Albuterol/Budesonide (AIRSUPRA) Inhaler
National Drug Monograph
March 2024
VA Pharmacy Benefits Management Services and National Formulary Committee

The purpose of VA PBM Services drug monographs is to provide a focused drug review for making formulary decisions. Updates will be made if new clinical data warrant additional formulary discussion. The Product Information or other resources should be consulted for detailed and most current drug information.

FDA Approval Information

Description/Mechanism of Action

- Fixed-dose combination of albuterol, a short-acting beta2-adrenergic agonist (SABA) and budesonide, an inhaled corticosteroid (ICS).

Indication(s) Under Review in This Document

- Indicated for the as-needed treatment or prevention of bronchoconstriction and to reduce the risk of exacerbations in patients with asthma 18 years of age and older

Dosage Form(s) Under Review

- Inhalation aerosol: Pressurized metered dose inhaler that delivers a combination of albuterol 90 mcg and budesonide 80 mcg per actuation. There are 120 actuations per canister.
- Recommended Dosage: 180 mcg/160 mcg (administered as 2 actuations of albuterol/budesonide 90 mcg/80 mcg) by oral inhalation as needed for asthma symptoms.
- Do not take more than 6 doses (12 inhalations) in a 24-hour period.

Clinical Evidence Summary

Efficacy Considerations

MANDALA is a randomized, double-blind, event driven trial (minimum duration of 24 weeks continued until at least 570 first events of severe exacerbations) that evaluated the efficacy of fixed-dose combination albuterol/budesonide in patients with uncontrolled moderate-to-severe asthma.

The trial included a dose that is not marketed, and a small percentage of patients aged 12-17 years (5.3%) for whom the drug is not approved for use. Therefore, only the marketed strength and data for adults are discussed in the efficacy section, unless otherwise indicated.

Patients were randomized to albuterol/budesonide 180mcg/160mcg (2 actuations of 90mcg/80mcg) or albuterol 180mcg (2 actuations of 90mcg) as-needed for symptoms or before exercise. Patients continued to receive their maintenance therapies. Changes to maintenance therapies were discouraged unless clinically indicated. The maximum daily dose of study drug was 12 inhalations (6 doses).

Key inclusion criteria: ≥1 severe asthma exacerbation in the previous 12 months; FEV1 40% to <90% of predicted normal; FEV1 reversibility of at least 12% to albuterol; ACQ-5 ≥1.5; medium-high dose ICS or low-high dose ICS/LABA for at least 3 months +/- other controller agents

Key Exclusions: COPD or other notable lung disease; use of systemic steroids within 3 months of screening; use of biologic drugs within 3 months or for a duration of 5 half-lives before screening

The primary efficacy endpoint was the time to first severe asthma exacerbation defined as worsening or onset of asthma symptoms that required systemic corticosteroids for at least 3 days or an emergency room visit that led to the use of systemic corticosteroids for at least 3 days or a hospitalization for at least 24 hours due to asthma.

Demographic/baseline information of adult population: mean age of 52 years, 34% male, 82% Caucasian, 25% of Hispanic or Latino ethnicity, median duration of asthma 21 years, mean prebronchodilator percent predicted FEV1 63%. In the entire population (all ages), baseline medications included 30% low-dose ICS/LABA or medium dose ICS, 40% medium-dose ICS/LABA or high-dose ICS, and 28% high-dose ICS/LABA. Number of severe exacerbations in the prior 12 months were 1 (79%), 2 (17%), 3 (3%), ≥4 (1%), ACQ-5 score 2.6.

In the time-to-event analysis comparing albuterol 180mcg/budesonide 160mcg and albuterol alone, the risk of severe asthma exacerbation in adults was reduced by 28% (Hazard Ratio 0.72; 95% CI: 0.60, 0.86; p<0.001). Other efficacy data are summarized in table 1.

Table 1: Efficacy results from MANDALA in those Ages 18 or Older

	Albuterol 180mcg/ Budesonide 160mcg (n=979)	Albuterol 180mcg (n=980)
Number of severe exacerbations	324	403
Annualized rate of severe exacerbations	0.46	0.60
	Rate ratio 0.76 (0.62, 0.93); p=0.008	
ACQ-5 responders	67%	63%
AQLQ+12 responders	52%	47%
Annualized systemic corticosteroid dose (mg)	87	127
% of days with </= 2 inhalations	53.7	51
Mean inhalations/day	2.6	2.8
Mean doses/day	1.3	1.4

ACQ5-responders defined as improvement of 0.5 or more in overall ACQ-5 score at Week 24 compared to baseline.
AQLQ+12 responders defined as improvement of 0.5 or more in AQLQ score at Week 24 compared to baseline

Lung function was evaluated in the 12-week DENALI trial in patients with mild to moderate asthma who were previously treated with as-needed SABA alone or with low-dose ICS plus as-needed SABA. Results for adults and the FDA-approved dose are shown in table 2. This study was conducted to fulfill FDA requirements which requires a combination product to demonstrate that each component contributes to its safety or efficacy. Although albuterol/budesonide is intended to be used on an as-needed basis, the required study design was for all treatments to be administered as four times daily. At baseline, approximately 47% were using an ICS and mean pre-bronchodilator FEV1 was 69% predicted.

Table 2: Lung Function (DENALI)

	Albuterol/budesonide 180/160 N=193	Albuterol 180 N=196	Budesonide 160 N=194	Placebo N=192
FEV1 AUC0-6h, change from baseline over 12 weeks (mL)	258.6	152.7	178	96.7
Trough FEV1, change from baseline at Week 12 (mL)	135.5	2.7	108.9	35.6
Median time to onset of bronchodilation (min)	7.5	9.5	Not shown	Not shown
Median duration of bronchodilation (min)	186.9	168.2	Not shown	Not shown
≥ 15% increase in FEV1 post-dose within 30min (Day 1)	49.7	42.9	13.6	13.3

A small cross-over trial in patients with asthma and exercise-induced asthma (n=31) compared a single dose of albuterol/budesonide 180/160mcg versus placebo taken approximately 30 minutes before exercise. The maximum percentage fall in FEV1 up to 60 minutes post-exercise was 5.5% and 19% in subjects treated with albuterol/budesonide and placebo respectively. More subjects receiving albuterol/budesonide were fully protected (defined as maximum percentage fall in FEV1 post-exercise challenge < 10%) then those receiving placebo (78% vs. 28%). A study comparing albuterol/budesonide to albuterol alone is needed.

Safety Considerations

Safety Results from Clinical Trials:

- Adverse reactions shown in the product labeling are shown in Table 2. Nasopharyngitis was also reported in the trial publication (7.5% for albuterol/budesonide and 5.1% for albuterol).

Table 2: Adverse Reactions from MANDALA Trial in >/= 1% of Patients

Study	Albuterol 180mcg/ Budesonide 160mcg	Albuterol 180mcg
Headache (%)	4.3	4.9
Oral candidiasis (%)	1.3	0.5
Cough (%)	1.0	1.1

Data from product package insert in overall population (all age groups)

- **Boxed warnings:** None
- **Contraindications:** Hypersensitivity to albuterol, budesonide, or to any of the excipients
- **Other warnings/precautions:** Shares the same general warnings and precautions as the individual components. Additional warnings/precautions include
  - If symptoms continue after using albuterol/budesonide, this may be a marker of destabilization of asthma and requires reevaluation of treatment.
  - Excessive use may be fatal.
  - Do not exceed maximum recommended dosage.
- **Adverse reactions**
  - **Common** Most common adverse reactions (incidence ≥ 1%) are headache, oral candidiasis, cough, dysphonia
  - **Serious Adverse events:** 5.2% vs. 4.5%
  - **Deaths:**
    - **Albuterol/Budesonide 180mcg/160mcg:** 4 (0.4%)- 2 from COVID, 1 elevated glucose, 1 cardiac arrest

- **Albuterol 189mcg:** 1 (0.1%) COVID

None of the deaths were considered to be drug-related according to the study investigators.

- **Discontinuations due to adverse events:** 1% vs. 0.9%

Other Considerations

- Potential for misuse as maintenance therapy
- Potential for error or confusion in patients who are familiar with using ICS or ICS/LABA for maintenance and albuterol as needed for symptoms
- Potential for misuse in patients with COPD
- guidelines position the use of ICS/SABA (either in fixed combination or separately one after the other) as a treatment option

Other Therapeutic Options

- **Formulary:** Albuterol as needed
- **Formulary:** Albuterol and mometasone or ciclesonide one after the other as needed- this option could be potentially confusing for many patients and would be reserved for those who clearly understand how to use.
- **Non-formulary:** Budesonide/formoterol single maintenance and as-needed therapy (SMART). See Appendix

Projected Place in Therapy

National and international guidelines position the use of ICS/SABA (either in fixed combination or separately one after the other) as a treatment option (see Appendix).

In the MANDALA trial, albuterol/budesonide was studied as reliever therapy in patients with uncontrolled moderate-to-severe asthma who have had at least 1 severe asthma exacerbation in the preceding 12 months. The use of as-needed albuterol/budesonide should be reserved as an option for uncontrolled patients with asthma while receiving optimized therapy.

REFERENCES:

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LaForce C, Chipps BE, Albers FC, Reilly L,et al. Albuterol/budesonide for the treatment of exercise-induced bronchoconstriction in patients with asthma: The TYREE study. Ann Allergy Asthma Immunol. 2022 Feb;128(2):169-177. doi: 10.1016/j.anai.2021.10.020.

AIRSUPRA (albuterol and budesonide) inhalation aerosol. Wilmington, DE: AstraZeneca Pharmaceuticals LP. January 2023 Available at: label (fda.gov)

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Appendix A. GINA and NAEPP Asthma Guidelines

Global Initiative for Asthma (GINA) 2023

- Step 1 ICS/formoterol prn OR ICS/SABA prn (either fixed-dose-combination or separately one after the other)
- Step 2 ICS/formoterol prn OR low-dose ICS + (SABA prn or ICS/SABA prn)
- Step 3 low-dose ICS/formoterol + ICS/formoterol prn OR low-dose ICS/LABA + (SABA prn or ICS/SABA prn)
- Step 4 medium dose ICS/formoterol + ICS/formoterol prn OR medium-high dose ICS/LABA + (SABA prn or ICS/SABA prn)

National Asthma Education and Prevention Program (NAEPP) 2020 Asthma Management Guidelines

- Step 1 (intermittent asthma) SABA prn
- Step 2 (mild persistent) low-dose ICS + SABA prn OR concomitant ICS/SABA prn
- Step 3 (moderate persistent) low-dose ICS/formoterol + ICS/formoterol prn (preferred) OR medium dose ICS + SABA prn (alternate)
- Step 4 (moderate persistent) medium-dose ICS/formoterol + ICS/formoterol prn (preferred) or medium-dose ICS/LABA + SABA prn (alternate)

Note: for ICS/formoterol only budesonide/formoterol has been studied