Umeclidinium/Vilanterol (Anoro Ellipta)

National PBM Drug Monograph

VA Pharmacy Benefits Management Services,   
Medical Advisory Panel, and VISN Pharmacist Executives

*The purpose of VACO PBM-SHG drug monographs is to provide a comprehensive drug review for making formulary decisions.  These documents will be updated when new data warrant additional formulary discussion.  Documents will be placed in the Archive section when the information is deemed to be no longer current.*

**Executive Summary**

* Umeclidinium/vilanterol (UMEC/VI) is a combination long-acting anticholinergic/long-acting beta-agonist inhaler (LABA) that is administered once daily.
* UMEC/VI is FDA-approved for the long-term, once-daily, maintenance treatment of airflow obstruction in patients with chronic obstructive pulmonary disease (COPD), including chronic bronchitis and/or emphysema.
* UMEC/VI is administered via a breath-actuated multi-dose dry powder inhaler. The dose is 62.5/25mcg once daily.
* There are four 6-month primary studies one 52-week safety study, and two 12-week exercise endurance studies (results of exercise studies not available at time of this writing) conducted in patients with moderate-severe COPD. The primary studies evaluated 2 strengths of UMEC/VI (62.5/25 and 125/25), the individual components, tiotropium (2 trials), and placebo. The 52-week safety study evaluated a dose of UMEC/VI 125/25 that is not marketed; there is no long-term safety study evaluating the marketed dose of UMEC/VI 62.5/25.
* The primary outcome was change in trough FEV1 at day 169. Weighted mean change in post-dose FEV1 over 0-6 hours was a secondary lung function outcome. The marketed dose 62.5/25 showed significantly greater improvement in pulmonary function than placebo, the individual components, and monotherapy with tiotropium.
* Across the primary trials, average rescue inhaler use was reduced by 2.0-2.7 puffs/day (UMEC/VI 62.5/25), 1.7 (UMEC 62.5), 1.8-2.4 (vilanterol), 1.4-1.8 (tiotropium), and 1.4 (placebo)
* The transitional dyspnea index (TDI) was used to assess dyspnea. For the TDI, a difference in score of ≥ 1 unit is considered to be clinically meaningful. Across the primary trials, average score was improved by 2.4-2.4 (UMEC/VI 62.5/25), 2.2 (UMEC 62.5), 2.1 (vilanterol), 2.2 (tiotropium), and 1.2 (placebo)
* Health-related quality of life was measured using the St George’s Respiratory Questionnaire (SGRQ). An improvement in score of ≥4 units is considered to be clinically meaningful. Across the primary trials, average score was improved by 8.1-9.9(UMEC/VI 62.5/25), 7.3 (UMEC 62.5), 7.8-8.3 (vilanterol), 7.6-9.8 (tiotropium), and 2.6 (placebo)
* The 4 primary trials were not designed to evaluate COPD exacerbations; however, data were collected (note that GSK is not seeking an exacerbation claim for UMEC/VI). 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). In the integrated primary efficacy trials, the percentage of patients on active treatment with a COPD exacerbation ranged between 6-9% compared with 13% of those in the placebo group.
* In the 6-month primary trials, adverse events (AEs) resulting in study dropout and adjudicated nonfatal serious AEs were generally balanced among the groups in the primary efficacy studies. The most common reasons were respiratory-related (e.g., COPD, pneumonia).

* The most commonly reported events in the primary trials with an incidence of ≥3% with UMEC/VI 62.5/25 were headache (8-10%), nasopharyngitis (6-10%), upper respiratory tract infection (3-4%), and cough (1-3%).
* Analysis of major adverse cardiovascular events (MACE) was conducted on the pooled intent-to-treat population from COPD studies that were ≥12-weeks duration. The exposure adjusted event rate marketed dose of UMEC/VI indicates a lower risk of MACE relative to placebo. The exception was for nonfatal MI where the adjusted event rate was 7.4 for UMEC/VI 62.5/25 and 2.7 for placebo (number of events was 3 and 1 respectively). 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 of UMEC/VI in these patients are unknown.
* The incidence of anticholinergic events (urinary retention, urinary hesitation, micturition frequency decreased, and urine flow decrease) in the pooled primary studies ranged from 3.0-5.2% for any of the treatment groups using UMEC, 3.9% for vilanterol alone, 3.5% for tiotropium, and 4% for placebo. In the 52 week study, the incidence was 2% each for the 3 study arms.
* Umeclidinium/vilanterol offers the advantage of combining 2 long-acting bronchodilators into a single inhaler; however, studies comparing UMEC/VI to tiotropium + LABA and long-term studies beyond 6-months using the marketed dose are needed.

**Introduction**

Umeclidinium/vilanterol (UMEC/VI) is the first combination long-acting anticholinergic/beta-agonist inhaler. Umeclidinium is a novel long-acting anticholinergic. 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. Vilanterol is a relatively new long-acting beta-agonist and is also available in combination with fluticasone. The beta2-receptor selectivity for vilanterol is similar to salmeterol. Vilanterol is not available as an individual product in the US; umeclidinium just received FDA approval to be marketed as an individual product.

**Pharmacokinetics**

Pharmacokinetic parameters are shown in **Table 1**. There was no significant impact on the pharmacokinetics of umeclidinium or vilanterol based on age, ethnicity, gender, ICS use, weight, moderate hepatic impairment. In patients with severe renal impairment (CrCl <30mL/min), systemic exposure of umeclidinium was not increased; the area under the curve (0-24h) for vilanterol was 56% higher compared to healthy subjects. Adjustment for dosing is not needed for geriatric patients, patients with renal impairment, or patients with moderate hepatic impairment.

**Table 1: Pharmacokinetics of Umeclidinium and Vilanterol**

|  |  |  |
| --- | --- | --- |
|  | **Umeclidinium** | **Vilanterol** |
| Time to peak plasma concentration | 5-15min via inhalation healthy subjects | 5-15min via inhalation healthy subjects |
| Time to steady state | 14 days after repeat inhalation  Up to 1.8 fold accumulation | 14 days after repeat inhalation  Up to 1.7 fold accumulation |
| Oral bioavailability (swallowed portion) | Minimum contribution from oral absorption | Negligible contribution from oral absorption |
| Volume of distribution | 86L following IV admin | 165L following IV admin |
| Protein binding | 89% following IV admin | 94% following IV admin |
| Metabolism | Primarily via CYP2D6 (Hydroxylation, O-dealkylation followed by glucuronidation)  Substrate for P-gp transporter | Primarily via CYP 3A4  Substrate for P-gp transporter |
| Metabolites | Range of metabolites with reduced activity or for which the p-col activity has not been established | Range of metabolites with significantly reduced ẞ1- andẞ2-agonist activity |
| Elimination | 58% feces; 22% urine after IV dosing  92% feces; <1% urine following oral dosing | 70% urine; 30% feces after oral administration |
| Half-life | 11 hours after once daily dosing | 11 hours after inhalation of multiple doses |

Information obtained from product package insert

**FDA Approved Indication(s)**

Umeclidinium/vilanterol 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](http://vaww.national.cmop.va.gov/PBM/Directives%20Policies%20and%20Information%20Letters/Guidance%20on%20Off%20Label%20Prescribing.pdf) (available on the VA PBM Intranet site only).

* Treatment of asthma

**Current VA Formulary Alternatives**

Anticholinergics: tiotropium, ipratropium, ipratropium/albuterol

LABA: formoterol

**Dosing/Administration**

One oral inhalation of 62.5/25mcg 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**

UMEC/VI is available via a multi-dose dry powder inhaler containing 62.5mcg of umeclidinium and 25mcg of vilanterol. 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 UMEC/VI in a dry place between 68-77°F; excursions between 59-86°F are permitted. UMEC/VI 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 efficacy of umeclidinium and vilanterol as separate agents has been evaluated in several dose-ranging and dose-regimen studies in patients with COPD and asthma. The fixed-dose combination UMEC/VI has been evaluated in four 6-month trials in patients with moderate-severe COPD (**Table 2**). Two trials are placebo controlled and 2 are active-comparator trials. The study by Celli et al. evaluated UMEC/VI 125/25 in a dose that is not marketed and will not be discussed individually in the efficacy section of this monograph. The results of this trial showed that the 125/25 dose did not offer greater bronchodilator efficacy over 62.5/25 dose. Tiotropium monotherapy was a treatment arm in the 2 active-comparator trials. There is a 52-week safety study that evaluated UMEC/VI 125/25; there is no long-term safety study evaluating the marketed dose of UMEC/VI 62.5/25. Lastly, there are two 12-week exercise endurance studies (results not available).

The 6-month trials were similar in design. 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 were allowed.

The mean demographic and baseline characteristics of patients include: 63 years old, 68% male, 84% Caucasian, 50% current smokers, 45 pack-years smoking history, post-albuterol FEV1% predicted 48, FEV1/FVC 0.47, and 14% reversibility.

**Table 2: Clinical Trials in COPD**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** |  | **n** | **Duration** | **Treatment Arms** |
| Donohue 2013  Celli 2014  Decramer 2014 (study 1)  Decramer 2014 (study 2) | Primary trials | 1532  1489  843  869 | 6-months  6-months  6-months  6-months | UMEC/VI 62.5/25; UMEC 62.5; VI25; PBO  UMEC/VI 125/25; VI25; UMEC 125; PBO  UMEC/VI 62.5/25; UMEC/VI 125/25; TIO18; VI 25  UMEC/VI 62.5/25; UMEC/VI 125/25; UMEC 125; TIO18 |
| Study 113359 | Safety | 335 | 12-months | UMEC/VI 125/25; UMEC 125; PBO |
| Study 114417  Study 114418 | Exercise endurance | 641  554 | 12-weeks  12-weeks | UMEC/VI 62.5/25; UMEC/VI 125/25; UMEC125; UMEC 62.5; VI25; PBO (both studies) |

*Pulmonary function*

The primary outcome was change in trough FEV1 at day 169. Weighted mean change in post-dose FEV1 over 0-6 hours was a secondary lung function outcome. The study by Donohue showed significantly greater improvement in pulmonary function for the combination than placebo and the individual components. In Decramer (study 1), both combination doses were significantly better than tiotropium or vilanterol alone. There was no significant difference between tiotropium and vilanterol. In study 2, the improvement in trough FEV1 with both combination doses was significantly greater than tiotropium, but not UMEC 125. For change in WM FEV1 0-6h, both combination doses had significantly greater improvement than tiotropium or UMEC125 alone. There was no significant difference in trough FEV1 between UMEC 125 and tiotropium.

**Table 3: Improvement in Pulmonary Function in 24 weeks Trials**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Treatment Arms** | **Change in Trough FEV1 (ml)** | **Change WM FEV1 0-6h (ml)** |
| Donohue 2013 | UMEC/VI 62.5/25  UMEC 62.5  VI25  PBO | 171±12\*ⱡ  119±12.6\*  76±12.7\*  4±15.8 | 243±12.7\*ⱡ  151±12.8\*  123±12.8\*  1.0±15.8 |
| Decramer 2014  (study 1) | UMEC/VI 62.5/25  UMEC/VI 125/25  TIO18  VI 25 | 211±18.3§  209±18.7§  121±18.6  121±18.9 | 254±18.3§  263±18.7§  181±18.7  178±18.9 |
| Decramer 2014  (study 2) | UMEC/VI 62.5/25  UMEC/VI 125/25  TIO18  UMEC125 | 208±18^  223±17.9^  149±17.6  186±17.8 | 276±16.8^¶  282±16.7^¶  180±16.5  206±16.7 |

\*Significant vs. placebo

ⱡSignificant vs. both monotherapy treatments

§Significant vs. TIO and VI

^Significant versus TIO

¶Significant versus UMEC

*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 a significantly greater improvement in TDI focal score compared to placebo. In Decramer studies, all active treatments had clinically meaningful improvement. The only comparison where there was a significant difference was between UMEC/VI 125/25 and VI25 (**Table 4**).

**Table 4: TDI Focal Score on Day 168**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **UMEC/VI 62.5/25** | **UMEC/VI 125/25** | **UMEC 62.5** | **UMEC 125** | **VI25** | **TIO18** | **PBO** |
| **Donohue**  Score at day 168  % responders (≥ 1 unit) | 2.4±0.16\*  58\* | N/A | 2.2±0.16\*  53\* | N/A | 2.1±0.16\*  51\* | N/A | 1.2±0.2  41 |
| **Decramer (study 1)**  Score at day 168  % responders (≥ 1 unit) | 2.3±0.2  55 | 2.9±0.2\*\*  63\*\* | N/A | N/A | 2.1±0.2  49 | 2.4±0.2  60 | N/A |
| **Decramer (study 2)**  Score at day 168  % responders (≥ 1 unit) | 2.3±0.3  57 | 2.4±0.2  55 | N/A | 1.9±0.2  50 | N/A | 2.1±0.2  51 | N/A |

\*Significant vs. PBO

\*\*Significant vs. VI25

*Rescue inhaler use*

In the placebo-controlled trial, the need for rescue inhaler use was significantly reduced with UMEC/VI 62.5/25 compared to placebo or UMEC alone. There was no significant difference vs. vilanterol alone.

In Decramer (study1), both combination doses significantly reduced rescue inhaler use compared to monotherapy with tiotropium. In study 2, only the 125/25 dose was shown to significantly reduce rescue inhaler use compared to monotherapy with umeclidinium or tiotropium.

**Table 5: Rescue Inhaler Use (Puffs/Day)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **UMEC/VI 62.5/25** | **UMEC/VI 125/25** | **UMEC 62.5** | **UMEC 125** | **VI25** | **TIO18** | **PBO** |
| Donohue | -2.3±0.16\*§ | N/A | -1.7±0.16 | N/A | -2.4±0.9\* | N/A | -1.4±0.2 |
| Decramer (Study 1) | -2.0±0.2ⱡ | -2.0±0.2ⱡ | N/A | N/A | -1.8±0.2 | -1.4±0.2 | N/A |
| Decramer (Study 2) | -2.7±0.2 | -3.2±0.2ⱡ§ | N/A | -2.1±0.2 | N/A | -2.1±0.2 | N/A |

\*Significant vs. placebo

§Significant vs. UMEC

ⱡSignificant vs. TIO

*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 UMEC 62.5/25 and the individual components than placebo (**Appendix 1)**.

For the active comparator trials, all active treatments had significant improvement vs. baseline; there was no significant difference between active treatments **(Appendix 2).**

*COPD Exacerbations*

The 4 primary trials were not designed to evaluate COPD exacerbations; however, data were collected (note that GSK is not seeking an exacerbation claim for UMEC/VI). 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).

In the integrated primary efficacy trials, the percentage of patients on active treatment with a COPD exacerbation ranged between 6-9% compared with 13% of those in the placebo group **(Table 6**).

**Table 6: COPD Exacerbation (Integrated Primary Efficacy Trials)**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **UMEC/VI 62.5/25** | **UMEC/VI 125/25** | **UMEC 62.5** | **UMEC 125** | **VI25** | **TIO18** | **PBO** |
| n | 837 | 826 | 418 | 629 | 1030 | 418 | 555 |
| Patients with event n(%) | 67 (8) | 50 (6) | 33 (8) | 58 (9) | 88 (9) | 25 (6) | 73 (13) |

Data obtained from FDA review

*Exercise Endurance*

Two identically designed studies evaluated both doses of UMEC/VI, the individual components and placebo and their effect on the exercise shuttle walk test. Results were not available at the time of this writing.

**Adverse Events (Safety Data)**

The safety database for UMEC/VI include the 4 primary efficacy studies (24 weeks), the 52-week safety trial, 2 exercise endurance trials (12 weeks), 3 UMEC dose-ranging trials (7-28 days), 1 UMEC study (12 weeks), 28-day PK/PD study, and the VI and placebo arms from 4 trials from the fluticasone furoate/vilanterol (BREO Ellipta) program (24-52 weeks). The number of exposed patients in the database by drug are UMEC/VI 62.5/25 (n=1124), UMCE/VI 125/25 (n=1330), UMEC62.5 (n=670), UMEC125 (n=1181), VI25 (n=2501), TIO (n=514), and placebo (n=1864). For the approved dose, 326 patients were treated for at least 24 weeks.

Adverse events (AEs) resulting in study dropout and adjudicated nonfatal serious AEs were generally balanced among the groups in the primary efficacy studies. The most common reasons were respiratory-related (e.g., COPD, pneumonia). **Table 7**

**Table 7: Incidence of Dropouts due to AEs, Nonfatal SAEs, and Deaths**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Pooled-Primary Studies (6-month)** | | | | | | | | **52-week Study** | | |
|  | **UMEC/VI 62.5/25** | **UMEC/VI 125/25** | **UMEC 62.5** | **UMEC 125** | **VI25** | **TIO18** | **PBO** | **UMEC/VI 125/25** | | **UMEC**  **125** | **PBO** |
| n | 842 | 832 | 418 | 629 | 1034 | 423 | 555 | 226 | | 227 | 109 |
| Dropout 2° any AE n(%) | 50 (6) | 47 (6) | 31 (7) | 41 (7) | 59 (6) | 20 (5) | 26 (5) | 17 (8) | | 20 (9) | 12 (11) |
| Adjudicated  nonfatal SAEs n(%) | 49 (6) | 45 (5) | 27 (6) | 37 (6) | 57 (6) | 20 (5) | 25 (5) | 14 (6) | | 15 (7) | 7 (6) |
| Deaths | 5 (0.6) | 1 (0.1) | 3 (0.7) | 2 (0.3) | 6 (0.6) | 2 (0.5) | 2 (0.4) | 0 | | 4 (1.8) | 1 (0.9) |

Data obtained from FDA review

Pooled results for the primary trials for events occurring at an incidence of ≥1% and more often with UMEC/VI 61.5/25 are shown in **Table 8**. Adverse events for the primary trials by individual trial are shown in **Table 9**. The most commonly reported events with an incidence of ≥3% were headache, nasopharyngitis, upper respiratory tract infection, and cough. For the 52 week safety trial events reported more often with UMEC/VI 125/25 than placebo were back pain (4% vs. 3%), sinusitis (4% vs. 3%), and cough (3% vs. 0.09%).

**Table 8: Adverse Events with Incidence ≥ 1% and More Common than with Placebo (Pooled 24-week trials)**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
|  | **UMEC/VI 62.5/25**  **(n=842)** | **UMEC 62.5 (n=418)** | **VI 25 (n=1034)** | **Placebo (n=555)** |
| Pharyngitis | 2 | 1 | 2 | <1 |
| Sinusitis | 1 | <1 | 1 | <1 |
| Lower respiratory tract infection | 1 | <1 | <1 | <1 |
| Constipation | 1 | <1 | <1 | <1 |
| Diarrhea | 2 | <1 | 2 | 1 |
| Pain in extremity | 2 | <1 | 2 | 1 |
| Muscle spasms | 1 | <1 | <1 | <1 |
| Neck pain | 1 | <1 | <1 | <1 |
| Chest pain | 1 | <1 | <1 | <1 |

Data obtained from product package insert

**Table 9: Adverse Events with Incidence ≥ 3%**

|  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | **Donohue** | | | | **Decramer (study 1)** | | | | **Decramer (study 2)** | | | |
| **UMEC/VI 62.5/25** | **UMEC 62.5** | **VI 25** | **PBO** | **UMEC/VI 62.5/25** | **UMEC/VI 125/25** | **TIO 18** | **UMEC 125** | **UMEC/VI 62.5/25** | **UMEC/VI 125/25** | **TIO 18** | **VI25** |
| N | 413 | 418 | 421 | 280 | 217 | 215 | 215 | 222 | 212 | 214 | 208 | 209 |
| Headache | 8 | 8 | 6 | 9 | 10 | 9 | 7 | 11 | 9 | 7 | 4 | 10 |
| Nasopharyngitis | 9 | 7 | 6 | 6 | 6 | 7 | 8 | 3 | 10 | 7 | 8 | 8 |
| URI | 3 | 5 | 4 | 5 | 3 | 5 | 7 | 8 | 4 | 3 | 4 | 2 |
| Cough | 1 | 4 | 4 | 3 | 2 | 4 | 3 | 6 | 3 | 3 | 2 | 2 |
| Oropharyngeal pain | 3 | 1 | 3 | 1 | 1 | 3 | 1 | 4 | <1 | 3 | <1 | 2 |
| Back pain | 3 | 2 | 2 | 3 | 4 |  |  |  | 5 | 3 | 2 | 1 |
| COPD | 2 | 3 | 2 | 1 | 3 | 3 | <1 | <1 | - | - | - | - |
| Arthralgia | <1 | 3 | <1 | 1 | - | - | - | - | - | - | - | - |
| HTN | - | - | - | - | <1 | 2 | 3 | 4 | 1 | 1 | <1 | 3 |
| Diarrhea | - | - | - | - | 2 | <1 | 2 | 3 | - | - | - | - |
| Gastritis | - | - | - | - | 3 | 2 | <1 | 3 | - | - | - | - |
| UTI | - | - | - | - | <1 | 2 | 2 | 3 | 0 | 0 | 3 | <1 |
| Lower RTI | - | - | - | - | 4 | 1 | <1 | <1 | - | - | - | - |
| Dyspnea | - | - | - | - | <1 | 0 | 1 | 3 | - | - | - | - |
| Pain in extremity | - | - | - | - | 3 | 3 | 2 | <1 | - | - | - | - |
| Influenza | - | - | - | - | 1 | <1 | 2 | 3 | - | - | - | - |

*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 included the trials shown in **Table 10** plus 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.

The exposure adjusted event rate marketed dose of UMEC/VI indicates a lower risk of MACE relative to placebo. The exception was for nonfatal MI where the adjusted event rate was 7.4 for UMEC/VI 62.5/25 and 2.7 for placebo (number of events was 3 and 1 respectively). 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 of UMEC/VI in these patients are unknown.

**Table 10: MACE analysis for Trials ≥ 12 weeks Duration**

|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
|  | **UMEC/VI 62.5/25** | **UMEC/VI 125/25** | **UMEC 62.5** | **UMEC 125** | **VI25** | **TIO18** | **PBO** |
| No. of patients  Patient-years | 1124  408 | 1330  573 | 576  202 | 1016  449 | 1174  441 | 173  173 | 1053  369 |
| MACE (n)  Broad definition  Narrow definition | 16  5 | 22  6 | 11  2 | 15  7 | 18  8 | 6  1 | 22  8 |
| Incidence Rate (E/1000 pt-yrs)  Broad definition  Narrow definition  Adjudicated CV death  Nonfatal cardiac ischemia  Nonfatal MI  Nonfatal stroke | 36.8  12.3  4.9  31.9  7.4  0 | 38.4  10.5  0  33.2  5.2  5.2 | 44.5  9.9  0  39.5  4.9  4.9 | 31.2  15.6  2.2  24.5  8.9  4.5 | 38.5  18.1  4.5  27.2  4.5  9.1 | 34.7  5.8  0  28.9  0  5.8 | 54.3  19.0  5.4  38.0  2.7  10.9 |

Data obtained from summary of FDA review

*Cardiac*

Mean changes in systolic and diastolic blood pressure, heart rate, and 12-lead ECG were balanced across the treatment groups or were not considered as clinically relevant.

Clinically significant ECG abnormalities reported in ≥3% of patients were assessed in the 24 week primary trials; events that were reported more often with UMEC/VI than placebo were:

* 24-week trials UMEC/VI 62.5/25 vs. placebo: ectopic supraventricular beats (4% vs. 3%)
* 24-week trials UMEC/VI 125/24 vs. placebo: ectopic supraventricular beats (4% vs. 3%) and ectopic supraventricular rhythm (3% vs. 2%).
* 52-week trial UMEC/VI 125/25 vs. placebo: VPD ≥ 3 (5% vs. <1%), right bundle branch block with QTcF <530sec (4% vs. 2%), ectopic supraventricular beats (3% vs. <1%) and first degree AV block (2% vs. <1%).

24-hour Holter monitoring: Approximately 13% of patients in the placebo controlled trials underwent 24-hour Holter monitoring. The incidence of any clinically significant abnormality in the treatment arms ranged from 25%-42% in the active treatment groups compared to 39% with placebo.

A study evaluating effect on QTc was conducted using UMEC/VI 125/25, UMEC 500/100, UMEC 500, and moxifloxacin (control) in healthy subjects. There was no significant QTc prolongation for UMEC/VI 125/25 and UMEC 500. For the mean difference between UMEC/VI 500/100 and placebo, the largest upper bound of the 90% confidence interval was 10.7ms (the threshold for regulatory concern is 10ms).

*Anticholinergic Adverse Events*

Terms used for anticholinergic events included urinary retention, urinary hesitation, micturition frequency decreased, and urine flow decreased. In the 24 week primary studies, the pooled incidence ranged from 3.0-5.2% for any of the treatment groups using UMEC, 3.9% for vilanterol alone, 3.5% for tiotropium, and 4% for placebo. In the 52 week study, the incidence was 2% each for the 3 study arms.

**Contraindications**

* Severe hypersensitivity to milk proteins
* Hypersensitivity to umeclidinium, vilanterol or any of the excipients

**Warnings and Precautions**

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

* Asthma-related death
* Deterioration of disease and acute episodes
* Excessive use with other long-acting beta2-agonists
* Drug interactions with strong cytochrome P450 3A4 inhibitors
* Paradoxical bronchospasm
* Hypersensitivity reactions
* Cardiovascular effects
* Coexisting conditions (e.g., convulsive disorders, thyrotoxicosis)
* Worsening of narrow-angle glaucoma
* Worsening of urinary retention
* Hypokalemia and hyperglycemia

**Special Populations**

*Pregnancy Category C:* There are no adequate trial data in pregnant women. In laboratory animals, systemic administration of corticosteroids and beta-agonists has been shown to be teratogenic. There were no teratogenic effects noted in rats and rabbits receiving inhaled UMEC or VI at doses that exceed human doses, with the exception of fetal skeletal variation (i.e., decreased or absent ossification in cervical vertebral centrum and metacarpals) in rabbits with VI at 450 times the maximum recommended human daily dose . UMEC/VI 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. Because beta-agonists may potentially interfere with uterine contractility, UMEC/VI should be used during labor only if potential benefits justify potential risk.

*Nursing Women:* It is unknown if UMEC/VI is excreted in human breast milk. Because other beta-agonists have been detected in human milk and administration of UMEC to lactating rats at 25x maximum recommended human daily dose resulting in quantifiable level of UMEC in pups , a decision should be made whether to discontinue nursing or discontinue UMEC/VI.

*Geriatric Use:* Among the patients participating in the COPD clinical trials, 2,143 and 478 were ≥ 65 and ≥ 75 years old respectively. No overall differences in effectiveness or safety were noted between these patients and younger patients.

**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 /vilanterol | None | None | None | Aclidinium  Ventolin  Undecylenic acid |
| Anoro Ellipta | None | None | None | Alora  Breo Ellipta |

**Drug Interactions**

* Vilanterol is a substrate of CYP3A4. Concomitant administration of ketoconazole (potent CYP3A4 inhibitor) increases systemic exposure to vilanterol. Exercise caution when considering coadministration of UMEC/VI with ketoconazole or other strong CYP3A4 inhibitors (e.g., ritonavir, clarithromycin, conivaptan, indinavir, itraconazole, lopinavir, nefazodone, nelfinavir, saquinavir, telithromycin, troleandomycin, voriconazole)
* Beta2-agonists, including vilanterol, should be administered with extreme caution to patients receiving MAOIs, tricyclic antidepressants, or drugs known to prolong QTc interval or within 2 weeks of discontinuation of such drugs. The effect of beta-agonists on the cardiovascular system may be potentiated by these agents. Drugs that prolong the QTc interval have an increased risk of ventricular arrhythmias.
* Beta blockers can block the pulmonary effects of beta agonists and may produce severe bronchospasm in patients with reversible obstructive airway disease. Therefore, patients with COPD should not normally be treated with beta- blockers. If there are no acceptable alternatives to the use of beta-blockers for these patients, cardioselective beta-blockers could be considered and used with caution.
* The use of beta-agonists can acutely worsen hypokalemia that may occur with non-potassium-sparing diuretics. Although the clinical significance of these effects is not known, caution should be used in co-administration of these agents.
* There can be a potential for additive adverse effects with concomitant use of anticholinergics. Avoid co-administration of UMEC/VI with other anticholinergic containing drugs

**Comparative Cost**

Please refer to VA pricing sources for updated information.

**Conclusions**

Umeclidinium/vilanterol is the first fixed-dose combination long-acting anticholinergic and LABA. It is currently approved for use in COPD. There was a greater improvement in pulmonary function UMEC/VI than placebo, the individual components, and monotherapy with tiotropium. Improvement in TDI and quality of life scores was similar among all active treatment groups. The 4 primary trials were not designed to evaluate COPD exacerbations; however, in the integrated primary efficacy trials, the percentage of patients on active treatment with a COPD exacerbation ranged between 6-9% compared with 13% of those in the placebo group.

There was a lower risk of major adverse cardiovascular events in patients receiving any active treatment including UMEC/VI 62.5/25 relative to placebo; however, the adjusted event rate for nonfatal MI was 7.4 for UMEC/VI 62.5/25 and 2.7 for placebo (number of events was 3 and 1 respectively). It should be noted that 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 of UMEC/VI in these patients are unknown.

To better understand the safety and efficacy of UMEC/VI, studies comparing UMEC/VI to tiotropium + LABA and long-term studies beyond 6-months using the marketed dose are needed.

**References**

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Product Package Insert for Anoro Ellipta 12/2013

FDA Medical Review for umeclindinium/vilanterol.

<http://www.accessdata.fda.gov/drugsatfda_docs/nda/2013/203975Orig1s000TOC.cfm>

**Prepared by: Deb Khachikian, PharmD**

**Appendix 1: Placebo-Controlled Trials**

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Study** | **Entry Criteria** | **Treatment arms** | **Demographic and Baseline** | **Results** |
| Donohue 2013  R, DB PC  24-weeks  N=1532  ITT analysis | **Inclusions**  Established COPD  ≥40 years old  Current/former smoker  ≥10 pack-year smoking history  Post-albuterol FEV/FVC <0.70  Post-albuterol FEV1 ≤70% pred  MMRC score ≥2  **Exclusions**  Asthma or other known respiratory disorders (including α-1antitrypsin deficiency, active TB, bronchiectasis, sarcoidosis, lung fibrosis, pulmonary HTN, interstitial lung disease); any clinically significant uncontrolled disease (including CV-related, abnormal clinically significant ECG, or 24-h Holter ECG, abnormal clinical lab finding) | 3:3:3:2 randomization  UMEC/VI 62.5/25 (n=413)  UMEC 62.5 (n=418)  VI 25 (n=421)  Placebo (n=280)  Rescue albuterol and stable doses of ICS equivalent to ≤1000mcg/day of fluticasone were allowed | Values for UMEC/VI; UMEC; VI, PBO respectively  **Age (y):** 63.1; 64; 62.7; 62.2  **Male (%):** 74; 71; 68; 70  **Current smoker (%):** 49; 50; 47; 54  **Smoking pack-years:** 46.5±25.8; 46.8±27; 44.7±23.2; 47.2±27.2  **ICS use (%):** 51; 52; 50; 49  **Post-albuterol FEV1% pred:** 47.8±13.2; 46.8±13.4; 48.2±13.3; 46.7±12.7  **GOLD stage**  **II (%):** 49; 46; 47; 43  **III (%):** 40; 41; 43; 48  **IV (%):** 11; 13; 10; 10  **% Reversibility to albuterol:** 13.9±15.1; 13.9±14.9; 15.7±15.6; 15.3±15.5  **Reversible to albuterol (% pts):** 31; 29; 37; 33  **% reversibility to albuterol and ipratropium:** 22.2±18.8; 22.3±18.5; 23.6±19.4; 22.7±19.6  **Reversible to albuterol and ipratropium (% pts):** 56; 54; 56; 54 | |  |  |  |  |  | | --- | --- | --- | --- | --- | |  | **UMEC/VI**  **62.5/25** | **UMEC 62.5** | **VI25** | **PBO** | | Withdrawals (%) | 20 | 22 | 24 | 27 | | Withdrew due to AE (%) | 6 | 8 | 6 | 3 | | Withdrew due to LOE (%) | 5 | 5 | 8 | 13 | | Δ Trough FEV1 (ml) | 171±12\*ⱡ | 119±12.6\* | 76±12.7\* | 4±15.8 | | Δ WM FEV1 0-6h (ml) | 243±12.7\*ⱡ | 151±12.8\* | 123±12.8\* | 1.0±15.8 | | Δ Peak FEV1 (ml) | 320±13.5\*ⱡ | 226±13.6\* | 108±13.6\* | 96±16.8 | | Δ Trough FVC (ml) | 262±20.6\*ⱡ | 188±20.7\* | 118±20.8\* | 14±25.8 | | TDI focal score | 2.4±0.16\* | 2.2±0.16\* | 2.1±0.16\* | 1.2±0.2 | | TDI focal score responders (%) | 58 | 53 | 51 | 41 | | Δ SGRQ score | -8.07±  0.75\* | -7.25± 0.75\* | -7.75± 0.76\* | -2.56± 0.95 | | SGRQ responders (%) | 49 | 44 | 48 | 34 | | SGRQ responder OR vs. PBO | 2.0  [1.4, 2.8]\* | 1.6  [1.2, 2.3]\* | 1.9  [1.3, 2.6]\* | N/A | | Rescue albuterol (puffs/day) | -2.3±0.16\*§ | -1.7±0.16 | -2.4±0.9\* | -1.4±0.2 | | Time to 1st COPD exacerbation  (HR vs. PBO) | 0.5  [0.3, 0.8]\* | 0.6  [0.4, 1.0]\* | 0.7  [0.4, 1.1]\* | N/A |   \*Significant vs. placebo  ⱡSignificant vs. both monotherapy treatments  §Significant vs. UMEC alone |

**Appendix 2: Active-Control Trials**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Decramer 2014  Study 1  R, DB, DD, AC  24-weeks  N=843 | **Inclusions**  same as in Donohue  **Exclusions**  Asthma, α-1antitrypsin deficiency, any clinically significant uncontrolled disease, significant ECG or clinical lab finding, lower respiratory tract infection or recent COPD exacerbation | 1:1:1:1 randomization  UMEC/VI 62.5/25 (n=207)  UMEC/VI 125/25 (n=204)  TIO 18 (n=203)  VI 25 (n=205)  ICS at stable doses was allowed | Values for UMEC/CI 62.5/25; UMEC/VI 125/25; TIO; VI respectively  **Age (y):** 63; 62.9; 62.6; 63.2  **Male (%):** 69.8; 70.6; 67.3; 68.4  **Current smoker (%):** 46; 58; 48; 51  **Smoking pack-years:** 44.8±27.7; 43.5±25; 41.9±24.4; 41.6±25.4  **ICS use (%):** 44; 48; 43; 40  **Post-albuterol FEV1% pred:** 48±12.9; 47.2±12.8; 47.8±13.4; 47.7.2±12.7  **% Reversibility to albuterol:** 12.4±15; 12.2±14.2; 10.8±13.6; 11.3±13.7  **≥1 COPD exacerbation in previous year NOT requiring hosp (%):** 30; 28; 34; 31  **≥1 COPD exacerbation in previous year requiring hosp (%):** 15; 11; 19; 16 | |  |  |  |  |  | | --- | --- | --- | --- | --- | |  | **UMEC/VI**  **62.5/25** | **UMEC/VI**  **125/25** | **TIO 18** | **VI 25** | | Withdrawals n(%) | 31 (15) | 41 (19) | 31 (15) | 44 (21) | | Withdrew due to AE n(%) | 10 (5) | 15 (7) | 9 (4) | 44 (5) | | Withdrew due to LOE n(%) | 9 (4) | 5 (2) | 7 (3) | 17 (8) | | Δ Trough FEV1 (ml) | 211±18.3\* | 209±18.7\* | 121±18.6 | 121±18.9 | | Δ WM FEV1 0-6h (ml) | 254±18.3\* | 263±18.7\* | 181±18.7 | 178±18.9 | | TDI focal score | 2.3±0.2 | 2.9±0.2 | 2.4±0.2 | 2.1±0.2 | | Δ SGRQ‡  Responder (%) | -6.87±1.02  49 | -9.03±1.05  53 | -7.62±1.05  52 | -8.29±1.06  52 | | Rescue albuterol (puffs/day) | -2.0±0.2§ | -2.0±0.2§ | -1.4±0.2 | -1.8±0.2 | | COPD exacerbations (%) | 7 | 5 | 5 | 8 |   \*Significant vs. TIO and VI  ‡All active treatments had significant improvement vs. baseline; there was no significant difference between active treatments  §Significant vs. TIO |

**Appendix 2: Active-Control Trials (continued)**

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Decramer 2014  Study 2  R, DB, DD, AC  24-weeks  N=869 | **Inclusions**  same as in Donohue  **Exclusions**  Asthma, α-1antitrypsin deficiency, any clinically significant uncontrolled disease, significant ECG or clinical lab finding, lower respiratory tract infection or recent COPD exacerbation | 1:1:1:1 randomization  UMEC/VI 62.5/25 (n=217)  UMEC/VI 125/25 (n=215)  TIO 18 (n=215)  UMEC 125 (n=222)  ICS at stable doses was allowed | Values for UMEC/CI 62.5/25; UMEC/VI 125/25; TIO; UMEC 125 respectively  **Age (y):** 65; 63.8; 65.2; 64.5  **Male (%):** 65; 69; 71; 67  **Current smoker (%):** 42; 45; 47; 44  **Smoking pack-years:** 47.8±26.1; 46.9±24.9; 54±31.6; 47.6±27.6  **ICS use (%):** 47; 53; 53; 56  **Post-albuterol FEV1% pred:** 47.7±13.6; 47.1±12.9; 47.4±13.1; 46.2±13  **Post-albuterol FEV1 (L):** 1.32±0.49; 1.31±0.42; 1.33±0.43; 1.29±0.47  **% Reversibility to albuterol:** 14.9±15; 15.8±15.2; 15.5±15.6; 16.1±15.3  **≥1 COPD exacerbation in previous year NOT requiring hosp (%):** 28; 35; 31; 29  **≥1 COPD exacerbation in previous year requiring hosp (%):** 4; 7; 7; 6 | |  |  |  |  |  |  |  | | --- | --- | --- | --- | --- | --- | --- | |  | **UMEC/VI**  **62.5/25** | **UMEC/VI**  **125/25** | | **TIO 18** | | **UMEC 125** | | Withdrawals n(%) | 54 (25) | 49 (23) | | 39 (18) | | 57 (26) | | Withdrew due to AE n(%) | 20 (9) | 15 (7) | | 11 (5) | | 17 (8) | | Withdrew due to LOE n(%) | 12 (6) | 9 (4) | | 13 (6) | | 22 (10) | | Δ Trough FEV1 (ml) | 208±18\* | 223±17.9\* | | 149±17.6 | | 186±17.8 | | Δ WM FEV1 0-6h (ml) | 276±16.8\*ⱡ | 282±16.7\*ⱡ | | 180±16.5 | | 206±16.7 | | COPD exacerbations (%) | 12 | 7 | | 7 | | 12 | | TDI focal score | 2.3±0.3 | 2.4±0.2 | | 2.1±0.2 | | 1.9±0.2 | | TDI responder  OR vs. TIO 18  OR vs. UMEC 125 | 1.3[0.9, 1.9]  1.3[0.9, 2.0] | | 1.2[0.8, 1.8]  1.2[0.8, 1.8] | | N/A | | | Δ SGRQ¶  Responder (%) | -9.95±0.98  54 | -10.52±0.97  51 | | -9.78±0.95  55 | | -8.4±0.97  48 | | Rescue albuterol (puffs/day) | -2.7±0.2 | -3.2±0.2\*ⱡ | | -2.1±0.2 | | -2.1±0.2 | | COPD exacerbations (%) | 12 | 7 | | 7 | | 12 |   \*Significant versus TIO  ⱡSignificant versus UMEC  ¶All active treatments had significant improvement vs. baseline; there was no significant difference between active treatments |