INDIAN HEALTH SERVICE
National Pharmacy and Therapeutics Committee
Formulary Brief: ***Budesonide/formoterol for asthma***
-April/May 2024-

Background:
In May 2024, the Indian Health Service (IHS) National Pharmacy and Therapeutics Committee (NPTC) reviewed budesonide/formoterol for asthma management. The NPTC last reviewed long-acting beta agonists (LABAs) and inhaled corticosteroids (ICS) in 2019. Fluticasone/salmeterol was added to the National Core Formulary (NCF) in May 2019, replacing mometasone/formoterol. Medications on the NCF relevant for use in asthma include fluticasone/salmeterol, mometasone, and tiotropium. Following the clinical review, the NPTC voted to **ADD budesonide/formoterol** to the NCF.

Discussion:
Asthma is a chronic lung disease characterized by bronchial tube contraction and airway inflammation.[1] Historically, inhaled short-acting beta agonists (SABAs) were first-line treatments; however, regular use can lead to reduced effectiveness and worse outcomes. Using ≥3 SABA canisters annually is associated with a higher risk of exacerbations, whereas using ≥12 canisters annually is associated with increased mortality risk.[2]

The Global Initiative for Asthma (GINA) guidelines no longer recommend as-needed SABA-only treatment but recommend an anti-inflammatory reliever (AIR) strategy, incorporating an ICS whenever a beta-2 agonist is used for asthma symptoms.[2,3] The Single and Maintenance Reliever Therapy (SMART) strategy utilizes ICS-formoterol for daily maintenance and as-needed treatment. The SMART approach using budesonide/formoterol is not yet FDA-approved and is not reflected in the package insert (which currently states "not indicated for the relief of acute bronchospasm").[4]

=Guidelines=
The 2023 GINA guidelines recommend as-needed, low dose ICS-formoterol as the preferred treatment for Steps 1 and 2, with SMART recommended for Step 3 (low dose ICS-formoterol) and Step 4 (medium dose ICS-formoterol) for patients aged 12 years and older.[2] For children aged 6 to 11 years, SMART is the preferred treatment at Step 3 (very low dose ICS-formoterol) and Step 4 (low dose ICS-formoterol).[2]

Age Group	Budesonide/ formoterol dose	Step 1	Step 2	Step 3	Step 4	Max total daily inhalations
≥12 years	160/4.5 mcg	1 puff as-needed		1 puff once or twice daily PLUS 1 puff as-needed	2 puffs twice daily PLUS 1 puff as-needed	12
6 to 11 years	80/4.5 mcg			1 puff once daily PLUS 1 puff as-needed	1 puff twice daily PLUS 1 puff as-needed	8

**Chart adapted from 2023 GINA guidelines*

The 2020 National Asthma Education and Prevention (NAEPP) guidelines recommend as-needed SABA as the preferred treatment for Step 1 and daily low dose ICS and as-needed SABA for Step 2.[5] SMART is the preferred treatment in patients ≥4 years for Step 3 (low dose ICS-formoterol) and Step 4 (medium dose ICS-formoterol). The maximum number of budesonide/formoterol inhalations per day is 12 for patients aged 12 and older and 8 for children aged 4 to 11 years.[5]

The National Institute for Health and Care Excellence (NICE) guidelines recommend offering low or moderate dose maintenance and reliever therapy (MART) with an ICS and a fast-acting LABA (e.g., formoterol) in patients aged 5 years and older with uncontrolled asthma.[6]

=Clinical Studies=
The SYGMA 1 and 2 studies were 52-week, double-blind, randomized controlled trials (RCTs), which included patients 12 years and older with mild asthma (GINA Step 2).[7,8] In the SYGMA 1 trial, as-needed budesonide/formoterol was superior to as-needed terbutaline for mean percentage of weeks with well controlled asthma (OR 1.14; 95% CI: 1.0-1.3; p=0.046) and reduced severe exacerbations by 64% (RR=0.36; 95% CI: 0.27-0.49; p<0.001).[7] However, as-needed budesonide/formoterol was inferior to maintenance budesonide twice daily for mean percentage of weeks with well controlled asthma (OR 0.64; 95% CI: 0.57-0.73; no p-value) and had no significant differences in severe exacerbation rates (RR=0.83; 95% CI: 0.59-1.16; p=0.28). In the SYGMA 2 trial, as-needed budesonide/formoterol was non-inferior to low-dose budesonide maintenance treatment with an annualized rate of severe exacerbations (RR=0.97; one-sided 95% upper confident limit, 1.16) and showed no difference in time to first severe exacerbation (HR=0.96; 95% CI: 0.78-1.17;

p=0.66).[8] The authors noted that the as-needed budesonide/formoterol group utilized lower median daily ICS doses compared to the maintenance budesonide group (66 mcg vs. 267 mcg).[8]

A 2011 Cochrane review compared fluticasone/salmeterol to budesonide/formoterol in patients aged 12 years and older with chronic asthma.[6] The review found no significant differences in asthma exacerbations requiring oral steroids (OR 0.89; 95% CI: 0.74-1.07; *p*=0.22), hospital admissions due to asthma exacerbations (OR 1.29; 95% CI: 0.68-2.47; *p*=0.43), asthma-related serious adverse events (OR 1.47; 95% CI: 0.75-2.86; *p*=0.26), and general adverse event rates (OR 1.00; 95% CI: 0.88-1.15; *p*=0.98). *Additionally*, a 2021 Cochrane review found no significant differences in all-cause mortality (OR 1.03; 95% CI: 0.06-16.44; *p*=0.98), all-cause non-fatal serious adverse events (OR 1.14; 95% CI: 0.82-1.59; *p*=0.43), and asthma-related non-fatal serious adverse events (OR 0.69; 95% CI: 0.37-1.26; *p*=0.23) between the two ICS/LABAs.[10]

A 2022 meta-analysis and systematic review of five RCTs evaluated whether switching to SMART with budesonide/formoterol from maintenance standard therapy (ICS/LABA plus as-needed SABA) in patients with poorly controlled asthma was associated with improved clinical outcomes.[11] A 29% decrease in exacerbation risk was seen in patients who were switched to SMART at either Steps 3 or 4 compared to Step 4 maintenance standard therapy doses (HR=0.71; 95% CI, 0.52-0.97; *p*=0.03). Similarly, a 30% decrease in exacerbation risk was seen when patients were switched to SMART at the same or lower treatment step versus those remaining on their existing maintenance standard therapy doses (HR=0.70; 95% CI: 0.58-0.85; *p*<0.001).[11]

Findings:

The addition of budesonide/formoterol to the NCF is supported by current asthma guidelines for managing both chronic and acute symptoms in patients with moderate to severe asthma. When used as an as-needed reliever, budesonide/formoterol has been shown to reduce exacerbations compared to SABA-only therapy and has comparable safety and efficacy to fluticasone/salmeterol when used as maintenance therapy.

The following outlines several key clinical pearls to aid in implementing budesonide/formoterol as SMART:

- Providers should inform patients of updates to asthma guidelines and highlight the differences in the package insert. A SMART asthma action plan[12] can facilitate shared decision making.
- For as-needed doses of budesonide/formoterol, one inhalation per dose is recommended.[13] An extra dose can be taken a few minutes later and additional doses can be taken when symptoms recur within 4 hours of last use.[2]
- Patients currently on fluticasone/salmeterol should not use budesonide/formoterol as an as-needed reliever. Additionally, fluticasone/salmeterol cannot be used for SMART due to the salmeterol's slower onset of action.[13]

If you have any questions regarding this document, please contact the NPTC at IHSNPTC1@ihs.gov. For more information about the NPTC, please visit the NPTC website.

References:

1. Fanta CH, Carter EL, Stieb ES. The asthma educator's handbook. New York: McGraw-Hill Medical; 2007.
2. Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2023. Updated July 2023.
3. Zaeh SE, Eakin MN, Chupp G. Implementing antiinflammatory reliever strategies in asthma. *CHEST*. 2024 Feb;165(2):250–2.
4. Breyna™ [package insert]. Morgantown, WV: Mylan Pharmaceuticals Inc.; 2020.
5. Cloutier MM, Baptist AP, Blake KV, et al. 2020 focused updates to the Asthma Management Guidelines: A report from the National Asthma Education and Prevention Program Coordinating Committee Expert Panel Working Group. *J Allergy Clin Immunol*. 2020 Dec;146(6):1217–70.
6. National Institute for Health and Care Excellence (2017). Asthma: diagnosis, monitoring and chronic asthma management. NICE guideline NG80. Last updated 2021.
7. O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. *N Engl J Med*. 2018 May 17;378(20):1865-1876.
8. Bateman ED, Reddel HK, O'Byrne PM, et al. As-Needed Budesonide-Formoterol versus Maintenance Budesonide in Mild Asthma. *N Engl J Med*. 2018 May 17;378(20):1877-1887.
9. Lasserson TJ, Ferrara G, Casali L. Combination fluticasone and salmeterol versus fixed dose combination budesonide and formoterol for chronic asthma in adults and children. Cochrane Database Syst Rev. 2011 Dec 7;(12):CD004106.
10. O'Shea O, Stovold E, Cates CJ. Regular treatment with formoterol and an inhaled corticosteroid versus regular treatment with salmeterol and an inhaled corticosteroid for chronic asthma: serious adverse events. Cochrane Database Syst Rev. 2021 Apr 14;4(4):CD007694.
11. Beasley R, Harrison T, Peterson S, et al. Evaluation of Budesonide-Formoterol for Maintenance and Reliever Therapy Among Patients With Poorly Controlled Asthma: A Systematic Review and Meta-analysis. *JAMA Netw Open*. 2022 Mar 1;5(3):e220615.
12. Allergy & Asthma Network. SMART asthma action plan [Internet]. [Fairfax (VA)]:; c2024. [2022 Dec, cited 2024 May 1].
13. Reddel HK, Bateman ED, Schatz M, et al. A Practical Guide to Implementing SMART in Asthma Management. *J Allergy Clin Immunol Pract*. 2022 Jan;10(1S):S31-S38.