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*EDITORIAL*

# A new FDA approved drug combination for adults with asthma: albuterol and budesonide

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**ABSTRACT**

With a prevalence at around 5.1-8.2%, asthma is considered an important public health problem which decreases the quality of life of an ever-increasing number of patients, as its incidence is on the rise every year. After the recent Global Initiative for Asthma (GINA) guidelines modifications in 2019, there is a growing need of changing the perspective and habits of patients who have lived with asthma for many years, as it has been discovered that using short-acting beta-2 agonists (SABAs) as relievers without simultaneously using inhaled corticosteroids (ICS) is dangerous and could lead to increased mortality if SABAs are overused. In January 2023, FDA has approved the first drug combination of an ICS with a SABA marketed as a reliever therapy, Airsupra (PT027; 90 μg albuterol/80 μg budesonide), which has shown promising results in mild-to-moderate and moderate-to-severe cases of asthma in adult patients (≥18 years-old). Using this fixed-dose combination might decrease the risk of asthma exacerbation through its anti-inflammatory properties, while also relieving acute symptoms of bronchoconstriction and simplifying the patients' therapeutic scheme.

**Keywords**

Asthma, Airsupra, albuterol, budesonide, drug combination, inhaled corticosteroids, SABA.

## Introduction

Asthma is a chronic inflammatory disorder of the airways, which has recently been declared by the World Health Organization (WHO) as one of the major non-communicable diseases worldwide (alongside heart disease, stroke, cancer and diabetes)[1,2]. The prevalence of asthma in the population of the United States of America (USA) was 7.7% in 2021 (24,963,874 adult and pediatric patients with asthma in the USA, 20,288,399 being adults). The highest mortality occurs in adults (3,372 of the 3,517 deaths caused by asthma in the year 2021 in the USA)[3]. Similar numbers were found in Europe, where asthma prevalence in 2023 was 5.1-8.2% (with great differences found between countries: the maximum prevalence was 17.6%, found in the United Kingdom, whereas the minimum number of asthma cases was found in Bosnia: 1.3%). Overall, a global statistic made in 2019 has stated that 262 million people around the world suffered from asthma, causing 455,000 deaths[1].

While talking about asthma treatment, there are 2 important medical terms that need to be understood: the 'reliever' and 'controller' medication. Relievers are used in acute cases of bronchoconstriction in order to treat asthma attacks, as they act quickly and efficiently, while controllers are more useful for the long-term approach of treating asthma because their effects appear more slowly and their aim is chronic prevention of asthma attacks and bronchoconstriction, rather than momentarily 'relieving' the symptoms[4].

Inhaled corticosteroids (ICSs) are the most commonly used controller drugs, because their antiinflammatory effects are important for managing the inflammation present in the bronchial walls of asthma-patients - asthma should be, therefore, considered a chronic inflammatory disease[5]. The daily use of ICS has been associated with a better quality of life, through decreasing the frequency of asthma attacks and serious exacerbations[6]. Alongside ICS, long acting inhaled beta-2 agonists (LABAs) can be used in combination with steroid drugs for alleviating the symptoms of bronchoconstriction, while leukotriene antagonists may be administered orally as a different, less effective (if used alone) approach on the inflammatory cascade present in asthma[4].

Short-acting beta-2 agonists (SABAs) are used as a reliever therapy, or 'rescue' inhalers[7]. Traditionally, asthma patients would use the SABAs as needed to alleviate symptoms, and the first line of treatment included SABAs as a sole drug, without adding ICS from the beginning (ICS were added only if the symptoms would not subside, stepping up the asthma treatment). This has led to the overuse of SABA inhalers, without them having a proper effect on the cause of the symptoms (which is, inherently, inflammation). However, the new Global Initiative for Asthma (GINA) 2019 guidelines have shifted the paradigm of asthma treatment by recommending that the first class of drugs that is to be administered after diagnosing a patient with asthma are corticosteroids, because asthma is an inflammatory disease, and the use of ICS from the beginning of asthma treatment is beneficial for preventing disease progression and the occurrence of asthma attacks. It was also demonstrated that SABAs used alone impose a great risk of exacerbations, allergic responses, inflammation, and the need of frequent oral corticosteroid use, as well as a decrease in lung function, and that hospitalizations and asthma mortality increase when patients use more than 12 canisters of SABA per year[8–10].

Therefore, according to GINA 2019, the current approach for Step 1 treatment in asthma includes either only as-needed low-dose ICS-formoterol, or taking ICS whenever SABA is administered for alleviating symptoms (in combination, or in separate inhalers), while SABA-only treatment (without ICS) is not recommended in any case[11].

**Novel Drug Combination**

On January 11, 2023, the United States Food & Drug Administration (FDA) approved the use of Airsupra (PT027, a combination drug containing albuterol, a SABA, and budesonide, an ICS) inhalation aerosol[12] in adult patients (18 years of age and older) diagnosed with asthma, for both treating and preventing bronchoconstriction. This is the first drug combination containing ICS that was approved as a reliever treatment for asthma, while also being the first ICS-SABA combination approved in the USA[13].

PT027 is a combination of 90 µg albuterol (salbutamol) and 80 µg budesonide, with a recommended dosage of albuterol 180 µg and budesonide 160 µg (administered as 2 actuations), according to the drug dosage and administration, with a maximum of 6 doses (12 inhalations) in a 24-hour period[12]. This drug combines the beneficial anti-inflammatory effects of budesonide (ICS) with the relaxation of smooth muscles found in the bronchial walls, for which albuterol is responsible, in order to alleviate the acute symptoms of bronchoconstriction and bronchial hyper-reactivity, while also preventing severe asthma attacks (defined as: asthma symptoms requiring systemic corticosteroids administration for at least 3 days / an emergency room visit that led to the use of systemic corticosteroids for at least 3 days / hospitalization for at least 24 hours due to asthma)[13].

According to the full prescribing information, PT027 is only contraindicated in cases of hypersensitivity to one of its components (albuterol, budesonide or any of the excipients). Patients should also be warned that this combination can rarely produce life-threatening paradoxical bronchospasm, hypokalemia, cardiovascular effects, oropharyngeal candidiasis, hypercorticism and adrenal suppression, reduction in bone mineral density, glaucoma and cataracts. However, these are the classic adverse reactions of beta-2 agonists and corticosteroids,

which can appear in any drug schemes administered to asthma patients – the combination does not seem to have any new or specific adverse effects associated with this particular drug combination[12]. This product should be used with caution by patients with a history of cardiovascular diseases, epilepsy (in treatment with anticonvulsant drugs), hyperthyroidism, diabetes mellitus, ketoacidosis[13].

Two clinical trials have been conducted in order to certify the safety of PT027: MANDALA[14] and DENALI[15].

The MANDALA study is a randomized, double-blind, multicenter, parallel-group, variable-length study which included 3132 adults, adolescents, and children (aged 4–11 years) with moderate-to-severe asthma[10] sorted in 3 groups of patients (1st group: 1016 patients who received budesonide/albuterol sulfate, BDA MDI, PT027 high dose - 160/180 μg - 'the PT027 group'; 2nd group: 1057 patients who received budesonide/albuterol sulfate, BDA MDI, PT027 low dose - 80/180 μg; 3rd group: 1059 patients who received albuterol sulfate MDI, PT007 - 180 μg)[14]. In the first group (comprising patients who received the albuterol and budesonide drug combination), compared to the third one (receiving only albuterol), the incidence of severe asthma attacks was reduced with 27%[10].

The DENALI study is a randomized, double-blind, placebo-controlled, multicenter, parallel group study which included 1,001 patients, aged ≥ 12 years, with mild-to-moderate asthma sorted in 5 equal groups of patients (1:1:1:1:1 to four-times-daily albuterol-budesonide 180/160 μg or 180/80 μg, albuterol 180 μg, budesonide 160 μg, or placebo for 12 weeks)[15,16]. This study was conducted according to the FDA rule of combination products, in order to verify the contribution of both of the components to the efficacy of the final product[16]. The results concluded that both budesonide and albuterol contributed to an increased forced expiratory volume in one second (FEV1) in asthma patients and a statistically significant improvement of lung function[10].

## Conclusion

In conclusion, after the new GINA regulations from 2019, it is important that both medical practitioners and asthma patients are familiar with the modified dogma regarding the treatment of asthma. The physicians should thoroughly explain to their patients suffering from asthma that it is not beneficial and safe to use SABAs in the absence of ICSs, and they should change the therapeutic scheme together accordingly. In this regard, AstraZeneca comes up with PT027, which combines albuterol (SABA) with formoterol (ICS) into one product meant for both relieving acute symptoms of asthma and managing the inflammatory component in the etiology of this complex disease, while also preventing exacerbations.

## Conflict of Interest

The authors declare no conflict of interest.

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