

## GINA 2021 Executive summary. Online supplement

### Supplementary information

#### *Global Initiative for Asthma (GINA) Strategy 2021 – Executive Summary and Rationale for Key Changes*

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**Table E1. Diagnostic criteria for asthma in adults, adolescents, and children 6–11 years**

<b>1. History of variable respiratory symptoms</b>	
<b>Feature</b>	<b>Symptoms/features that support the diagnosis of asthma</b>
Wheeze, shortness of breath, chest tightness and cough (descriptors may vary between cultures and by age group)	<p>More than one type of respiratory symptom. In adults, isolated cough is seldom due to asthma.</p> <p>Symptoms occur variably over time and vary in intensity</p> <p>Symptoms often worse at night or on waking</p> <p>Symptoms often triggered by exercise, laughter, allergens, cold air</p> <p>Symptoms often appear or worsen with viral respiratory infections</p>
<b>2. Confirmed variable expiratory airflow limitation</b>	
<b>Feature</b>	<b>Considerations, definitions, criteria</b>
<b>2.1 Documented* expiratory airflow limitation</b>	At a time when FEV <sub>1</sub> is reduced, confirm that FEV <sub>1</sub> /FVC is reduced compared with the lower limit of normal (usually >0.75–0.80 in adults, >0.90 in children).
<b>AND</b>	
<b>2.2 Documented* excessive variability in lung function (one or more of the following):</b>	The greater the variations, or the more occasions excess variation is seen, the more confident the diagnosis. If initially negative, tests can be repeated during symptoms or in the early morning.
Positive bronchodilator (BD) responsiveness test (reversibility)*	<p><b>Adults:</b> increase in FEV<sub>1</sub> &gt;12% and &gt;200 ml (greater confidence if increase &gt;15% and &gt;400 ml)</p> <p><b>Children:</b> increase in FEV<sub>1</sub> &gt;12% predicted</p> <p>Measure change 10–15 minutes after 200–400 mcg albuterol or equivalent, compared with pre-BD readings. Positive test more likely if BD withheld before test: withhold SABA for ≥4 hours, twice-daily LABA 24 hours, once-daily LABA 36 hours.</p>
Excessive variability in twice-daily PEF <sup>§</sup> over 2 weeks	<p><b>Adults:</b> average daily diurnal PEF variability &gt;10%<sup>‡</sup></p> <p><b>Children:</b> average daily diurnal PEF variability &gt;13%<sup>‡</sup></p>
Significant increase in lung function after 4 weeks of anti-inflammatory treatment	<b>Adults:</b> increase in FEV <sub>1</sub> by >12% and >200 ml (or PEF <sup>§</sup> by >20%) from baseline after 4 weeks of treatment, outside respiratory infections
Positive exercise challenge test	<p><b>Adults:</b> fall in FEV<sub>1</sub> of &gt;10% and &gt;200 ml from baseline</p> <p><b>Children:</b> fall in FEV<sub>1</sub> of &gt;12% predicted, or PEF &gt;15%</p>
Positive bronchial challenge test (usually only for adults)	Fall in FEV <sub>1</sub> from baseline of ≥20% with standard doses of methacholine, or ≥15% with standardized hyperventilation, hypertonic saline or mannitol challenge
Excessive variation in lung function between visits (good specificity but poor sensitivity)	<p><b>Adults:</b> variation in FEV<sub>1</sub> of &gt;12% and &gt;200 ml between visits, outside of respiratory infections</p> <p><b>Children:</b> variation in FEV<sub>1</sub> of &gt;12% in FEV<sub>1</sub> or &gt;15% in PEF<sup>§</sup> between visits (may include respiratory infections)</p>

Source: Box 1-2 in Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention, 2021 [cited September 2021]. 2021. Available from: [www.ginasthma.org](http://www.ginasthma.org).

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BD: bronchodilator (SABA or rapid-acting LABA such as ICS-formoterol); FEV<sub>1</sub>: forced expiratory volume in 1 second; ICS: inhaled corticosteroid; LABA: long-acting beta<sub>2</sub>-agonist; PEF: peak expiratory flow (highest of three readings); SABA: short-acting beta<sub>2</sub>-agonist.

\* If possible, confirm the diagnosis before starting controller treatment.

† BD responsiveness may be lost after starting ICS treatment, during severe exacerbations or viral respiratory infections, or if airflow limitation has become persistent over time. If responsiveness is not present at initial presentation, the next step depends on the availability of other tests and the urgency of the need for treatment. For patients already on controller treatment, see GINA 2021, Box 1-3.

‡ Daily diurnal PEF variability is calculated from twice daily PEF as (day's highest minus day's lowest) divided by (mean of day's highest and lowest), averaged over one week.

§ Use the same peak flow meter each time, as PEF may vary by up to 20% between different meters.

Table E2. Summary of medications and dosages for asthma treatment regimens containing anti-inflammatory reliever

	Anti-inflammatory reliever (AIR) therapy alone GINA Steps 1–2	Maintenance and reliever therapy (MART) GINA Steps 3, 4 and 5	
Definition	Combination ICS-formoterol taken as needed for symptom relief†, without maintenance therapy <i>or, if not available, low-dose ICS taken whenever SABA is taken for symptom relief</i>	Daily maintenance ICS-formoterol PLUS Low-dose ICS-formoterol taken as needed for symptom relief†	
Indications	Mild asthma: GINA Steps 1–2	Moderate-to-severe asthma: GINA Steps 3, 4 and 5	
Explanation	Whenever symptom relief is needed, the patient takes an inhaler containing a combination of a low dose of ICS and formoterol (instead of a SABA), without daily maintenance treatment  <i>or, if ICS-formoterol is not available, they take a low dose of ICS whenever SABA is taken</i>	The patient takes <b>regular daily maintenance</b> controller treatment with low-dose (Step 3) or medium dose (Step 4) combination ICS-formoterol <b>PLUS</b> whenever needed for symptom relief, the patient uses an inhaler containing a combination of a low dose of ICS and formoterol (instead of a SABA)	
MEDICATIONS AND SUGGESTED DOSAGES BY AGE-GROUP			
Anti-inflammatory reliever therapy AIR alone: GINA Steps 1–2		MAINTENANCE AND RELIEVER THERAPY (MART): GINA STEP 3	MAINTENANCE AND RELIEVER THERAPY (MART): GINA STEPS 4–5
Budesonide-formoterol			
Adults and adolescents ≥12 years	Budesonide-formoterol 200/6 mcg [160/4.5 delivered dose), 1 inhalation as needed for symptom relief.	Budesonide-formoterol 200/6 mcg [160/4.5 delivered dose]: 1 inhalation twice daily (or once daily) as <b>maintenance</b> treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief.	Budesonide-formoterol 200/6 mcg [160/4.5 delivered dose]: 2 inhalations twice daily as <b>maintenance</b> treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief
	If symptom persist after a few minutes, another inhalation of ICS-formoterol can be taken. No more than 6 inhalations should be taken on a single occasion. A maximum total of 12 doses (reliever doses plus maintenance doses, if used) can be taken temporarily in a single day; if more is needed, medical attention should be sought the same day.		
Children 4–11 years	<i>[ICS-formoterol not studied]</i>	Budesonide-formoterol 100/6 mcg [80/4.5 delivered dose]: 1 inhalation once daily as <b>maintenance</b> treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief.	Suggested dose: budesonide-formoterol 100/6 mcg [80/4.5 delivered dose]: 1 inhalation twice daily as <b>maintenance</b> treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief.
		If symptom persist after a few minutes, another inhalation can be taken. For children, no more than 4 inhalations should be taken on a single occasion. A maximum total of 8 doses (reliever doses plus maintenance doses) can be taken temporarily in a single day; if more is needed, medical attention should be sought the same day.	
Beclometasone dipropionate-formoterol (BDP-formoterol)			
Beclometasone-formoterol – adults ≥18 years (not studied in children or adolescents)	<i>[BDP-formoterol not studied]</i>	BDP-formoterol 100/6 mcg [87.5/5 mcg delivered dose]: 1 inhalation twice daily (or once daily) as <b>maintenance</b> treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief.  If symptoms persist, another inhalation can be taken. No more than 6 doses should be taken on a single occasion. A maximum total of 8 doses (reliever doses plus maintenance doses) can be taken temporarily in a single day; if more is needed, medical attention should be sought the same day.	<i>[BDP-formoterol not studied]</i>
Beclometasone dipropionate-albuterol (BDP+SABA)			
Adults ≥18 years, adolescents 12–17 years and children 6–11 years	Beclometasone 50 mcg and albuterol 100 mcg [40 mcg and 90 mcg delivered dose, respectively] 2 inhalations of each separate inhaler (or 2 inhalations of combination inhaler) as needed for symptom relief. Currently there is no different recommendation for maximum daily use compared with albuterol alone (12 puffs).	<i>[ICS-SABA not studied]</i>	<i>[ICS-SABA not studied]</i>

AIR: anti-inflammatory reliever; BDP: beclometasone dipropionate; ICS: inhaled corticosteroid; MART: maintenance and reliever therapy with ICS-formoterol (also called SMART); SABA: short-acting beta2-agonist

ICS-formoterol contains an inhaled corticosteroid (e.g., budesonide or beclometasone) and formoterol, a rapid-onset long-acting beta2-agonist.

- **Budesonide-formoterol** is approved for adults and adolescents ≥12 years in many countries for use in as-needed-only ICS-formoterol therapy and MART, and in some countries for MART in children 4–11 years. For budesonide-formoterol, the maximum total number of inhalations that can be taken temporarily in any single day (reliever plus maintenance inhalations, if used) is based on the total dose of formoterol in any day. (72 mcg of formoterol [54 mcg delivered dose] for adults and adolescents, 48 mcg [36 mcg delivered dose] for children 4–11 years)
- Most of the studies with budesonide-formoterol as reliever used a dry powder inhaler, but budesonide-formoterol pressurized metered dose inhaler 200/6 mcg [160/4.5 delivered dose] was used in one Step 4 MART study, also with 1 inhalation per as-needed dose (E1).
- **Beclometasone-formoterol** is approved for MART in adults 18 years and older in many countries. A maximum total of 8 inhalations (total of reliever inhalations and maintenance inhalations) can be taken temporarily in a single day.

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- **Other ICS-formoterol formulations** (e.g., mometasone-formoterol, fluticasone-formoterol) have not been studied with either as-needed-only anti-inflammatory reliever (AIR) therapy or MART, but may be able to be substituted if budesonide-formoterol or beclometasone-formoterol are not available. Some ICS-formoterol devices are currently approved only for adults 18 years and older.

Before prescribing any inhaler, ensure that the patient can use it correctly.

The above recommended maximum doses refer to the maximum total dose that can be taken temporarily on any single day. If a patient needs to take more, they should seek medical care the same day. In clinical trials of as-needed-only anti-inflammatory reliever therapy in mild asthma, average use of as-needed low dose budesonide-formoterol was 3–4 inhalations per week, and <0.1% of patients took >8 inhalations of budesonide-formoterol on more than 1 day during the 12-month studies (E2, E3).

For all patients prescribed as-needed only Anti-Inflammatory Reliever (AIR) therapy alone or Maintenance And Reliever Therapy (MART), the *average* frequency of as-needed use of ICS-formoterol in the previous 4 weeks should be reviewed at each visit as part of the assessment of their treatment needs.

Combinations of ICS with non-formoterol long-acting beta<sub>2</sub>-agonists (LABA), or combinations of ICS, LABA and long-acting muscarinic antagonists (LAMA), should not be used as-needed. These medications are recommended only for maintenance treatment. For patients prescribed ICS-LABA-LAMA with a non-formoterol LABA, the reliever should be SABA.

See [downloadable resource: GINA 2021 Summary of medications and dosages for asthma treatment regimens containing an anti-inflammatory reliever](#).

## References

- E1. Patel M, Pilcher J, Pritchard A, Perrin K, Travers J, Shaw D, Holt S, Harwood M, Black P, Weatherall M, Beasley R, The SMART Study Group. Efficacy and safety of maintenance and reliever combination budesonide–formoterol in patients with asthma at risk of severe exacerbations: a randomised controlled trial. *Lancet Respir Med* 2013; 1: 32-42.
- E2. O'Byrne PM, FitzGerald JM, Bateman ED, Barnes PJ, Zhong N, Keen C, Jorup C, Lamarca R, Ivanov S, Reddel HK. Inhaled combined budesonide–formoterol as needed in mild asthma. *N Engl J Med* 2018; 378: 1865-1876.
- E3. Bateman ED, Reddel HK, O'Byrne PM, Barnes PJ, Zhong N, Keen C, Jorup C, Lamarca R, Siwek-Posluszna A, FitzGerald JM. As-needed budesonide-formoterol versus maintenance budesonide in mild asthma. *N Engl J Med* 2018; 378: 1877-1887.



## **GINA 2021**

### **Summary of medications and dosages for asthma treatment regimens containing an anti-inflammatory reliever**

## GINA 2021 - asthma treatment regimens containing an anti-inflammatory reliever

Adults & adolescents  
12+ years

## Personalized asthma management

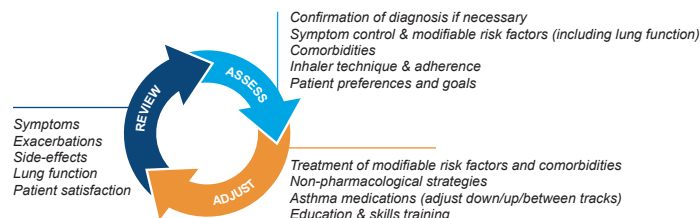
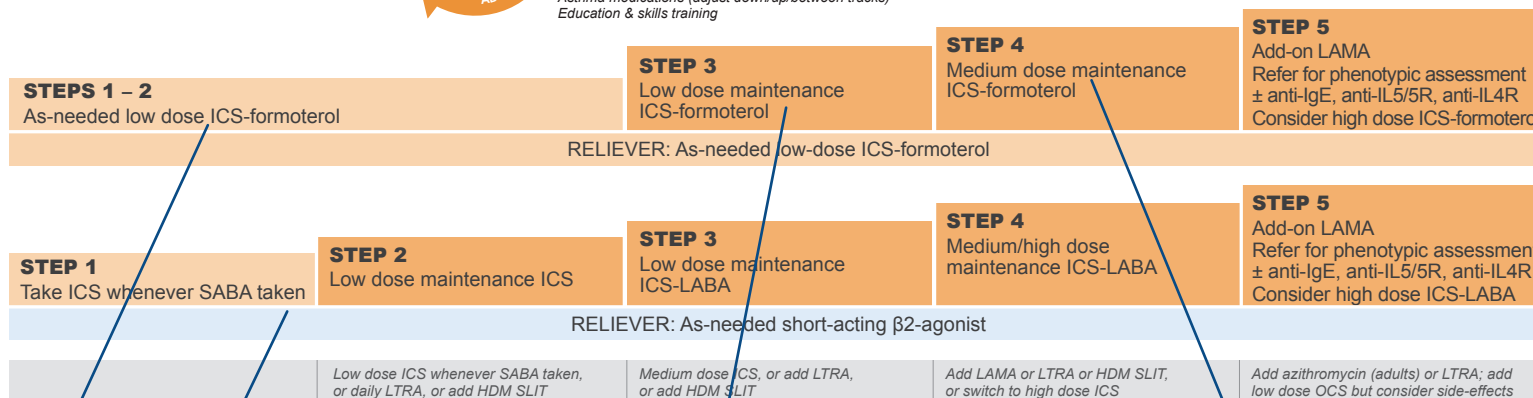
Assess, Adjust, Review  
for individual patient needs

Figure source: Box 3-5A in GINA 2021 Strategy Report

**CONTROLLER and PREFERRED RELIEVER** (Track 1). Using ICS-formoterol as reliever reduces the risk of exacerbations compared with using a SABA reliever

**CONTROLLER and ALTERNATIVE RELIEVER** (Track 2). Before considering a regimen with SABA reliever, check if the patient is likely to be adherent with daily controller

Other controller options for either track



## MEDICATIONS AND SUGGESTED DOSAGES\* – ADULTS AND ADOLESCENTS ≥12 YEARS

ANTI-INFLAMMATORY RELIEVER (AIR) THERAPY ALONE: GINA STEPS 1–2	MAINTENANCE AND RELIEVER THERAPY (MART): GINA STEP 3	MAINTENANCE AND RELIEVER THERAPY (MART): GINA STEPS 4–5
<b>BUDESONIDE-FORMOTEROL</b> 200/6 mcg, 1 inhalation as needed for symptom relief.	<b>BUDESONIDE-FORMOTEROL</b> 200/6 mcg: 1 inhalation twice daily (or once daily) as <b>maintenance</b> treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief.	<b>BUDESONIDE-FORMOTEROL</b> 200/6 mcg: 2 inhalations twice daily as <b>maintenance</b> treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief
[Beclometasone dipropionate (BDP)-formoterol not studied]	<b>BDP-FORMOTEROL</b> 100/6 mcg: 1 inhalation twice daily (or once daily) as <b>maintenance</b> treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief. Studied only in adults.	[BDP-formoterol not studied]
If symptom persist after a few minutes, another inhalation of ICS-formoterol can be taken. No more than 6 inhalations should be taken on a single occasion. A maximum total of 12 doses (reliever doses plus maintenance doses, if used) can be taken temporarily in a single day (8 inhalations for BDP-formoterol); if more is needed, medical attention should be sought the same day.		
<b>BECLOMETASONE DIPROPIONATE</b> 50mcg <b>AND</b> <b>ALBUTEROL</b> 100 mcg: 2 inhalations of each separate inhaler (or 2 inhalations of combination inhaler) as needed for symptom relief. Currently there is no different recommendation for maximum daily use compared with albuterol alone (12 puffs).	[ICS-SABA not studied]	

AIR: Anti-Inflammatory Reliever; BDP: beclometasone-dipropionate; ICS: inhaled corticosteroid; MART: Maintenance And Reliever Therapy with ICS-formoterol; SABA: short-acting beta<sub>2</sub>-agonist.

\*Doses are metered doses. See page 4 for corresponding delivered doses and for more details about medications and dosing. Copyright © 2021 · All Rights Reserved · Global Initiative for Asthma – GINA



## GINA 2021 - asthma treatment regimens containing an anti-inflammatory reliever



## Children 6-11 years

Figure source: Box 3-5B in GINA 2021 Strategy Report

## Personalized asthma management:

Assess, Adjust, Review

## Asthma medication options:

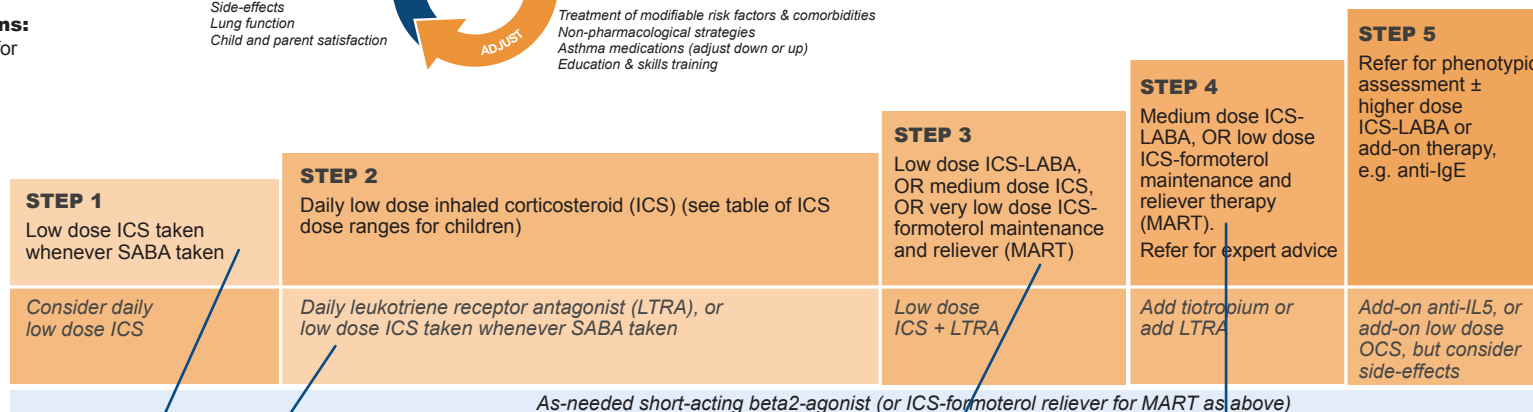
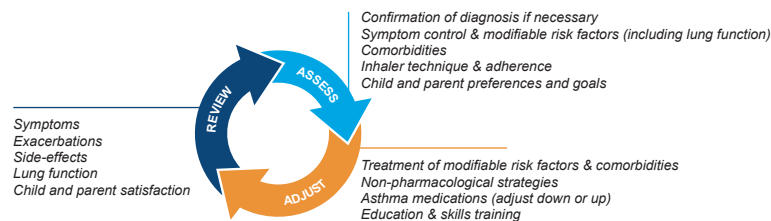
Adjust treatment up and down for individual child's needs

## PREFERRED CONTROLLER

to prevent exacerbations and control symptoms

Other controller options

## RELIEVER



## MEDICATIONS AND SUGGESTED DOSAGES\* – CHILDREN 4 –11 YEARS

ANTI-INFLAMMATORY RELIEVER (AIR) THERAPY ALONE: GINA STEPS 1–2	MAINTENANCE AND RELIEVER THERAPY (MART): GINA STEP 3	MAINTENANCE AND RELIEVER THERAPY (MART): GINA STEP 4
<p>[As-needed-only ICS-formoterol not studied in children]</p> <p><b>BECLOMETASONE DIPROPIONATE 50 mcg AND ALBUTEROL 100 mcg:</b> 2 inhalations of each separate inhaler (or 2 inhalations of combination inhaler) as needed for symptom relief. Currently there is no different recommendation for maximum daily use compared with albuterol alone.</p>	<p><b>BUDESONIDE-FORMOTEROL 100/6 mcg:</b> 1 inhalation once daily as maintenance treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief.</p>	<p>Suggested dose: <b>BUDESONIDE-FORMOTEROL 100/6 mcg:</b> 1 inhalation twice daily as maintenance treatment, <b>PLUS</b> 1 inhalation as needed for symptom relief.</p>
	<p>If symptom persist after a few minutes, another inhalation can be taken. For children, no more than 4 inhalations should be taken on a single occasion. A maximum total of 8 doses (reliever doses plus maintenance doses) can be taken temporarily in a single day; if more is needed, medical attention should be sought the same day.</p> <p>[ICS-SABA not studied]</p>	





## METERED DOSES AND DELIVERED DOSES FOR MEDICATIONS LISTED IN THIS RESOURCE

MEDICATION	METERED DOSE	DELIVERED DOSE
<b>Combination inhalers</b>		
Budesonide-formoterol	200/6 mcg	160/4.5 mcg
	100/6 mcg	80/4.5 mcg
Beclometasone-formoterol	100/6 mcg	87.5/5 mcg
<b>Separate inhalers</b>		
Beclometasone dipropionate	50 mcg	40 mcg
Albuterol (salbutamol)	100 mcg	90 mcg

- **Budesonide formoterol** is approved for adults and adolescents 12 years and older in many countries for use in AIR and MART, and in some countries for MART in children 4–11 years. For budesonide-formoterol, the maximum total number of inhalations that can be taken temporarily in any single day (reliever plus maintenance inhalations, if used) is based on the total dose of formoterol in any day (72mcg of formoterol [54 mcg delivered dose] for adults and adolescents, 48 mcg [36 mcg delivered dose] for children 4–11 years). Most of the studies with budesonide-formoterol as reliever used a dry powder inhaler, but budesonide-formoterol pressurized metered dose inhaler 200/6 mcg [160/4.5 delivered dose] was used in one Step 4 MART study, also with 1 inhalation per as-needed dose [Patel et al, Lancet Respir Med 2013; 1: 32–42].

- **Beclometasone-formoterol** is approved for MART in adults 18 years and older in many countries. A maximum total of 8 inhalations (total of reliever inhalations and maintenance inhalations) can be taken temporarily in a single day.
- **Other ICS-formoterol formulations** (e.g. mometasone-formoterol, fluticasone-formoterol) have not been studied with either AIR or MART, but may be able to be substituted if budesonide-formoterol or beclometasone-formoterol are not available. Some ICS-formoterol devices are currently approved only for adults 18+ years.

Before prescribing any inhaler, ensure that the patient can use it correctly.

The above recommended maximum doses refer to the maximum total dose that can be taken on any single day. In clinical trials in mild asthma, average use of as-needed low dose budesonide-formoterol was 3–4 inhalations per week, and <0.1% of patients took >8 inhalations of budesonide-formoterol on more than 1 day during the 12-month studies.

For all patients prescribed Anti-Inflammatory Reliever (AIR) therapy alone or Maintenance And Reliever Therapy (MART), *average* frequency of as-needed use of ICS-formoterol should be reviewed at each visit as part of the assessment of their treatment needs.

ICS-LABA combinations and ICS-LABA-LAMA combinations that contain a non-formoterol LABA should not be used as-needed. These medications are recommended only for maintenance treatment.

The tables displayed are intended to summarize medication classes and dosages that have been studied with AIR and MART therapy (by GINA step). It is not an exhaustive list of all possible medications, and readers are asked to investigate locally available medications as well as local regulatory constraints. Medication names and formulations vary greatly country to country, and this table is intended to serve as framework for clinical decision support rather than exact, specific prescribing guidance.