be taken at the same time every day.
No dosage adjustment is needed for geriatric patients, renal impairment, or moderate hepatic impairment.

Dosage Form/Strengths and Handling
Umeclidinium 62.5mcg is available via a multi-dose dry powder inhaler. Each inhaler is preloaded with 30 doses of the drug. The inhaler has a dose indicator that shows the number of remaining doses. Patients should be informed that if they open and close the inhaler cover without inhaling the drug, they will lose the dose.

Store umeclidinium in a dry place between 68-77°F; excursions between 59-86°F are permitted. Umeclidinium is supplied in a moisture protective foil tray. The inhaler should be discarded 6 weeks after opening the foil tray or when the dose counter reads "0", whichever comes first.

Efficacy
The clinical trial data for umeclidinium comes from a 24-week fixed-dose combination trial comparing umeclidinium/vilanterol to the individual components and placebo, a 12-week trial comparing umeclidinium to placebo, and a 7-day dose-ranging trial.

Patients were required to have a post bronchodilator FEV1/FVC ratio ≤ 0.70, post bronchodilator FEV1 ≤ 70% predicted, Modified Medical Research Council (mMRC) dyspnea score ≥ 2, and ≥10 pack-year smoking history. Rescue albuterol and stable doses of inhaled steroids ≤ 1000mcg/day of fluticasone or equivalent was allowed. Patients with asthma or other known respiratory disorder or any clinically significant uncontrolled disease (including CV-related, abnormal clinically significant ECG, or 24-h Holter ECG, abnormal clinical lab finding)

Patient demographic and baseline values for the 24 week study include: 63 years old, 70% male, 50% current smokers, 46 pack-years smoking history, post-albuterol FEV1% predicted 47, FEV1/FVC 0.47, 15% reversibility, 50% using inhaled corticosteroids (ICS). Approximately 47% were classified as GOLD stage II, 43% as GOLD stage III, and 10% as GOLD stage IV. Baseline values for patients in the 12-week trial were similar except that 24% of patients were using ICS.

Pulmonary function

The primary outcome was change in trough FEV1. Weighted mean change in post-dose FEV1 over 0-6 hours was a secondary lung function outcome. Umeclidinium 62.5mcg had significantly greater improvement in pulmonary function than placebo. However, the 24-week trial showed significantly greater improvement for the combination than placebo and the individual components (**Table 1**).

A 7-day dose ranging trial compared various doses of umeclidinium (n=59 for UMEC 62.6) to placebo (n=60). A tiotropium arm (n=58) was included as an active comparator. This study was not designed to compare umeclidinium to tiotropium. The mean difference for umeclidinium 62.6mcg from placebo for trough FEV1 on day 7 was 74mL [95%CI 24, 124; p=0.004). For tiotropium, the adjusted mean difference from placebo was 92mL [95%CI 41, 142; p<0.001). The mean difference for umeclidinium 62.6mcg from placebo for $FEV1_{0-24}$ hour was 132mL [95%CI 87, 178; p<0.001). For tiotropium, the mean difference from placebo was 157mL [95%CI 113, 202; p<0.001].

Dyspnea

The transitional dyspnea index (TDI) score is used to assess dyspnea. For the TDI, a difference in score of ≥ 1 unit is considered to be clinically meaningful. In Donohue et al, all active treatment groups had significantly greater improvement in TDI focal score compared to placebo (**Table 1**).

Rescue inhaler use

In the 12-week trial, reduction in rescue inhaler use was significantly greater with umeclidinium 62.5 than placebo; there was no significant difference with the higher dose vs. placebo. In the 24-week trial, the need for rescue inhaler use was significantly reduced with UMEC/VI 62.5/25 compared to placebo and umeclidinium monotherapy. There was no significant difference between umeclidinium 62.5mcg and placebo (**Table 1**).

Quality of Life

Health-related quality of life was measured using the St George's Respiratory Questionnaire (SGRQ). The SGRQ is widely used in clinical trials to measure symptoms, activities, and impact of COPD on daily life as reported by patients. An improvement in score of ≥4 units is considered to be clinically meaningful. The improvement in SGRQ was significantly greater with all active treatment than placebo (**Table 1**).

Table 1: Efficacy Outcomes

	n	Treatment arms	Trough FEV1 (ml)	FEV1 0-6h (ml)	TDI focal score	% TDI responders	Rescue inhaler (puffs/day)	Δ SGRQ score	% SGRQ responders
Trivedi	69	UMEC 62.5	120*	166(vs. PBO)	0.7^	38*	-0.7 (vs. PBO)*	-3.14*	
2014	68	UMEC 125	152*	191(vs. PBO)	1.0*	38*	-0.6 (vs. PBO)	-6.12*	NA
12-weeks	69	PBO	-7	-	-0.3	15	-	4.75	
Donohue	413	UMEC/VI 62.5/25	171±12*ǂ	243±12.7*ǂ	2.4±0.16*	58*	-2.3±0.16*§	-8.07± 0.75*	49
2013	418	UMEC 62.5	119±12.6*	151±12.8*	2.2±0.16*	53*	-1.7±0.16	-7.25± 0.75*	44
24-weeks	421	VI25	76±12.7*	123±12.8*	2.1±0.16*	51*	-2.4±0.9*	-7.75± 0.76*	48
	280	PBO	4±15.8	1.0±15.8	1.2±0.2	41	-1.4±0.2	-2.56± 0.95	34

Abbreviations: NA= not available; PBO=placebo; SGRQ=St. George's Respiratory Questionnaire; TDI=transitional dyspnea index; UMEC=umeclidinium; VI=vilanterol

*Significant vs. placebo

^difference from placebo p=0.05

ǂSignificant vs. both monotherapy treatments

§Significant vs. UMEC

COPD Exacerbations

The trials were not designed to evaluate COPD exacerbations; however, data were collected (note that GSK is not seeking an exacerbation claim for umeclidinium). COPD exacerbation was defined as an acute worsening of symptoms of COPD requiring emergency treatment, hospitalization, or use of additional drug therapy beyond study drug or rescue albuterol (e.g., oral steroids, antibiotics).

There were a total of 16 exacerbations in the 12-week study; 5 (7.2%), 4(5.8%), and 7 (10.3%) in the UMEC 62.5, UMEC 125, and placebo groups respectively. In the 24-week trial, 7-9% of patients in the active treatment arms and 13% receiving placebo had an exacerbation. Time to first exacerbation analysis showed a lower risk of exacerbation with the active treatments compared to placebo.

Table 2: Time to First COPD Exacerbation in 24-week Trial

	UMEC/VI 62.5/25	UMEC 62.5	VI25	PBO
Time to 1st COPD exacerbation relative to placebo HR [95%CI]	0.5 [0.3, 0.8]*	0.6 [0.4, 1.0]*	0.7 [0.4, 1.1]*	N/A

Abbreviations: CI=confidence interval; HR=hazard ratio; PBO=placebo; UMEC=umeclidinium; VI=vilanterol
*Significant vs. placebo

Adverse Events (Safety Data)

Deaths

In the 24-week trial, there were 9 deaths in the active treatment groups and none in the placebo group; 3 of the deaths occurred in the umeclidinium 62.5 group (COPD/acute respiratory failure, sudden death, and cholecystitis/peritonitis). There were no deaths reported in the 12-week trial **(Table 3)**.

Other Serious Adverse Events (SAEs)

There were 4 SAEs in the 12 week trial, none of which were considered to be drug-related. One event (lung neoplasm) occurred in the umeclidinium 62.5mcg group. In the 24-week trial, 6% and 3% of patients in the umeclidinium 62.5% and placebo groups respectively had a SAE. Causes for the SAEs were not reported **(Table 3).**

Tolerability

More patients receiving active treatment withdrew from the study due to adverse events than placebo. The reasons for withdrawal in the 12-week study were supraventricular tachycardia (UMEC 62.5) and tachyarrhythmia, coronary artery stenosis, and COPD (UMEC 125). The reasons for withdrawal due to adverse events were not presented in the 24-week trial **(Table 3)**.

Table 3: Incidence of Dropouts due to AEs, SAEs, and Deaths

	Trivedi (12-week)			Donohue (24-week)			
	UMEC 62.5	UMEC 125	PBO	UMEC/VI 62.5/25	UMEC 62.5	VI25	PBO
n	69	69	68	413	418	421	280
Withdrew due to AE n (%)	1 (1.4)	3 (4.3)	0	23 (6)	34 (8)	24 (6)	9(3)
SAEs n (%)	1(1.4)	2 (3)	1 (1.4)	21 (5)	27 (6)	24 (6)	9 (3)
Deaths	-	-	-	3 (0.7)	3 (0.7)	3 (0.7)	0

Abbreviations: AE=adverse event; PBO=placebo; SAE=serious adverse event; UMEC=umeclidinium; VI=vilanterol

Common Adverse Events

Pooled results for the 12- and 24-week trials for events occurring at an incidence of ≥1% and more often with umeclidinium are shown in **Table 4**. The most commonly reported events were nasopharyngitis, upper respiratory tract infection, and cough.

Table 4: Adverse Events with Incidence ≥ 1% and More Common than Placebo

	Umeclidinium (n=487)	Placebo (n=348)
Nasopharyngitis	8	7
Upper respiratory tract infection	5	4
Pharyngitis	1	<1
Cough	3	2
Arthralgia	2	1
Myalgia	1	<1
Abdominal pain	1	<1
Toothache	1	<1
Contusion	1	<1
Tachycardia	1	<1

Data obtained from product package insert

Other Adverse Events

Major Adverse Cardiovascular Events (MACE)

Analyses of MACE were conducted on the pooled intent-to-treat population from COPD studies that were ≥12-weeks duration and a 12-week dose-ranging study. The sponsor analyzed the data based on a broad definition and narrow definition of MACE. The broad definition includes all MedDRA preferred terms that fall under the category of myocardial infarction Standardized Medra Query (SMQ) and other ischemic disease SMQ. The narrow definition used the preferred terms of acute myocardial infarction and myocardial ischemia.

There were fewer MACE-related events with umeclidinium 62.5mcg compared to placebo. Indirect comparison shows a higher rate of MACE with umeclidinium 62.5mcg than tiotropium 18mcg **(Table 5)**. Patients who had any clinically significant uncontrolled CV-related disease, abnormal clinically significant ECG, or 24-h Holter ECG were excluded from the clinical trials. Therefore, the potential risks in these patients cannot be determined from these studies.

Table 5: MACE analysis for Trials ≥ 12 weeks Duration

	UMEC/VI 62.5/25	UMEC 62.5	UMEC 125	VI25	TIO18	PBO
No. of patients	1124	576	1016	1174	173	1053
Patient-years	408	202	449	441	173	369
MACE (n)						
Broad definition	16	11	15	18	6	22
Narrow definition	5	2	7	8	1	8
Incidence Rate (E/1000 pt-yrs)						
Broad definition	36.8	44.5	31.2	38.5	34.7	54.3
Narrow definition	12.3	9.9	15.6	18.1	5.8	19.0
Adjudicated CV death	4.9	0	2.2	4.5	0	5.4
Nonfatal cardiac ischemia	31.9	39.5	24.5	27.2	28.9	38.0
Nonfatal MI	7.4	4.9	8.9	4.5	0	2.7
Nonfatal stroke	0	4.9	4.5	9.1	5.8	10.9

Data obtained from summary of FDA review for umeclidinium/vilanterol

Contraindications

- Severe hypersensitivity to milk proteins
- Hypersensitivity to umeclidinium or any of the excipients

Warnings and Precautions

The following warnings and precautions are those typically mentioned for the anticholinergic drug class. *Consult product package insert for further information and instructions.*

- Deterioration of disease and acute episodes
- Paradoxical bronchospasm
- Hypersensitivity reactions
- Worsening of narrow-angle glaucoma

- Worsening of urinary retention

Special Populations

Pregnancy Category C: There are no adequate trial data in pregnant women. There were no teratogenic effects noted in rats and rabbits receiving inhaled umeclidinium. Umeclidinium should be used during pregnancy only if the potential benefits justify potential risk to the fetus.

Labor and Delivery: there are no adequate and well-controlled human trials during labor and delivery. Umeclidinium should be used during labor only if potential benefits justify potential risk.

Nursing Women: It is unknown if umeclidinium is excreted in human breast milk. Subcutaneous administration of umeclidinium to lactating rats at 25x maximum recommended human daily dose resulted in a quantifiable level of umeclidinium in pups. A decision should be made whether to discontinue nursing or discontinue umeclidinium.

Geriatric Use: Among the patients participating in the COPD clinical trials, 810 and 183 were ≥ 65 and ≥ 75 years old respectively. No overall differences in effectiveness or safety were noted between these patients and younger patients.

Hepatic Impairment: There was no relevant increase in Cmax, or AUC, or change in protein binding in patients with moderate hepatic impairment (Child-Pugh score 7-9) and healthy controls. Studies in patients with severe impairment have not been conducted.

Renal Impairment: There was no relevant increase in Cmax, or AUC, or change in protein binding in patients with severe renal impairment (creatinine clearance <30mL/min) and healthy controls. No dosage adjustment is required in patients with renal impairment.

Look-alike / Sound-alike (LASA) Error Risk Potential

As part of a Joint Commission standard, LASA names are assessed during the formulary selection of drugs. Based on clinical judgment and an evaluation of LASA information from three data sources (Lexi-Comp, First Databank, and ISMP Confused Drug Name List), the following drug names may cause LASA confusion:

Table 11: Results of LASA Search

NME Drug Name	Lexi-Comp	First DataBank	ISMP	Clinical Judgment
Umeclidinium	None	None	None	Aclidinium Undecylenic acid
Incruse Ellipta	None	None	None	

Drug Interactions

There can be a potential for additive adverse effects with concomitant use of anticholinergics. Avoid co-administration of umeclidinium with other anticholinergic containing drugs.

Conclusions

The number of studies for umeclidinium is limited. Studies designed to directly compare umeclidinium and tiotropium are needed. There is a 12-week trial comparing umeclidinium 62.5mcg to tiotropium 18mcg (results pending).

The formulary agent tiotropium is primarily renally eliminated. Renal impairment had no significant impact on the pharmacokinetics of umeclidinium and aclidinium (another long-acting anticholinergic). A trial of umeclidinium or aclidinium can be considered for renally impaired patients having anticholinergic-related adverse effects with tiotropium.

References

Mehta R, Hardes K, Brealey N,et al. Effect of severe renal impairment on umeclidinium and umeclidinium/ vilanterol pharmacokinetics and safety: a single-blind, nonrandomized study. Int J Chron Obstruct Pulmon Dis. 2014 Dec 18;10:15-23.

Triverdi R, Richard N, Mehta R, et al. Umeclidinium in patients with COPD: a randomized, placebo-controlled study. Eur Respir J 2014; 43: 72-81.

Donohue, JF, Maleki-Yazdi MR, Kilbride S, et al. Efficacy and safety of once-daily umeclindinium/vilanterol 62.5/25mcg in COPD. Respir Med 2013; 107: 1538-1546.

Church A, Beerahe M, Brooks J, et al. Dose response of umeclidinium administered once or twice daily in patients with COPD: a randomized cross-over study. BMC Pulm Med 2014; 14: 2.

Product package insert for Umeclidinium (INCRUSE) Ellipta, 6/ 2014.

FDA Medical Review for umeclindinium/vilanterol.
http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203975Orig1s000TOC.cfm

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