

## Efficacy and safety of two dry-powder inhalers for the administration of mometasone furoate in asthma patients\*

Eficácia e segurança de dois inaladores de pó seco usados para a aplicação de furoato de mometasona em pacientes com asma

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### Abstract

**Objective:** Mometasone furoate (MF) is a new potent synthetic inhaled corticosteroid. Internationally, MF is administered via a dry-powder inhaler that contains multiple doses. As a preparation that would be more cost-effective, single-dose MF capsules were developed in Brazil. The objective of the present study was to evaluate the efficacy and safety of the two inhalers for MF administration in patients with asthma. **Methods:** A randomized, multicenter, open-label, parallel-group clinical trial involving 74 adult patients with moderate persistent asthma who were randomized into two groups to receive approximately 400 µg of MF once a day for 60 days, either via the multiple-dose inhaler or via the newly developed single-dose inhaler. **Results:** No significant differences were observed between the two groups regarding the primary endpoints (FEV<sub>1</sub> and rescue medication use) or the secondary endpoints (morning PEF, tolerability, and safety, the last as assessed on the basis of hypothalamic-pituitary-adrenal axis function). **Conclusions:** The use of the single-dose inhaler developed in Brazil for MF administration is as effective and safe as is that of a standard inhaler in the treatment of patients with asthma.

**Keywords:** Anti-asthmatic agents; Pregnadienediols; Metered dose inhalers.

(ClinicalTrials.gov identifier: NCT00975741 [<http://www.clinicaltrials.gov/>])

### Resumo

**Objetivo:** O furoato de mometasona (FM) é um novo corticosteroide inalatório sintético potente. Internacionalmente, o FM é fornecido em um inalador de pó seco que permite sua administração em múltiplas doses. Para se obter uma preparação com melhor relação custo-eficácia, foram desenvolvidas no Brasil formulações de FM em cápsulas de pó seco para serem administradas em dose única. O presente estudo teve como objetivo avaliar a eficácia e a segurança dos dois inaladores usados para a administração de FM em pacientes asmáticos. **Métodos:** Estudo clínico, aberto, comparativo, paralelo e multicêntrico com 74 adultos portadores de asma persistente e moderada, randomizados em dois grupos para receber FM em uma dose de aproximadamente 400 µg, fornecida por um inalador de dose múltipla ou pelo novo inalador de dose única, uma vez ao dia durante 60 dias. **Resultados:** Não foram observadas diferenças significantes entre os dois grupos estudados nos desfechos primários (VEF<sub>1</sub> e frequência do uso de medicação de resgate) ou nos desfechos secundários (PFE matinal, tolerabilidade e segurança, essa última avaliada pelo estudo do eixo hipotálamo-hipófise-adrenal). **Conclusões:** A administração de FM com o novo inalador de dose única desenvolvido no Brasil tem eficácia e segurança comparáveis à administração com o inalador de dose múltipla no tratamento de pacientes asmáticos.

**Descritores:** Antiasmáticos; Pregnadienodióis; Inaladores dosimetrados.

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## Introduction

Inhaled glucocorticoids are considered the most effective anti-inflammatory agents in the treatment of persistent asthma, promoting improvement in symptoms and pulmonary function with a decrease in the frequency and severity of exacerbations.<sup>(1)</sup> Mometasone furoate (MF) is a corticosteroid, obtained by using 2-furoyl chloride to esterify mometasone, and has potent anti-inflammatory effects. Its *in vitro* affinity for glucocorticoid receptors is 12 times greater than is that of dexamethasone and 5 times greater than is that of budesonide. In addition, MF has significantly lower oral bioavailability than do budesonide and beclomethasone, which translates to a lower risk of adverse effects from systemic exposure to glucocorticoids.<sup>(2)</sup>

A complete clinical program was developed to investigate the efficacy and safety of MF in the treatment of asthma in individuals over 4 years of age.<sup>(3,4)</sup> The formulation used in those studies was MF administered via a dry-powder inhaler (MF-DPI). The systemic bioavailability of MF after administration of MF-DPI 400 µg was estimated at < 1%.<sup>(5)</sup> The patients treated with MF-DPI showed significant improvement in pulmonary function and a reduction in the need for oral corticosteroids.<sup>(6)</sup> The dose of 400 µg administered in a single dose or in two sequential doses of 200 µg, once a day, was established as the preferred dosage regimen in terms of efficacy and safety.<sup>(7-9)</sup>

Inhaled dry-powder MF can be stored in two ways: in a DPI that releases MF each time the device is rotated, during opening and closing, and that can contain multiple doses, or in a single-dose DPI that pierces a single-use capsule. Internationally, MF is administered via a multiple-dose DPI containing 30 or 60 doses of 100 µg or 200 µg. As a preparation that would be more cost-effective, single-dose MF capsules (200 µg and 400 µg), to be administered via a DPI, were developed in Brazil.

The objective of the present non-inferiority clinical trial, which was carried out to complement the evaluation of the equivalence between the two DPIs, was to determine whether the two DPIs for MF-DPI administration (≈ 400 µg) are comparable in terms of efficacy and safety in the treatment of adult asthma patients.

## Methods

This was a randomized, multicenter, open-label, parallel-group clinical trial approved by the ethics committees of the five centers involved and conducted in accordance with the principles of the Declaration of Helsinki. Ninety-seven patients with symptomatic, moderate persistent asthma that was classified as stable (diagnosed at least six months prior), and aged 18 or older, were randomized. We included only those patients with a baseline FEV<sub>1</sub> ≥ 55% and < 85% of predicted that increased by 12% or more (absolute volume increase ≥ 200 mL) after the reversibility test at the screening visit. Another criterion for inclusion was presenting with a PEF (as measured by a portable meter) > 50% of predicted, as proposed in the table devised by Leiner et al.,<sup>(10)</sup> and we considered the highest value obtained in three consecutive measurements. Women of childbearing age were included only if they were using contraception. Patients were asked to avoid using asthma medications prior to the tests, for a period consistent with the duration of action of the medication used.<sup>(11)</sup>

Women who were pregnant or lactating were excluded from the study, as were the following individuals: those receiving immunotherapy; those with other lung diseases (including obstructive lung diseases); those hospitalized for asthma in the last three months, requiring ventilatory support because of asthma attacks in the last 5 years, or admitted to the hospital for control of airway obstruction at least two times in the last six months; those with respiratory tract infection within the last two weeks prior to inclusion in the study; those with clinically significant chest X-ray abnormalities or oropharyngeal candidiasis; smokers; former smokers (at least 20 pack-years); and those with altered hypothalamic-pituitary-adrenal axis function. Patients were withdrawn from the study if classified as cases of treatment failure (clinically significant worsening of asthma), defined as follows: a reduction of 20% or more in FEV<sub>1</sub> (absolute value); a reduction in the highest morning or night PEF value to less than the critical reference value (calculated as 70% of the highest morning PEF value, measured between days 1 and 7, on two consecutive days) on at least two consecutive days; a significant increase in bronchodilator use (for example, the use of

more than 12 puffs of albuterol or more than two treatments with nebulized beta-agonists on any two consecutive days); or a clinical exacerbation requiring emergency treatment or treatment with additional medication (other than inhaled short-acting beta-agonists).

Eligible patients were randomized into two groups to receive a dose of MF-DPI  $\approx$  400  $\mu$ g at bedtime. The multiple-dose group used a DPI with a drug reservoir (Asmanex<sup>®</sup> Twisthaler, 440  $\mu$ g; Schering-Plough, Kenilworth, NJ, USA), whereas the single-dose group used a DPI containing a single-use capsule (Oximax<sup>®</sup>, 400  $\mu$ g; Mantecorp Indústria Química e Farmacêutica, Rio de Janeiro, Brazil). Each actuation of the multiple-dose DPI (nominal dose) releases  $\approx$  400  $\mu$ g of MF (effective dose), the same dose released by the single-dose DPI. After the screening visit, designated visit 1 (V1), the patients were evaluated on days 7 (V2), 15 (V3), 30 (V4), 45 (V5) and 60 (V6).

The primary objective of this study was to evaluate efficacy by determining the difference between the FEV<sub>1</sub> values obtained at V1 and those obtained at the subsequent visits (after therapy with MF administered either via a multiple-dose DPI or a single-dose DPI). In addition, the two groups were compared in terms of daily PEF values, as determined by a domestic peak flow meter, and in terms of treatment response, as assessed by the investigator and by the patients themselves. The number of daily applications of rescue medication (albuterol) used by the patients throughout the study period was also determined.

The secondary objective was to assess the safety and tolerability of both treatments on the basis of hypothalamic-pituitary-adrenal axis function, as determined through application of the cosyntropin test and determination of plasma cortisol levels prior to and 60 min after administration of 250 mg of i.m. adrenocorticotrophic hormone (ACTH), as well as the biochemical profile (results of a blood workup and determination of aspartate aminotransferase levels, alanine aminotransferase levels and creatinine levels), vital signs and adverse events prior to or after treatment. All patients gave written informed consent.

Two-way ANOVA with repeated measures, complemented by Tukey's test, was used to compare the two groups in terms of the FEV<sub>1</sub> values obtained at each visit of the study. The

Kruskal-Wallis test was used to analyze the differences between the baseline and post-stimulus values, including plasma concentrations of cortisol (cosyntropin test results) and other nonparametric variables. The level of significance was set at 0.05, and the statistical power was above 80%.

## Results

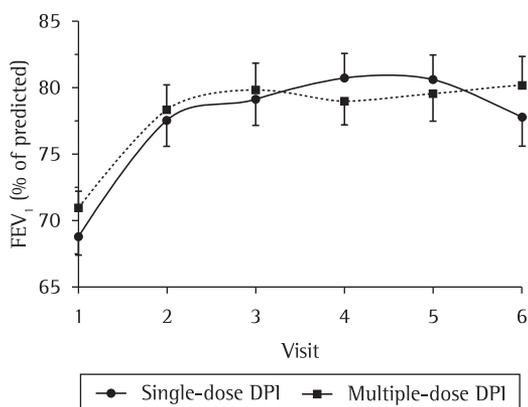
A total of 97 patients were included. Of those 97 patients, 23 were excluded: 15 because they were ineligible; 5 because they experienced treatment failure (3 cases in the multiple-dose group and 2 cases in the single-dose group); and 3 because they were lost to follow-up. Therefore, the number of patients who completed the treatment (evaluable population) was 74 (40 in the single-dose group and 34 in the multiple-dose group). All randomized patients who received at least one dose of medication were considered in the tolerability analysis. The two treatment groups were comparable regarding baseline demographic and asthma-related characteristics (Table 1).

Figure 1 shows the FEV<sub>1</sub> values, expressed as mean percentage of predicted value, at each visit, after administration of MF-DPI  $\approx$  400  $\mu$ g via each of the two DPIs. At V6, there was a mean increase of 14% in the two treatment groups, there being no statistically significant difference between them. The comparison of the baseline values with the values obtained in the subsequent visits revealed a statistically

**Table 1** - Summary of the patient characteristics.

Characteristic	Single-dose group	Multiple-dose group
	(n = 40)	(n = 34)
Age, years <sup>a</sup>	45.5 (18.0-72.0)	46.0 (18.0-78.0)
M/F gender, %	35.0/65.0	32.4/67.6
Race: W/B/O, n	29/9/2	23/9/2
Duration of symptoms, years <sup>a</sup>	22.5 (1.00-61.0)	22.5 (0.60-71.0)
Pre-BD FEV <sub>1</sub> , L <sup>b</sup>	1.97 $\pm$ 0.10	2.12 $\pm$ 0.10
Pre-BD FEV <sub>1</sub> , % of predicted <sup>b</sup>	67.0 $\pm$ 1.7	70.0 $\pm$ 1.9
Post-BD FEV <sub>1</sub> , L <sup>b</sup>	2.43 $\pm$ 0.1	2.63 $\pm$ 0.2
Increase in post-BD FEV <sub>1</sub> , % <sup>b</sup>	24.6 $\pm$ 2.0	25 $\pm$ 1.7

W: White; B: Black; O: other; and BD: bronchodilator.  
<sup>a</sup>Values expressed as median (range). <sup>b</sup>Values expressed as mean  $\pm$  SE.



**Figure 1** – FEV<sub>1</sub> values, expressed as mean percentage  $\pm$  SE of the predicted FEV<sub>1</sub> value, at each visit of the study, after administration of  $\approx$  400  $\mu$ g of mometasone furoate via two dry-powder inhalers (DPIs): a multiple-dose DPI and a single-dose DPI.

significant difference between V1 and all the subsequent visits, for the multiple-dose group and the single-dose group.

The comparison of the groups regarding the frequency of use of albuterol revealed no significant difference, as evidenced by the median (range) for the number of puffs used in each of the five weeks of the study by the patients in the single-dose and multiple-dose groups, respectively: week 2–3 (0-28) and 4 (0-28); week 3–3 (0-25) and 1 (0-30); week

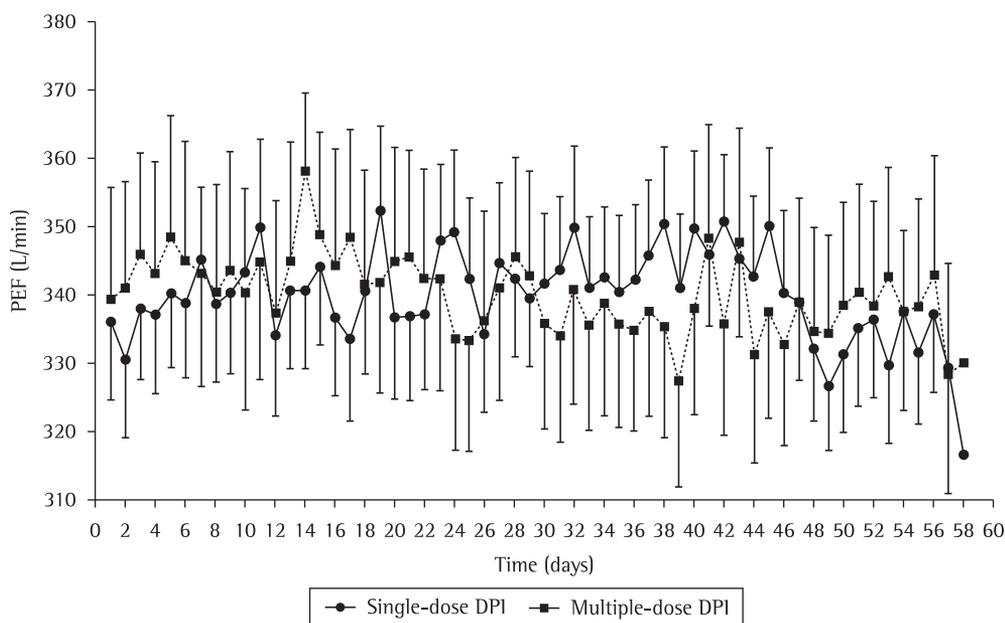
4–2 (0-94) and 4 (0-86); week 5–2 (0-64) and 0 (0-72); and week 6–2 (0-58) and 1 (0-86).

There was no difference between the two treatment groups regarding the morning PEF values, as measured by the patients on a daily basis (Figure 2).

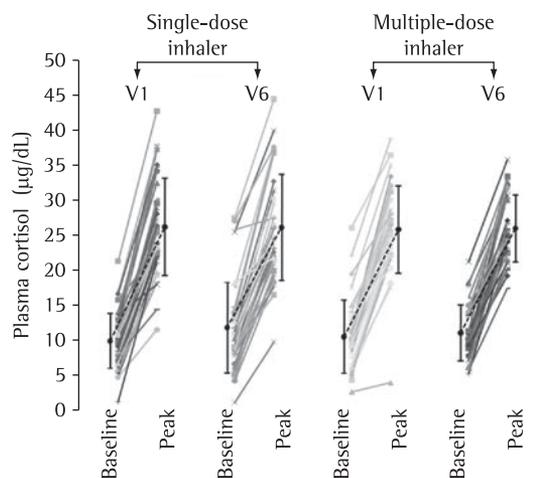
The assessment of hypothalamic-pituitary-adrenal axis function revealed no statistically significant differences in plasma cortisol concentrations (baseline values or values obtained after stimulation with ACTH) between the pre-treatment and the post-treatment period in either of the two groups that received MF, demonstrating that the administration of this corticosteroid via either of the DPIs tested did not affect the integrity of hypothalamic-pituitary-adrenal axis function (Figure 3).

There were no significant differences between the two treatment groups regarding the biochemical profile, vital signs, or adverse event profile after 60 days of exposure to MF-DPI. We observed only a few treatment-related adverse effects, all of which were considered mild to moderate in intensity, and the most common were headache and pharyngitis (44.0% and 8.8% in the multiple-dose group and 32.5% and 7.5% in the single-dose group, respectively). None of the patients had or developed oral candidiasis.

Figure 4 shows the treatment response, as evaluated by the investigator, at each follow-up

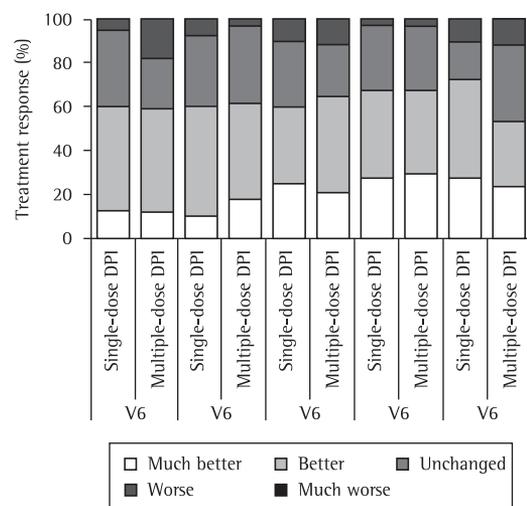


**Figure 2** – Changes in morning PEF (mean  $\pm$  SE) throughout the period of treatment with  $\approx$  400  $\mu$ g of mometasone furoate administered via two dry-powder inhalers (DPIs): a multiple-dose DPI and a single-dose DPI.



**Figure 3** - Mean  $\pm$  SD of the serum levels of cortisol before and after the administration of adrenocorticotropic hormone at visit 1 (V1, before treatment) and at visit 6 (V6, after treatment with  $\approx$  400  $\mu$ g of mometasone furoate administered via two dry-powder inhalers [DPIs]: a multiple-dose DPI and a single-dose DPI). The serum levels of cortisol after stimulation with adrenocorticotropic hormone are shown for each of the study patients.

visit in comparison with the baseline visit. The proportion of patients considered to have gotten “much better” or “better” from V2 to V6 was similar in the two treatment groups (60.0%, 60.0%, 60.0%, 67.5%, and 72.5% in the single-



**Figure 4** – Evaluation of treatment response performed by the investigator at each follow-up visit (V2, V3, V4, V5, and V6) in comparison with the baseline visit for the two treatment groups (single-dose group and multiple-dose group). The results are expressed as percentage of patients considered “much better”, “better”, “unchanged”, “worse”, or “much worse”.

dose group vs. 58.9%, 61.7%, 64.7%, 67.6%, and 52.9% in the multiple-dose group, respectively). The treatment response, as evaluated by the patient, at each follow-up visit in relation to the baseline visit, was also similar in the two groups, and the proportion of patients who reported having gotten “much better” or “better” from V2 to V6 was, respectively, 70.0%, 75.0%, 70.0%, 67.5%, and 80.0% in the single-dose group vs. 58.8%, 79.4%, 79.4%, 82.4%, and 70.6% in the multiple-dose group.

## Discussion

The present study has demonstrated that the use of a multiple-dose inhaler is as effective as is that of a single-dose inhaler for MF administration in patients with moderate persistent asthma, which supports the use of the MF administration system available in Brazil.

One limitation of the present study was that the magnitude of the increase in FEV<sub>1</sub> was reflected in the perception of symptom improvement by the patients. However, taken together, our results demonstrate that the improvement was not substantial, which might be due to the fact that most of the patients evaluated had mild asthma or that the power of the study sample was sufficient to reveal clinical differences among patients with mild symptoms. Studies employing longer follow-up periods (of several months) would allow the assessment of other endpoints, such as the number of exacerbations. However, exacerbations, which were uncommon, occurred at a similar frequency in the two groups.

Inhaled dry-powder glucocorticoid is a pharmaceutical formulation that is effective in the treatment of asthma patients and ensures that this medication is delivered directly to the airways.<sup>(1)</sup> In order to maximize the advantage of using inhaled glucocorticoids, it is necessary to ensure the use of drugs that have a high therapeutic index, are easily administered, and allow uniform, reproducible release.

Among aerosol delivery systems, DPIs have advantages, such as requiring no propellant, greater stability of the formulation, and lower cost.<sup>(1)</sup> As with any inhaled medication, adequate and efficient distribution of the glucocorticoid in the lung depends on the size of the inhaled particles. The smallest airways present internal diameters  $\leq$  2 mm. Particles  $<$  1 mm reach the

pulmonary alveoli and can be absorbed by the pulmonary capillaries, thereby reaching the bloodstream and increasing the possibility of unwanted systemic effects. Particles < 5 µm are more likely to deposit in the bronchi and bronchioles, anatomical structures affected by the asthmatic process, in comparison with particles > 5 µm, which frequently deposit in the mouth and oropharynx, where they can cause adverse events, such as oral candidiasis.<sup>(12,13)</sup> The particles that will effectively reach the therapeutic target sites in the lung, those measuring 1-5 µm, comprise what is the so-called respirable fraction.

In vitro studies utilizing the multiple plate method (Andersen cascade impactor), which simulates the various anatomical regions of the respiratory tree, are a reliable and reproducible way to measure and compare inhaled dry powder formulations, since the low concentrations of the active principle inhaled make it difficult to detect in vivo (in serum).<sup>(14)</sup> Studies using this method demonstrated that a single-dose DPI similar to that used in the present study produced a large number of small, low-dispersion particles.<sup>(15)</sup> It has been demonstrated that higher inspiratory flows are achieved with a single-dose DPI than with a multiple-dose DPI (Turbuhaler), and these higher flows can increase pulmonary deposition.<sup>(16)</sup> A large, multicenter, open-label study, similar to the present one, showed equivalent results when the effects of budesonide administered via a single-dose DPI (Aerolizer) were compared with those of the same drug administered via a multiple-dose DPI (Turbuhaler) in asthma patients.<sup>(17)</sup> Another study demonstrated that mometasone (400 µg/day) administered via a multiple-dose DPI is as effective in combating asthma as is budesonide (400 µg twice a day).<sup>(18)</sup> The results of the present study allow us to infer that similar results would be obtained with a single-dose DPI.

Patient preference for a given inhalation device should be considered, although this was not evaluated in the present study. In a study of COPD patients, the frequency of significant errors in the use of the inhaler was found to be greater for single-dose DPIs.<sup>(19)</sup>

Despite these potential limitations, our results found allow us to conclude that the use of the single-dose inhaler developed in Brazil

for MF administration once a day is as safe and effective as is that of a multiple-dose inhaler, thereby making it possible to provide treatment at a lower cost.

## References

1. Suissa S, Ernst P. Inhaled corticosteroids: impact on asthma morbidity and mortality. *J Allergy Clin Immunol.* 2001;107(6):937-44
2. Biggadike K, Uings I, Farrow SN. Designing corticosteroid drugs for pulmonary selectivity. *Proc Am Thorac Soc.* 2004;1(4):352-5..
3. Sharpe M, Jarvis B. Inhaled mometasone furoate: a review of its use in adults and adolescents with persistent asthma. *Drugs.* 2001;61(9):1325-50.
4. Berger WE, Milgrom H, Chervinsky P, Noonan M, Weinstein SF, Lutsky BN, Staudinger H. Effects of treatment with mometasone furoate dry powder inhaler in children with persistent asthma. *Ann Allergy Asthma Immunol.* 2006;97(5):672-80.
5. Affrime MB, Cuss F, Padhi D, Wirth M, Pai S, Clement RP, et al. Bioavailability and metabolism of mometasone furoate following administration by metered-dose and dry-powder inhalers in healthy human volunteers. *J Clin Pharmacol.* 2000;40(11):1227-36.
6. Fish JE, Karpel JP, Craig TJ, Bensch GW, Noonan M, Webb DR, et al. Inhaled mometasone furoate reduces oral prednisone requirements while improving respiratory function and health-related quality of life in patients with severe persistent asthma. *J Allergy Clin Immunol.* 2000;106(5):852-60.
7. Bernstein DI, Berkowitz RB, Chervinsky P, Dvorin DJ, Finn AF, Gross GN, et al. Dose-ranging study of a new steroid for asthma: mometasone furoate dry powder inhaler. *Respir Med.* 1999;93(9):603-12.
8. Nayak AS, Banov C, Corren J, Feinstein BK, Floreani A, Friedman BF, et al. Once-daily mometasone furoate dry powder inhaler in the treatment of patients with persistent asthma. *Ann Allergy Asthma Immunol.* 2000;84(4):417-24.
9. Kemp JP, Berkowitz RB, Miller SD, Murray JJ, Nolop K, Harrison JE. Mometasone furoate administered once daily is as effective as twice-daily administration for treatment of mild-to-moderate persistent asthma. *J Allergy Clin Immunol.* 2000;106(3):485-92.
10. Leiner GC, Abramowitz S, Small MJ, Stenby VB, Lewis WA. Expiratory peak flow rate. Standard values for normal subjects. Use as a clinical test of ventilatory function. *Am Rev Respir Dis.* 1963;88(5):644-51.
11. Bosquillon C, Lombry C, Pr at V, Vanbever R. Influence of formulation excipients and physical characteristics of inhalation dry powders on their aerosolization performance. *J Control Release.* 2001;70(3):329-39.
12. Vanden Burt JA, Busse WW, Martin RJ, Szeffler SJ, Donnell D. Efficacy and safety overview of a new inhaled corticosteroid, QVAR (hydrofluoroalkane-beclomethasone extraline inhalation aerosol), in asthma. *J Allergy Clin Immunol.* 2000;106(6):1209-26.
13. Derendorf H, Nave R, Drollmann A, Cerasoli F, Wurst W. Relevance of pharmacokinetics and pharmacodynamics of inhaled corticosteroids to asthma. *Eur Respir J.* 2006;28(5):1042-50.

14. Rudolph G, Kobrich R, Stahlhofen W. Modeling and algebraic formulation of regional aerosol deposition in man. *J Aerosol Sci* 1990; 21(suppl 1): 403-6.
15. Crieé CP, Meyer T, Petro W, Sommerer K, Zeising P. In vitro comparison of two delivery devices for administering formoterol: Foradil P and formoterol ratiopharm single-dose capsule inhaler. *J Aerosol Med*. 2006 ;19(4):466-72.
16. von Berg A, Kremer HJ, Ellers-Lenz B, Conrad F, Erb K, Maus J, Hermann R. Peak inspiratory flow rates generated through the Novolizer and the Turbuhaler dry powder inhaler devices by children with stable asthma. *J Aerosol Med*. 2007;20(1):50-8.
17. Chuchalin AG, Kremer HJ, Metzner P, O'Keefe E, Hermann R. Clinical equivalence trial on budesonide delivered either by the Novolizer multidose dry powder inhaler or the Turbuhaler in asthmatic patients. *Respiration*. 2002;69(6):502-8.
18. Bousquet J, D'Urzo A, Hebert J, Barraza CH, Boulet LP, Suárez-Chacón R, Harnest U, Lundbäck B, Martínez Morales G, Nieminen MM, Nolop KB, Visser S, Lutsky BN. Comparison of the efficacy and safety of mometasone furoate dry powder inhaler to budesonide Turbuhaler. *Eur Respir J*. 2000;16(5):808-16.
19. Wilson DS, Gillion MS, Rees PJ. Use of dry powder inhalers in COPD. *Int J Clin Pract*. 2007;61(12):2005-8.

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