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Adjustment of Inhaled Controller Therapy of Asthma in the Yellow Zone, Based on the Inhaler Product Used in the Green Zone

Age 16 Years and Older

The Canadian Thoracic Society and other international asthma guideline bodies recommend a temporary, 4-5 fold increase in the inhaled corticosteroid (ICS) dose in selected patients in response to acutely worsening asthma symptoms, as part of a self-management asthma action plan (AAP).[1] The green-yellow-red zone framework in the AAP describes stable asthma, acutely worsening asthma, and a severe asthma exacerbation, respectively.

However, as confirmed in a recent review,[2] there are several practical challenges in broadly applying these recommendations. For certain dosing situations, guidelines provide no clear approach. In other situations, such as patients on a moderate to high baseline inhaled corticosteroid (ICS) dose (either as ICS monotherapy or in combination with a long-acting beta agonist (LABA)], a 4-5 fold dose increase in the yellow zone would exceed the manufacturer's recommended maximum daily dose. In such situations, clinicians might either choose to temporarily exceed manufacturer-recommended doses, or to directly recommend oral corticosteroids. This decision must be individualized, and will require consideration of clinician comfort level, patient preferences, medication cost (inhaled corticosteroid medications are more costly than oral corticosteroids), and medication availability (patients can easily increase use of their existing ICS, but may not have rapid access to oral corticosteroids). In these cases, both options are presented, and are considered equivalent, with no intended preferential hierarchy. Also, where there is evidence of a ceiling ICS dose that is equivalent to a course of oral prednisone, we have listed dose increases that achieve the ceiling dose but may be less than a 4-fold increase from the patient's green zone baseline dose (e.g. see tables for fluticasone, budesonide, ciclesonide). Where there is no evidence to confirm an ICS ceiling dose equivalent to prednisone (e.g. mometasone) we have not included a recommendation in the table, but have included a recommendation in the footnotes to the table. Support for a possible ceiling dose (ie, producing a prednisone-like effect) for mometasone is inferred based on pharmacokinetic similarity of mometasone to fluticasone propionate.

Furthermore, dose increases in the yellow zone can be achieved in a variety of ways, including changes to the number and/or frequency of inhalations, through *addition* of a new inhaler, or through temporary *replacement* of the baseline medication with a more potent (ie, higher strength) inhaler. To address these various implementation challenges, we have adopted evidence-based approaches recommended by authors Kouri, et al.[2] These approaches seek to maximize patient satisfaction and adherence while minimizing patient errors. For example, recommended dose adjustments are based on use of the patient's existing inhaler where possible. A strategy of stepping up to an inhaler strength that is higher than the current green zone inhaler as a way of increasing the ICS dose may be logistically challenging for the patient and therefore is deemed a less desirable option (although such options can be considered and are listed in the table footnotes where applicable for completeness). However, we note that approaches to reaching each target ICS dose level in the AAP yellow zone may vary, and should be ideally individualized based on patient preferences.

We also note that there are certain special considerations, as follows:

1) In patients with a history of sudden and severe exacerbations, and/or presenting with peak expiratory flow (PEF) or forced expiratory volume in 1 second (FEV1) ≤60% of personal best/predicted, the preferred first line therapy for the yellow zone of the action plan is prednisone 30-50 mg daily for 5-7 days.

2) In patients who fail to improve clinically within 2-3 days of increase in inhaled controller medication, and/or have a rapid clinical deterioration, and/or a PEF or FEV1 that falls to ≤60% of their personal best value, rescue therapy with prednisone 30-50 mg daily for 5-7 days is recommended.

A 1-page, easy-to-follow, printable, paper-based chart with common green zone medications and corresponding yellow zone recommendations (for posting in an office environment) is also available for download at hcp.lunghealth.ca/clinical-tools.

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Tables below list dosing options that are convenient and do not exceed 4 puffs per dose time. Dose recommendations listed in red exceed the manufacturer's maximum recommended dose. The **footnotes for each table contain essential information** for interpreting table and applying the information in clinical practice.

Maintenance Controller Medication in the Green Zone	Total daily maintenance ICS dose in mcg	Recommended dose adjustment	Dose of ICS after adjustment	Total daily ICS dose after adjustment (mcg)	Degree of increase in ICS over baseline
Fluticasone propionate pMDI Flovent HFA®					
• 50 mcg/puff 1 puff bid	100	4 puffs bid	200 mcg bid	400	4-fold
• 50 mcg/puff 2 puff bid	200	4 puffs qid**	200 mcg qid	800	4-fold
• 125 mcg/puff 1 puff bid*	250	4 puffs bid	500 mcg bid	1000	4-fold
• 125 mcg/puff 2 puffs bid	500	4 puffs qid**	500 mcg qid	2000	4-fold
• 250 mcg/puff 1 puff bid*	500	4 puffs bid	1000 mcg bid	2000	4-fold
• 250 mcg/puff 2 puffs bid	1000	4 puffs bid	1000 mcg bid	2000	2-fold***

*Although the manufacturer recommends that the usual dose be obtained using 2 puffs from each available strength of Flovent HFA® pMDI**, one** puff dosing regimens may be in clinical use.
**A qid dosing regimen is required to achieve a 4-fold increase while avoiding an excessive number of puffs at each dose time.
***Although this represents less than a 4-fold dose increase, there is evidence that a transient dose increase to a dose of 2000 mcg/day has a comparable effect to oral corticosteroids, regardless of the baseline ICS dose.[2]

Maintenance Controller Medication in the Green Zone	Total daily maintenance ICS dose in mcg	Recommended dose adjustment	Dose of ICS after adjustment	Total daily ICS dose after adjustment (mcg)	Degree of increase in ICS over baseline
Fluticasone propionate Flovent® Diskus					
• 100 mcg/inh 1 inh bid	200	4 inh bid	400 mcg bid	800	4-fold
• 250 mcg/inh 1 inh bid	500	4 inh bid	1000 mcg bid	2000	4-fold
• 500 mcg/inh 1 inh bid	1000	2 inh bid	1000 mcg bid	2000	2-fold*
• 500 mcg/inh 2 inh bid	2000	Prednisone 30-50 mg daily			

*Although this represents less than a 4-fold dose increase, there is evidence that a transient dose increase to a dose of 2000 mcg/day has a comparable effect to oral corticosteroids, regardless of the baseline ICS dose.[2]

Maintenance Controller Medication in the Green Zone	Total daily maintenance ICS dose in mcg	Recommended dose adjustment	Dose of ICS after adjustment	Total daily ICS dose after adjustment (mcg)	Degree of increase in ICS over baseline
Fluticasone furoate® Arnuity® Ellipta					
• 100 mcg/inhalation 1 inh daily	100	*Option 1:* Increase to 4 puffs daily* *Option 2:* Prednisone 30-50 mg daily**	400 mcg daily	400	4-fold
• 200 mcg/inhalation 1 inh daily	200	*Option 1:* Increase to 4 puffs daily* *Option 2:* Prednisone 30-50 mg daily**	800 mcg daily	800	4-fold

* This dose exceeds product monograph total daily dose limits intended for chronic daily use. A short term dose increase beyond these limits is unlikely to carry any significant safety risks, however formal safety testing data are not available and the decision to pursue this approach should be based on patient and clinician comfort. We also note that this product is relatively new on the market, and effects of higher doses are less certain than for other formulations.
** Ask patients to contact the health care provider to consider a prednisone prescription and/or provide a standing prescription for prednisone 30-50 mg daily for 5-7 days. Ensure that patients are appropriately counseled about the risks of short-term prednisone use.

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Maintenance Controller Medication in the Green Zone	Daily maintenance ICS dose in mcg	Recommended dose adjustment	Dose of ICS after adjustment	Total daily ICS dose after adjustment (mcg)	Degree of increase in ICS over baseline
Budesonide Pulmicort® Turbuhaler® • 100 mcg/inhalation 1 inh bid • 200 mcg/inhalation 1 inh bid • 400 mcg/inhalation 1 inh bid • 400 mcg/inhalation 2 inh bid	 200 400 800 1600	 4 inhalations bid* 4 inhalations bid* 3 inhalations bid 3 inhalations bid	 400 mcg bid 800 mcg bid 1200 mcg bid 1200 mcg bid	 800 1600 2400 2400	 4-fold 4-fold 3-fold** 1.5-fold**

*Although maintaining the baseline dosing frequency is thought to reduce medication dosing errors, a qid regimen of budesonide (not shown in the table) may have superior efficacy to a bid regimen, and can be considered.
**Although this represents less than a 4-fold dose increase, there is evidence that a transient dose increase to a dose of 2400 mcg/day has a comparable effect to oral corticosteroids, regardless of the baseline ICS dose.[2]

Maintenance Controller Medication in the Green Zone	Daily maintenance ICS dose in mcg	Recommended dose adjustment	Dose of ICS after adjustment	Total daily ICS dose After adjustment (mcg)	Degree of increase in ICS over baseline
Beclomethasone pMDI Qvar®					
• 50 mcg/puff 1 puff bid	100	4 puffs bid (or 2 puffs qid)	200 mcg bid 100mcg qid	400 400	4-fold 4-fold
• 50 mcg/puff 2 puffs bid	200	4 puffs qid*	200 mcg qid	800	4-fold
• 100 mcg/puff 1 puff bid	200	4 puffs bid (or 2 puffs qid)	400 mcg bid 200mcg qid	800 800	4-fold 4-fold
• 100 mcg/puff 2 puffs bid	400	*Option 1:* Increase to 4 puffs qid*;** *Option 2:* Prednisone 30-50 mg daily***	400 mcg qid	1600	4-fold

*A qid dosing regimen is required to achieve a 4-fold increase while avoiding an excessive number of puffs at each dose time
** This dose exceeds product monograph total daily dose limits intended for chronic daily use. A short term dose increase beyond these limits is unlikely to carry any significant safety risks, however formal safety testing data are not available and the decision to pursue this approach should be based on patient and clinician comfort.
*** Ask patients to contact the health care provider to consider a prednisone prescription and/or provide a standing prescription for prednisone 30-50 mg daily for 5-7 days. Ensure that patients are appropriately counseled about the risks of short-term prednisone use.

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Maintenance Controller Medication in the Green Zone	Daily maintenance ICS dose in mcg	Recommended dose adjustment	Dose of ICS after adjustment	Total daily ICS dose after adjustment (mcg)	Degree of increase in ICS over baseline
Ciclesonide pMDI Alvesco®					
• 100 mcg/puff 1 puff daily	100	4 puffs daily	400 mcg daily	400	4-fold
• 100 mcg/puff 2 puffs daily	200	4 puffs bid	400 mcg bid	800	4-fold
• 200 mcg/puff 1 puff daily	200	4 puffs daily* (or 2 puffs bid)	800 mcg daily 400 mcg bid	800 800	4-fold 4-fold
• 200 mcg/puff 2 puffs daily	400	4 puffs bid**	800 mcg bid	1600	4-fold
• 200 mcg/puff 2 puffs bid	800	4 puffs bid**	800 mcg bid	1600	2-fold***

* Although maintaining the baseline dosing frequency is thought to reduce medication dosing errors, the manufacturer recommends splitting the dose into a bid schedule whenever the total administered dose is > 400 mcg/day, and this can be considered.
** This dose exceeds product monograph total daily dose limits intended for chronic daily use. However, a short term increase to this dose level was shown to be safe and effective in a clinical trial.[2]
***Although this represents less than a 4-fold dose increase, there is evidence that a transient dose increase to a dose of 1600 mcg/day has a comparable effect to oral corticosteroids, regardless of the baseline ICS dose.[2]

Maintenance Controller Medication in the Green Zone	Daily maintenance ICS dose in mcg	Recommended dose adjustment	Dose of ICS after adjustment	Total daily ICS dose after adjustment (mcg)	Degree of increase in ICS over baseline
Mometasone Asmanex® Twisthaler®					
• 100 mcg/inhalation 1 inh daily	100	4 inhalations daily	400 mcg daily	400	4-fold
• 200 mcg/inhalation 1 inh daily	200	4 inhalations daily* (or 2 inh bid)	800 mcg daily 400 mcg bid	800 800	4-fold 4-fold
• 200 mcg/inhalation 1 inh bid	400	*Option 1:* Increase to 4 inh bid** *Option 2:* Prednisone 30-50 mg daily****	800 mcg bid	1600	4-fold
• 400 mcg/inhalation 1 inh daily	400	*Option 1:* Increase to 4 inh daily** (or 2 inhalations bid) *Option 2:* Prednisone 30-50 mg daily****	1600 mcg daily 800 mcg bid	1600 1600	4-fold 4-fold
• 400 mcg/inhalation 1 inh bid***	800	Prednisone 30-50 mg daily****			

* Although maintaining the baseline dosing frequency is thought to reduce medication dosing errors, the manufacturer recommends splitting the dose into a bid schedule whenever the total administered dose is > 400 mcg/day, and this can be considered.
** This dose exceeds product monograph total daily dose limits intended for chronic daily use. A short term dose increase beyond these limits is unlikely to carry any significant safety risks, however formal safety testing data are not available and the decision to pursue this approach should be based on patient and clinician comfort.
*** Another possible approach would be to increase to 2 inhalations bid, and this can be considered (not shown in the table). Although this recommendation is not evidence-based, because the pharmacokinetic profile of mometasone is similar to fluticasone propionate, doubling of mometasone to 1600 mcg (twice the recommended usual maximum dose) may provide efficacy similar to fluticasone propionate 2000 mcg/day, a dose which has shown an effect comparable to oral corticosteroids.[2]
**** Ask patients to contact the health care provider to consider a prednisone prescription and/or provide a standing prescription for prednisone 30-50mg daily for 5-7 days. Ensure that patients are appropriately counseled about the risks of short-term prednisone use.

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Maintenance Controller Medication in the Green Zone	Daily maintenance ICS dose in mcg	Recommended dose adjustment	Dose of ICS after adjustment	Total daily ICS dose after adjustment (mcg)	Degree of increase in ICS over baseline
Advair® pMDI Fluticasone/salmeterol					
• 125/25 mcg 1 puff bid*	250	**Add** fluticasone 125 mcg/puff pMDI 3 puffs bid	Fluticasone/salmeterol 125 mcg bid + Fluticasone 375 mcg bid	1000	4-fold
• 125/25 mcg 2 puffs bid	500	**Add** fluticasone 250 mcg/puff pMDI 3 puffs bid	Fluticasone/salmeterol 250 mcg bid + Fluticasone 750 mcg bid	2000	4-fold
• 250/25 mcg 1 puff bid*	500	**Add** fluticasone 250 mcg/puff pMDI **3** puffs bid	Fluticasone/salmeterol 250 mcg bid + Fluticasone 750 mcg bid	2000	4-fold
• 250/25 mcg 2 puffs bid	1000	**Add** fluticasone 250 mcg/puff pMDI 2 puffs bid	Fluticasone/salmeterol 500 mcg bid + Fluticasone 500 mcg bid	2000	2-fold**

*Although the manufacturer-recommended dose is 2 puffs from each available strength of Advair® pMDI in order to obtain 50 mcg of salmeterol at each dose time, **one** puff dosing regimens may be in clinical use
**Although this represents less than a 4-fold dose increase, there is evidence that a transient dose increase to a dose of 2000 mcg/day has a comparable effect to oral corticosteroids, regardless of the baseline ICS dose[2]

Maintenance Controller Medication in the Green Zone	Daily maintenance ICS dose in mcg	Recommended dose after adjustment	Dose of ICS after adjustment (mcg)	Total daily ICS dose after adjustment (mcg)	Degree of increase in ICS over baseline
Advair® Diskus® Fluticasone/salmeterol*					
• 100/50 1 inhalation bid	200	**Add** fluticasone 100 mcg/inhalation 3 inhalations bid	Fluticasone/salmeterol 100 mcg bid + Fluticasone 300 mcg bid	800	4-fold
• 250/50 1 inhalation bid	500	**Add** fluticasone 250 mcg/inhalation 3 inhalations bid	Fluticasone/salmeterol 250 mcg bid + Fluticasone 750 mcg bid	2000	4-fold
• 500/50 1 inhalation bid	1000	**Add** fluticasone 500 mcg/inhalation 1 inhalation bid	Fluticasone/salmeterol 500 mcg bid + Fluticasone 500 mcg bid	2000	2-fold**

*Note: Since each inhalation from the Advair® Diskus delivers salmeterol 50 mcg, the manufacturer's recommended dose is 1 inhalation from each available strength of Advair® Diskus in order to obtain 50 mcg of salmeterol at each dose time. Increasing the number of inhalations from Advair Diskus is not appropriate since this will exceed the daily dose limit for salmeterol.
**Although this represents less than a 4-fold dose increase, there is evidence that a transient dose increase to a dose of 2000 mcg/day has a comparable effect to oral corticosteroids, regardless of the baseline ICS dose[2]

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Maintenance Controller Medication in the Green Zone	Daily maintenance ICS dose in mcg	Recommended dose after adjustment	Dose of ICS after adjustment	Total daily ICS dose after adjustment (mcg)	Degree of increase in ICS over baseline
Breo® Ellipta® Fluticasone furoate/vilanterol*					
• 100/25 1 inhalation daily	100	*Option 1:* Increase to 4 puffs od** *Option 2:* Prednisone 30-50 mg daily***	400 mcg od	400	4-fold
• 200/25 1 inhalation daily	200	*Option 1:* Increase to 4 puffs od** *Option 2:* Prednisone 30-50 mg daily***	800 mcg od	800	4-fold

*Note: Each inhalation from either strength of Breo® Ellipta® delivers vilanterol 25 mcg, which is the maximum recommended daily dose for routine usage.
** This dose exceeds product monograph total daily dose limits for fluticasone furoate and vilanterol intended for chronic daily use. A short term dose increase beyond these limits is unlikely to carry any significant safety risks, however formal safety testing data are not available and the decision to pursue this approach should be based on patient and clinician comfort. We also note that this product is relatively new on the market, and effects of higher doses are less certain than for other formulations.
*** Ask patients to contact the health care provider to consider a prednisone prescription and/or provide a standing prescription for prednisone 30-50 mg daily for 5-7 days. Ensure that patients are appropriately counseled about the risks of short-term prednisone use.

Maintenance Controller Medication in the Green Zone	Daily maintenance ICS dose in mcg	Recommended dose after adjustment	Dose of ICS after adjustment	Total daily ICS dose after adjustment (mcg)	Degree of increase in ICS over baseline
Zenhale® pMDI Mometasone/formoterol					
• 100/5 2 puffs bid*	400	*Option 1:* **Change to** Zenhale MDI 200/5 mcg 4 puffs bid** *Option 2:* Prednisone 30-50 mg daily****	200/5 mcg 4 puffs bid**	1600	4-fold
• 200/5 2 puffs bid***	800	Prednisone 30-50 mg daily****			

*Note: Since each puff from the Zenhale® pMDI delivers formoterol 5 mcg, the manufacturer's recommended dose is 2 puffs from each available strength of Zenhale® pMDI in order to obtain 10 mcg of formoterol at each dose time. Increasing the dose of 100/5 to 4 puffs bid complies with the manufacturer's maximum dose for formoterol of 40 mcg/day, but would only achieve a 2-fold increase in the ICS dose to 800 mcg. Since this strategy may be suboptimal, it may be considered, but is not listed in the table as an option.
** To achieve a 4-fold increase in mometasone to 1600 mcg/day, a higher strength inhaler is required (i.e. 200/5). This dose exceeds product monograph total daily dose limits intended for chronic daily use. A short term dose increase beyond these limits is unlikely to carry any significant safety risks, however formal safety testing data are not available and the decision to pursue this approach should be based on patient and clinician comfort.
*** Another possible approach would be to increase to 4 inhalations bid, and this can be considered (not shown in the table). Although this recommendation is not evidence-based, because the pharmacokinetic profile of mometasone is similar to fluticasone propionate, doubling of mometasone to 1600 mcg (twice the recommended usual maximum dose) may provide efficacy similar to fluticasone propionate 2000 mcg/day, a dose which has shown an effect comparable to oral corticosteroids.[2]

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**** Ask patients to contact the health care provider to consider a prednisone prescription and/or provide a standing prescription for prednisone 30-50 mg daily for 5-7 days. Ensure that patients are appropriately counseled about the risks of short-term prednisone use.

Maintenance Controller Medication in the Green Zone	Daily maintenance ICS dose in mcg	Recommended dose after adjustment	Total daily ICS dose after adjustment (mcg)	Degree of increase in ICS over baseline
Symbicort® Turbuhaler® Budesonide/formoterol*		Symbicort® Adjustable Maintenance Dosing		
• 100/6 1 inhalation daily	100	Increase to 4 inhalations/day	400	4-fold
• 100/6 1 inhalation bid	200	Increase to 4 inhalations bid	800	4-fold
• 100/6 2 inhalations daily	200	Increase to 4 inhalations bid	800	4-fold
• 100/6 2 inhalations bid***	400	**Add** budesonide 200 mcg 3 inhalations bid	1600	4-fold
• 200/6 1 inhalation daily	200	Increase to 4 inhalations/day	800	4-fold
• 200/6 1 inhalation bid	400	Increase to 4 inhalations bid	1600	4-fold
• 200/6 2 inhalations daily	400	Increase to 4 inhalations bid	1600	4-fold
• 200/6 2 inhalations bid***	800	**Add** budesonide 400 mcg 2 inhalations bid	2400	3-fold**
Symbicort® Maintenance and Reliever Therapy (SMART)****		Symbicort® Maintenance and Reliever Therapy (SMART)	Maximum:	
• 100/6 1 inhalations bid	200	In addition to the maintenance dose, may take 1 additional dose 'as needed' in response to symptoms. Not more than 6 inhalations on any single occasion. Not more than 8 inhalations per day in total (maintenance and reliever doses)	800/day	
• 100/6 2 inhalations bid	400		800/day	
• 100/6 2 inhalations daily	200		800/day	
• 200/6 1 inhalation bid	400		1600/day	
• 200/6 2 inhalations bid	800		1600/day	
• 200/6 2 inhalations daily	400		1600/day	

*Dose based on 1 inhalation from each available strength of Symbicort® Turbuhaler®.
**Although this represents less than a 4-fold dose increase, there is evidence that a transient dose increase to a dose of 2400 mcg/day has a comparable effect to oral corticosteroids, regardless of the baseline ICS dose.[2]
***Stepping up to 4 inhalations bid is a manufacturer-recommended option, but it falls short of the 4-fold increase in ICS or the 2400 mcg budesonide target dose.
****SMART dosing strategy has been shown to prevent acute exacerbations of asthma from becoming severe. There is no evidence-based recommendation for the use of supplemental budesonide with this dosing strategy. If satisfactory relief of asthma symptoms is not achieved with a maximum of 8 inhalations per day, seek medical attention.

References:

1. Lougheed MD, Lemière C, Ducharme FM, et al. Canadian Thoracic Society 2012 guideline update: Diagnosis and management of asthma in preschoolers, children and adults. Can Resp J 2012;19(2):127-164.
2. Kouri A, Boulet LP, Kaplan A, Gupta S. An evidence-based, point-of-care tool to guide completion of asthma action plans in practice. European Respiratory Journal. 2017; 49(5).

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