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Review Article

Effects of Dual and Triple Drug Therapy in Chronic Obstructive Pulmonary Disease Management: An Overview

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ABSTRACT

Background: A common and serious disease known as chronic obstructive pulmonary disease is currently the fourth leading cause of death worldwide. Studies have shown that inhaled triple therapy is superior to dual therapy, but side effects include pneumonia and cardiovascular events. The use of triple inhalation therapy has advanced the treatment of chronic obstructive pulmonary disease. The efficacy of inhaled corticosteroids in treating Chronic obstructive pulmonary disease exacerbations increases with higher blood eosinophil levels, has no effect in people with low blood eosinophil levels, and eosinopenia increases the risk of pneumonia. Patients with chronic obstructive pulmonary disease are at high risk of infection, and triple therapy, including inhaled corticosteroids, is not an option for patients with active tuberculosis. Studies have also shown the value of dual therapy for mild exacerbations, particularly in patients who cannot receive inhaled corticosteroid treatment. There doesn't seem to be a single article that covers all the basics of dual and triple therapy, including the different types of combinations and side effects. **Main parts of the summary:** GOLD recommends a personalized strategy for treatment initiation based on symptom severity and likelihood of exacerbation. The treatment course may be increased or decreased depending on the presence or absence of key symptoms such as shortness of breath or decreased performance, and the persistence of exacerbations during maintenance therapy. To achieve the best treatment and health outcomes, people with COPD need to understand the nature of their disease, the risk factors for progression, and the roles that patients and healthcare providers should play. People with COPD need to understand the nature of their disease, the risk factors for its progression, and the role they and their health care professionals must play in achieving the best management and health outcomes. The use of triple therapy was found to be associated with an increased risk of pneumonia compared to LABA/LAMA. This suggests that the use of triple therapy may have a higher risk of developing pneumonia compared to the use of LABA/LAMA. However, there were no significant differences between the triple therapy and the two-drug inhaler regarding other adverse events. **Conclusion:** The risk of pneumonia may be higher with his triple combination therapy, but in terms of other adverse events (e.g. side effects and complications) there is no statistical difference between the two treatment options. However, there was no significant difference. However, severe COPD exacerbations were treated with triple therapy. Additionally it helped to improve lung function and reduce exacerbations. In case of moderate exacerbation, dual treatment was given. Dual Therapy may help to reduce the negative effects of ICS.

Keywords: Dual therapy, Triple therapy, COPD, Inhaled corticosteroids, LABA, LAMA.

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INTRODUCTION

Despite continued research and medical efforts, Chronic Obstructive Pulmonary Disease (COPD) is a common illness that continues to be the fourth greatest cause of mortality worldwide.[1] Since exacerbations frequently result in further reductions in lung function and severe cost burdens associated with therapy, the main objectives of COPD management are to enhance lung function, quality of life, and reduce disease exacerbations. Long-Acting Beta-2 Agonists (LABA), Long-Acting Muscarinic Antagonists (LAMA), and/or Inhaled Corticosteroids (ICS) are the cornerstones of COPD treatment, along with quitting smoking, engaging in pulmonary rehabilitation, and/or using home oxygen therapy. Patients with COPD must start receiving these treatments right once because they run a higher risk of developing new exacerbations, continuing lung function decline, suffering from lower quality of life, and dying too soon. A LAMA or a LAMA/LABA dual inhaler is recommended as the first-line treatment for COPD by the Global Initiative for Obstructive Lung Disease (GOLD).[2]

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Long-acting inhaled bronchodilators should be used as the first line of maintenance therapy for COPD patients in GOLD Groups A and B, who have fewer symptoms but a low risk of exacerbations, according to the Global Initiative for Chronic Obstructive Lung Disease (GOLD) Global Strategy for Diagnosis, Treatment, and Prevention of COPD. Long-Acting Beta-2 Agonists (LABAs), long-acting muscarinic receptor antagonists (LAMAs), or a combination of the two can be used in this situation. As a maintenance medication, it is advised that patients in GOLD Group C, who have less symptoms but a high risk of exacerbations, receive a fixed dosage of Inhaled Corticosteroid (ICS)/LABA or LAMA. This can help regulate the inflammation brought on by COPD and lower the risk of exacerbations. The severity of the symptoms, the likelihood of exacerbations, and the patient's reaction to medication should all be taken into consideration while developing the COPD treatment plan, it is crucial to remember. Only patients in GOLD Group D, who have the most severe form of COPD, are given the option of receiving LAMA, LABA, and ICS triple therapy. Patients in GOLD Group D have severe or very severe airflow limitation (GOLD Grade 3 or 4) and have two or more exacerbations, or at least one exacerbation, that need hospitalisation per year.[3] Especially among patients with a low risk of exacerbations, there is currently insufficient evidence to prove that triple therapy is preferable to other forms of treatment. Only a certain subgroup of patients should begin triple therapy, according to the GOLD criteria, although doctors may not always follow this advice. However, overprescribing triple therapy can raise the risk of inhaled Actual prescribing practises may differ from the GOLD recommendations, according to empirical evidence? In comparison to non-adherent prescriptions, there were appreciable decreases in the percentages of patients who underwent hospitalizations for any reason, went to the Emergency Department (ED), and had ED visits specifically for respiratory problems.[4] The management of COPD involves the use of dual therapy and triple medication inhaler therapy. However, overprescribing of triple therapy can increase the risk of side effects associated with Inhaled Corticosteroid (ICS) adverse effects such as pneumonia.[5] Additionally, individuals who may have benefited from less expensive mono- or dual-treatment regimens for controlling COPD may face a greater financial burden because of triple therapy.

METHODOLOGY

The review process involved gathering a variety of recently published literature on dual and triple therapy from Google Scholar, PubMed, and EBSCOhost. The majority of the research was conducted in the hospital's pulmonary department. Results from Meta analyses and systematic reviews are also taken into account. It covers the drawbacks as well as the advantages of dual and triple therapy treatments. A total of thirty articles were considered in order to summarise the findings pertaining to dual and triple therapy.

MAIN TEXT

Dual Therapy for Chronic Obstructive Pulmonary Disease

To achieve the best clinical efficacy, physicians have traditionally integrated the treatment of COPD by prescribing different inhalers. Recent studies have shown that this strategy is as effective as administering the same drug with one inhaler.[6] On the other hand, in dual combination therapy, two drugs with different mechanisms of action are usually mixed in one inhaler. Several combination preparations are currently approved for use in his COPD and can be classified into three types:

Combination of beta-agonist and muscarinic antagonist

Short-Acting Beta-Agonists (SABA) and antimuscarinic drugs (SAMA/LAMA) have been used for many years since their combined effect on forced expiratory volume in 1 second was demonstrated have been combined into one inhaler over the years. (FEV1) is greater than the values of the individual components. The approval of various combinations of long-acting inhaled bronchodilators for the treatment of COPD is based on similar criteria. Although it has been difficult to show that these improvements in lung function translate into clinically relevant outcomes such as shortness of breath or changes in exercise capacity, all combinations of long-acting inhaled beta-agonists and Antimuscarinics. There is consistent data showing that it improves spirometry better than either drug alone. According to some studies, combination therapy may prevent mild symptom exacerbations and may have some effect on symptom control. However, more detailed and larger studies are needed to accurately calculate the magnitude of benefit from including additional bronchodilators in a standard treatment regimen.[7] In the most carefully designed study of exacerbations in patients with severe COPD, combination therapy of indacaterol-glycopyrronium (known as QVA) outperformed glycopyrronium and tiotropium in reducing mild exacerbations was also shown to be superior. QVA is superior only to glycopyrronium and not to tiotropium in reducing exacerbations shown by corticosteroids or antibiotic use.[8]

Combination therapy using long acting beta agonists and inhaled corticosteroids

Combination therapy using a Long-Acting Beta-Agonist (LABA) and an Inhaled Corticosteroid (ICS) has been a common method of treating COPD for many years.[9] This combination is superior to its separate components and a placebo in improving lung function, health status, and lowering the risk of exacerbation, according to a number of significant randomized clinical trials. However, due to problems with statistical power and dropouts in some trials, including the TORCH experiment, the evidence regarding lung function decline and mortality is less conclusive.[10]

The twice-daily regimen of Salmeterol and Fluticasone propionate (SFC) compared to once-daily tiotropium had similar benefits on overall exacerbation rates, but the SFC group experienced fewer dropouts and deaths and had better health.[11] The QVA bronchodilator combination significantly improved trough FEV1 in a 6-month study as compared to SFC, although there were no differences in health status. In comparison to either component taken alone, a different once-daily combination of the ICS Fluticasone Furoate (FF) and the LABA vilanterol has shown superior improvements in lung function.[12] In larger FF dosages (100 mcg and 200 mcg), this novel drug is also effective in preventing exacerbations, with a more noticeable effect.

Bronchodilator with PDE-4 inhibitor

Theophylline, a medication with bronchodilator and anti-inflammatory characteristics, is frequently used with inhaled bronchodilators in the treatment of COPD and is taken orally in various regions of the world. Theophylline is clinically useful at conventional or low doses when combined with long-acting inhaled bronchodilators, however, comprehensive data are lacking in this area.[13] The PDE-4 inhibitor roflumilast, on the other hand, has undergone comprehensive research in large numbers of COPD patients who are receiving a variety of background treatments over a lengthy period of time.[14] It has been consistently demonstrated that roflumilast decreases exacerbations in a subset of COPD patients who take standard LABA, and it is possible that this is also true for LAMA combos.[15] Roflumilast appears to work best in individuals, who are most likely to experience exacerbations, and it may also alter the phenotypic of patients who are more likely to experience exacerbations, however, additional evidence is required to support this theory.

The rational use of combined LAMA/LABA therapy in a single inhaler offers an alternative treatment strategy. Very often COPD patients are prescribed her ICS/LABA combination regimen. For some people, it seems safe to stop ICS. Using LAMA and LABA together improves quality of life and reduces the need for follow-up treatment.

Triple Therapy for the Management of Chronic Obstructive Pulmonary Disease

COPD patients who have significant symptoms despite prior treatment with an inhaled glucocorticoid-LABA or LAMA-LABA and who are at increased risk of frequent or severe exacerbations are advised to receive triple inhaled therapy, which consists of an inhaled glucocorticoid, a Long-Acting Muscarinic Antagonist (LAMA), and a long-acting 2-agonist (LABA). Compared to dual therapy, studies have shown triple therapy to have better effects on lung function and COPD symptoms; nevertheless, patients must use many inhalers several times day.[16] In group E patients, triple therapy is advised if the eosinophil level is greater than 300 cells/L.[17]

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Although the UK National Institute of Clinical Excellence (NICE) guidelines recommend triple therapy, which combines a Long-Acting Beta-Agonist (LABA), an Inhaled Corticosteroid (ICS), and a Phosphodiesterase-4 (PDE-4) inhibitor, the evidence for its effectiveness is mixed. In a well-conducted 3-month research, Welte *et al.* found that supplementing tiotropium with budesonide and formoterol resulted in considerably fewer exacerbations and morning symptoms than tiotropium alone.[18] However, there were no differences in exacerbation rates between the groups in a 1-year research comparing tiotropium alone with tiotropium plus salmeterol or tiotropium with the LABA/Inhaled Corticosteroid (ICS) Combination (SFC).[19] However, there were noticeably more hospitalisations and dropouts in those receiving only bronchodilators in these individuals with more severe illness.

In the Understanding Potential Long-Term Impacts on Function with Tiotropium (UPLIFT) study, many participants were receiving both ICS and LABA as background therapy; however, when tiotropium was added to these regimens, the results were superior to those of adding a placebo inhaler in terms of lung function, health status, and the number of exacerbations, providing some tangential evidence in favor of the use of triple therapy.[20]

Nevertheless, even with the use of two or three inhalers, some patients may still experience exacerbations. In the Roflumilast and Exacerbations during Appropriate Combination Therapy (REACT) research, individuals having a history of exacerbations despite these therapies received either roflumilast a PDE-4 inhibitor, or a placebo in addition to dual or triple therapy.[21] The PDE-4 inhibitors decreased both the overall rate of exacerbations and particularly the number of hospitalisations, indicating that combining medications with various mechanisms of action may still be advantageous in severe COPD cases. 4,444 patients with significant impairment in lung function and a history of frequent exacerbations received triple therapy via inhaler and experienced a reduction in mild and severe exacerbations. Compared with treatment with LAMA/LABA, compared with LABA/ICS, the frequency of moderate and severe exacerbations decreased by 15-52% with triple combination therapy. The absolute benefit appears to be greater in phenotypic subgroups with higher eosinophil counts or more frequent exacerbations in exacerbation history, and to some extent in former smokers. This value is reduced for some treatments, such as pneumonia as an SAE decreases in exacerbations are offset by a substantial increase in pneumonia cases.[22]

Apart from increased adherence, the main benefit of utilising a triple inhaler for COPD is that the ICS moiety will lower exacerbations by reducing the eosinophilic component of inflammation, while the LABA/LAMA will lessen symptoms and exacerbations by boosting the bronchodilator`s actions on the smooth muscle of the airway.[23] LAMA may have potential anti-inflammatory effects in addition to reducing mucus hypersecretion by competing with the paracrine-mediated effects of acetylcholine on mucosal inflammatory cell chemotaxis and activation.[23]

When compared to other treatments, single-inhaler triple therapy showed some improvements in lung function and health-related quality of life; however, responder analysis results, which used threshold definitions that reflect minimal clinically important differences, did not show any differences that were statistically significant when compared to LAMA/LABA. This implies that the improvements that were seen may not have been significant clinically.[22]

Open triple therapy

Compared to ICS/LABA or mono LAMA therapy, open triple therapy has been demonstrated to improve lung function, health status, the requirement for rescue medication, and the risk of Acute Exacerbations (AEs). Open triple therapy is defined as the addition of a LAMA to ICS/LABA.[24] Over time, the Fixed-Dose Combination (FDC) of ICS and Long-Acting 2-agonist (LABA) has changed to include Long-Acting Muscarinic Antagonist (LAMA). Observational research has shown that the majority of patients advance to MITT (multiple inhaler triple therapy) because to insufficient symptom improvements after either ICS/LABA combination therapy or LAMA Monotherapy.[25] Studies have shown that MITT is frequently given to COPD patients with a history of AECOPD or those with clinically significant symptoms, particularly in cases with more severe disease. In a previous study in Japanese clinical practise, stable COPD patients increased to inhaled triple therapy in more over half of instances due to inadequate symptom alleviation, regardless of the degree of airway obstruction.[25] Many medications are included in the LABA/ICS combination, including formoterol with budesonide and beclomethasone, which is offered as a Dry Powder Inhaler (DPI) and a Metered-Dose Inhaler (MDI) with 12 hr duration of action. Formoterol/mometasone in MDI form is another medication combination having 12 hr duration of action. Other alternatives include vilanterol/fluticasone furoate, which has 24 hr duration of action, and salmeterol/fluticasone propionate, which has a 12 hr half-life. There are many variations of LAMA inhalers. Both Dry Powder Inhalers (DPI) and Metered Dose Inhalers (MDI) of aclidinium bromide have duration of action of 12 hr. Glycopyrronium bromide, sold as DPI, has duration of action of 12 to 24 hr. Tiotropium has a long duration of action of 24 hr and is available in both DPI and MDI versions. Umeclidinium has a 24 hr duration of action and is also available as a DPI. Last but not least, glycopyrrolate has a half-life of 12 hr.[3]

Closed triple combination therapy

Private triple combination therapy consists of ICS/LABA/LAMA. "Closed triple therapy," also known as BDG/FF/G and FF/VI/UMEC, has been the focus of several studies. Closed triple therapy has been shown to be more effective than LABA/LAMA in reducing exacerbations and improving quality of life. Furthermore, they have been shown to be superior to ICS/LABA in reducing exacerbations and improving lung health, symptoms, and quality of life, particularly in ICS-responsive diseases.[16,26]

Ferguson *et al*. found both once-daily non-obstructive triple therapies with FF/VI/UMEC and twice-daily multiple-inhalation triple therapy with BUD/FOR+TIO have significant effects on lung function, health status, and safety profile.[27] Compared to triple therapy with closed inhalation, triple therapy with open inhalation requires multiple inhalers to be used several times a day. Inhaler treatment regimens can be made easier for COPD patients, increasing adherence and improving health outcomes.[27] The three most often used closed triple-drug regimens are fluticasone/umeclidinium/vilanterol (DPI), beclomethasone/formoterol/glycopyrronium (MDI), and budesonide/formoterol/glycopyrrolate (MDI), all of which have 12 hr durations of action.[3]

According to findings of a post hoc analysis from the GLOW6 study, the free triple combination (glycopyrronium+indacaterol+ICS) significantly improved lung function and dyspnea over the course of 12 weeks in symptomatic patients with moderate-to-severe COPD compared to the free double combination (indacaterol+ICS).[28]

Triple therapy not only demonstrates a promising effect on survival benefit, but also better improves symptoms and lung function while lowering risk of exacerbation and disease progression. According to the available research, triple therapy should be taken into consideration for patients who experience frequent or severe exacerbations, have previously been treated with "open triple" combinations, LABA/ICS, LAMA/LABA, or a single bronchodilator, have a history of asthma, or have blood eosinophil counts below 300 cells/L.

Comparison of Dual and Triple Combination Therapy

People who obtained triple remedy had been 25% much less in all likelihood than people who obtained twin remedy to enjoy moderate-to-excessive COPD exacerbations. Whether triple remedy turned into contrasted with ICS/LABA or LABA/LAMA, the findings held true. The pre-dose FEV1 reaction and large absolute FEV1 changes had been each related to the triple remedy. Triple remedy decreased the SGRQ (St. George Respiratory Questionnaire) rating via way of means of 1. eighty-three gadgets from baseline in evaluation to twin remedy, and greater sufferers noticed a fall of four or greater gadgets. There had been no

discernible variations among triple and twin inhalers in phrases of protection results.[29] For people receiving twin inhaler medicine for recurrent COPD exacerbations, triple remedy is suggested according with contemporary tips.[29]

Contrary to different medications, sufferers who begin on a LAMA appear to have the nice risk of shifting to triple remedy in 24 months, however about one-fourth of people who had been to start with suggested to begin on triple remedy appear to replace to LABA+ICS or LAMA inside that time.[30] The KRONOS trial (Randomised, Double-Blind, Parallel Group, 24 Week, Chronic Dosing, Multi-Center Study to Evaluate the Efficacy and Safety of PT010, PT003 and PT009 Compared With Symbicort® Turbuhaler® as an Active Control in Subjects with Moderate to Very Severe COPD) demonstrated a reduction in moderate-to-excessive COPD exacerbations with LABA's three times greater effectiveness.[31]

The Informing the Pathway of COPD Treatment (IMPACT) trial, a massive multicenter trial evaluating triple inhalers with one of a kind twin inhaler, validated the prevalence of triple remedy whilst in comparison to both twin inhalers, with 15% and 25% discounts in signs and symptoms for ICS/LABA and LAMA/LABA, respectively. Contrary to the FLAME trial, which tested Indacaterol, Glycopyrronium, and Fluticasone for COPD and mentioned decrease exacerbation quotes withinside the LABA/LAMA arm, an immediate evaluation of the ICS/LABA and LABA/LAMA fingers withinside the equal trial discovered drastically fewer COPD exacerbations withinside the ICS/LABA arm.[32] According to the KRONOS and IMPACT investigations, sufferers who obtained or did now no longer acquire ICS at some point of the run-in segment may also have mentioned worse exacerbations withinside the LABA/LAMA organization following ICS withdrawal.[29]

The GOLD tips advocate human beings with the maximum excessive COPD to reflect on consideration on triple remedy. The risk that a affected person will utilise an wrong inhalation method will increase in the event that they use many devices. Additionally, in advance studies have proven that people with COPD who use severe inhalers for remedy adhere to their regimens much less often than people who use an unmarried inhaler. Single-inhaler remedy is less difficult to administer, which may also growth affected person compliance, enhance scientific outcomes, and decrease the want for scientific assets in COPD sufferers. If those blessings are attained without elevating expenses, the economic and aid burden on healthcare can be decreased.[33]

In a real-international placing of scientific practise, it turned into determined that, in comparison to the ones beginning remedy with LAMA and LABA, sufferers with COPD who had currently been prescribed a triple mixture of LAMA, LABA, and ICS had a modest growth in all-reason mortality and excessive exacerbation over the primary year of use.

However, this increase was not seen in subgroups of patients who had previously been diagnosed with asthma, experienced two or more exacerbations in the previous year, or had moderate or severe breathing problems.[34] According to a meta-study analysis by Long *et al*. symptomatic COPD patients may benefit from triple therapy with inhalers in terms of lung function, mortality, and frequency of moderate or severe COPD exacerbations.[33] To ensure optimal control and reduce the side effects of drug therapy, the clinical response and possible side effects after adjusting drug therapy should also be evaluated, and if adverse outcomes (e.g., pneumonia) occur,, ICS must be discontinued immediately.

Safety of Dual and Triple Combination Drugs

Inhaled bronchodilators are typically safe, but they can have predictable side effects that may necessitate changing the course of treatment. Due to a buildup in the mouth and throat, inhaled corticosteroids can have local adverse effects as candidiasis (yeast infection) and dysphonia (voice hoarseness). By employing various inhaler devices, rinsing the mouth after inhalation, or using spacer devices with metered dose inhalers, these can be reduced. However, due to complicating circumstances such concurrent use of oral corticosteroids or the severity of the condition, it is more difficult to link the more severe systemic adverse effects of inhaled corticosteroids to the drug alone. Because severe COPD is linked to an increased risk of osteoporosis, it might be challenging to establish the risk of osteoporosis associated with using inhaled corticosteroids with significant osteoporosis prevalence. Using ICS increases the risk of a lower respiratory tract infection in people with COPD.[35]

An increased incidence of clinically diagnosed pneumonia in COPD patients is one of the more alarming adverse effects of inhaled corticosteroids, which has been seen with both newer and older medications. The reason for why inhaled corticosteroid treatment does not increase overall mortality or pneumonia-related mortality in COPD patients is unknown, despite this connection.[36] Pneumonia risk was higher with ICS/LAMA/LABA FDC compared to LABA/LAMA FDC. It was improbable that the risk of pneumonia would result in a higher risk of death from all causes.[29] The baseline incidence of AECOPD is greater than the baseline incidence of pneumonia, according to Mammen and colleagues. The decrease in the COPD exacerbation rate is anticipated to be more clinically relevant than the increase in the risk of pneumonia with the use of triple therapy as contrasted to dual LABA/LAMA therapy.[37]

On the other hand, PDE-IV inhibitors might have bothersome gastrointestinal side effects such nausea and diarrhoea, as well as headache and sleeplessness, unlike PDE-III blockers, which have serious adverse events like convulsions and ventricular tachycardia. Many times, these adverse effects cause a sizable portion of patients to temporarily stop their therapy. PDE-IV inhibitors can promote weight loss, especially in obese patients,

even if they do not cause serious cardiac issues. When the medicine is stopped, the weight loss usually returns. Better dosing regimens are being investigated in order to potentially lessen these bothersome side effects.[38]

CONCLUSION

Triple therapy of ICS, LABA, and LAMA reduces mortality, improves lung function, and reduces exacerbations of moderate to severe COPD. Pneumonia develops more often. However, taking ICS does not increase the mortality rate from pneumonia. However, triple therapy, but not LABA and LAMA, is superior to the two combinations of LABA and ICS. The combination of LABA and LAMA can also help reduce exacerbations without causing pneumonia. GOLD recommends triple therapy as initial treatment for severe COPD exacerbations.

CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

ABBREVIATIONS

GOLD: Global initiative for chronic Obstructive Lung Disease; **COPD:** Chronic Obstructive Pulmonary Disease; **AE:** Acute Exacerbations; **LABA:** Long-Acting Beta 2 Agonist; **SABA:** Short Acting Beta 2 Agonist; **LAMA:** Long-Acting Muscarinic Antagonist; **SAMA:** Short Acting Muscarinic Antagonists; **ICS:** Inhaled Corticosteroids; **FEV1:** Forced Expiratory Volume; **PDE:** Phospho di esterase; **DPI:** Dry Powder Inhaler; **MDI:** Metered Dose Inhaler; **SGRQ:** St.George Respiratory Questionnaire; **FDC:** Fixed Drug Combination; **BUD:** Budamate; **FF:** Fluticasone Furoate; **G:** Glucopyrronium; **VI:** Vilanterol; **UMEC:** Umeclidinium; **TIO:** Tiotropium.

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