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REVIEW

The dry powder inhaler features of the Easyhaler that benefit the management of patients

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ABSTRACT

Introduction: Inhaled therapies are likely to continue to dominate asthma and chronic obstructive pulmonary disease treatment. Dry powder inhalers (DPIs) have several advantages over pressurized metered-dose inhaler (pMDIs), that are most frequently marketed world-wide, but often difficult to use. This literature search focus on DPI features, with respect to Easyhaler, that may affect their use and patients' clinical benefit.

Areas covered: DPIs are breath-actuated, easy to use, convenient to use, and more environmentally friendly. During inhalation, the formulation in a DPI is disaggregated by a turbulent airflow energy to generate particles with the greatest likelihood of deposition into the airways. The resistance among DPIs varies from low to high and those with high resistance are wrongly considered as difficult to use. Multidose reservoir-type DPIs have been developed to efficiently deliver a wide range of medications, including the fixed-dose combination of budesonide and formoterol. Easyhaler® shares a similar shape with pMDIs and, as other DPIs, its performance is unaffected by environmental and storage conditions. Due to Easyhaler internal design, dose emission is consistent irrespective of the inhalation flow used by each patient.

Expert opinion: Easyhaler® may be considered one of the most convenient inhalers, for daily use, in patients with asthma or COPD.

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KEYWORDS
Asthma; COPD; Easyhaler; dry powder inhalers; inhaler resistance; inhalation flow; dose emission

1. Introduction

The main goals of pharmacological therapy for asthma, chronic obstructive pulmonary disease (COPD), and asthma/COPD overlap (ACO) are to control symptoms, reduce the frequency and severity of exacerbations, improve exercise tolerance and the health status, and reduce mortality. These goals can be reached by following new relevant recommendations from the updated GINA guidelines, e.g. the avoidance of SABA-only treatment and an ICS-containing controller treatment, either as-needed (in mild asthma) or daily [1,2]. Since medications are frequently administrated by inhalation and numerous inhaler devices have been specifically designed to deliver each class of inhaled drugs to patients, the choice of both drugs and device should be individualized in order to maximize the clinical benefit [1–3].

Technological innovations in inhaler devices have improved their efficiency in lung deposition up to 40% of the nominal dose, compared with 10–15% that was achieved in the past [4]. The high technological performances of drug formulation and inhalers can be totally wasted if these devices are not correctly used or inhaled according to the health-care provider instruction. In the real world, physicians and patients struggle to master the appropriate inhalation technique: among patients, errors in inhalation technique and medication delivery occur in 20–80% inhaler users [5] and among physicians, only 10–52% demonstrate adequate knowledge of the proper device use [5]. Less than 20% of patients are fully adherent with their inhaled therapy [6]. The most common clinically significant errors, irrespective of the type of inhaler, are not making an exhalation before each inhalation and no breath holding at the end [7]. Not inhaling as fast as possible [7] and not using a slow inhalation [8] are also clinically important for dry powder inhalers (DPIs) and pressurized metered-dose inhalers (pMDIs), respectively.

The increasing complexity of inhalers contributes to improve the clinical advantages, but unavoidability amplifies the problems associated with their use [5]. Therefore, standardized and simplified techniques for the use of inhalers in the treatment of asthma and COPD should be proposed [3], with the aim to limit the misuse of inhalers and improve the proper medication delivery and treatment [9]. Furthermore, adherence is also important [1,2] and low adherence is related to poor control [10]. This can be improved by counseling linked to feedback and patient satisfaction with their inhaler [10,11].

This literature search in Pubmed includes the main evidence on DPI features that may affect their use and the clinical benefit of patients. Data from clinical trials were considered, when available, as well as real-world evidence. The review examined technological and training issues associated with the use of DPI in clinical practice, focussing on features of the Easyhaler device.

2. Dry powder inhalers (DPIs)

DPIs have been designed to reproducibly deliver a predefined dose of the drug to the airways of the lung. The portion of the

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Article highlights

- Pharmacological therapy for asthma, chronic obstructive pulmonary disease (COPD), and asthma/COPD overlap should control symptoms, reduce the frequency and severity of exacerbations, improve exercise tolerance and the health status, and reduce mortality. The choice of both drugs and inhalers should be individualized to maximize the clinical benefit.
- An ideal inhaler should be easy-to-use as well as patient's acceptance and preference.
- Dry powder inhalers have been designed to reproducibly deliver a predefined dose of the drug to the airways of the lung.
- During an inhalation, a turbulent airflow energy is generated inside a DPI by the interaction between the inhaler's resistance and the inhalation flow. This energy deaggregates the formulation of the metered dose to provide a fine particle dose that is deposited into the airways.
- When patients use a DPI with the same inspiratory effort, the peak inhalation flows are lowest through an inhaler with high resistance and highest through those with low resistance. The resulting turbulent airflow energy is higher in DPIs with higher resistance.
- Easyhaler®, a multiple-dose DPI, demonstrates similar clinical efficacy to pMDIs and other DPIs and patients have no difficulties in using it.
- The consistency in the fine-particle dose, the performances regardless of inhalation flow, safety, and efficacy are other important parameters that should be considered in the choice of an inhaler. The Easyhaler meets these criteria.

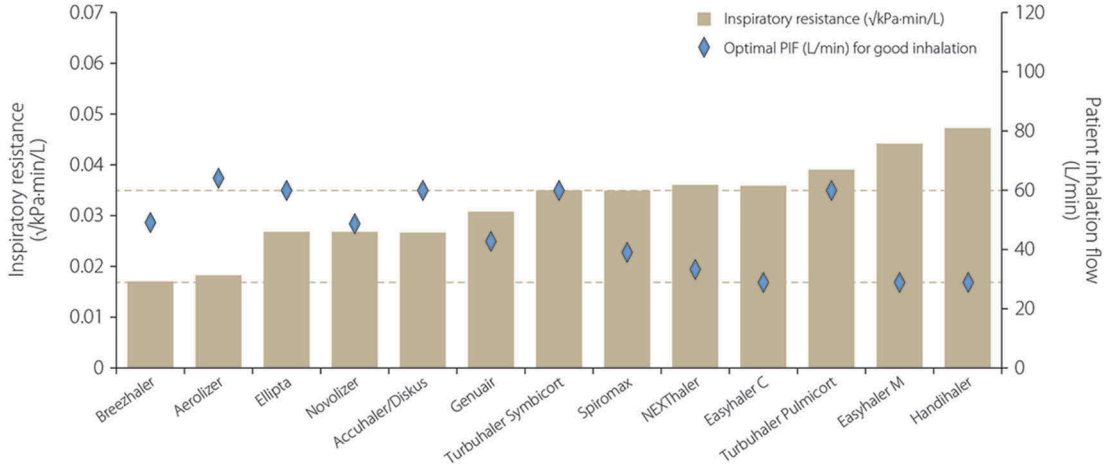
inhaled dose that can reach and deposit in the airways to exert its local clinical effects, contains aerosol particles in the fine-particle fraction range of 1–5 µm [3]. The mass of these particles, in the emitted dose, within this size range, is known as the fine-particle dose (FPD). The FPD varies widely among inhalers, with 12–35% for DPIs, 10–50% for pMDIs, and 30–50% for the soft mist inhaler [12–14]. A fast inhalation is clinically important [7] when using a DPI because these devices utilize the interaction between the patient's inhalation flow and the internal resistance of the inhaler to provide a turbluent airflow energy that de-aggregates (break-up) their drug formulations [15–18]. Figure 1 shows that the resistance of DPIs ranges from low to high. This figure shows that to achieve a set turbulent airflow energy, for example, an energy equivalent to a pressure change of 4 kPa, the higher the resistance then the lower is the required peak inhalation flow (PIF). The higher the resistance then the lower is the inter-patient variability of PIF [17]. Also, when patients use different inhalers with the same inspiratory effort the PIF is lower and the turbulent airflow energy is higher through DPIs with high resistance compared to those with low resistance [17]. In simple words, for the patient to receive the targeted treatment dose, with a high-resistance inhaler device a low PIF through the inhaler is enough, while with low resistance devices a higher PIF is required. This is highlighted in Figure 1 and explains why the Handihaler, that has the highest resistance, is widely used by COPD patients, regardless of the severity of their disease or the PIF that they can achieve [19].

An ideal device should be easy to use since this improves the inhalation technique as well as patient's acceptance and preference [10,20]. The consistency in the fine-particle dose, the performances regardless of inhalation flow, safety, and efficacy are other important parameters that should be considered in the choice of an inhaler [16].

3. How to overcome common technical mistakes in DPI use

Although DPIs were introduced to overcome the difficulties between inhaler actuation and inspiration [21], in their study on a total of 2288 records of inhaler technique Melani et al. showed that critical mistakes in the use of DPI were common with all kind of devices and were associated with older age ($p = 0.008$), lower schooling ($p = 0.001$), and lack of training on inhaler technique ($p < 0.001$).

The consequences of DPI incorrect use are clinically very relevant, with a significant increased risk of hospitalization, emergency room visits, courses of oral steroids and antimicrobials and poor disease control [21]. Therefore, inhaler



Abbreviations: Peak Inspiratory Flow = PIF; Easyhaler M = Easyhaler Monotherapy; Easyhaler C = Easyhaler Combination therapy.
Optimal PIF refers to the lower limit of desired inspiratory flow

Figure 1. Dry powder inhaler resistance and optimal peak inhalation flow for correct drug delivery [Reproduced with permission from ref [18]].

technique training to minimize errors is essential. Guidelines for asthma [1] and COPD [2] highlight the importance of patients' education and recommend that any new inhaler device should not be prescribed without a deepened training by health professionals who should illustrate the correct use [22].

Different levels of training – intuitive use without instructions, after reading the patient information leaflet and after health-care professional's instruction – were used to instruct patients to use inhalers from several manufacturers; the percentage of patients who correctly used the inhaler differentiated across the levels of training and across the devices [23]. Only when trained by health-care professionals, 95% of patients achieved device use mastery and used correctly the inhaler, independently of the kind of device proposed [23]. That instruction should be, however, followed up by additional visits confirming adequate performance with the inhaler.

4. Easyhaler®: technical performances and therapeutic efficacy

The Easyhaler® is a multiple-dose DPI developed by Orion Pharma (Espoo, Finland) for the administration of monotherapies salbutamol, beclometasone, budesonide, formoterol, and, combination therapies; salmeterol-fluticasone, and budesonide-formoterol. Like the Turbuhaler, resistances of the Easyhaler combination therapies are lower than the monotherapies (Figure 1). The resistance of the budesonide-formoterol Easyhaler is classified as medium/high, as that of the budesonide-formoterol Turbuhaler. This is why inhalation flow rates through the budesonide-formoterol Easyhaler are similar to those through the budesonide-formoterol Turbuhaler [24]. Furthermore, Easyhaler® was compared with a conventional metered-dose inhaler, demonstrating similar clinical efficacy and no difficulties in using it [25].

4.1. Dose uniformity and evaluation of flow rate

The effectiveness of an inhaled treatment may be compromised if the inhalation does not deliver a uniform dose of the drug. Storage temperature and humidity, device handling, and variations in inhalation flows are potential factors that may affect the uniformity of the delivered dose [26]. Easyhaler® has been tested in different environmental conditions that simulated real-world situations – significant temperature and humidity variations, dropping, and after vibration to investigate its consistency in delivered dose uniformity. All these conditions did not modify the uniformity of the delivered dose that remained consistent when different inhalation flows (31, 43, 54 L/min) were applied [26]. Inhalation flow parameters using Easyhaler® were evaluated in 187 patients with asthma and COPD. The mean PIF was 64 L/min, ranging from 35 to 101 L/min, in 143 asthmatic patients (age range - 6–82 years) and 56 L/min, ranging from 27 to 83.7 L/min, in 44 COPD patients (47 to 80 years old). *In-vitro* studies, using the 10th, 50th and 90th percentile of these patient PIF results, revealed that there was only a small inhalation flow rate dependent dose emission effect, as shown in Figure 2, Panel A [18]. Over a range of PIF values, which are representative of patient use, the dose emission of budesonide and formoterol was even more consistent than that achieved by Turbuhaler (Figure 2 Panel B). Even at the 10th percentile inhalation flow, the delivered and fine particle doses were 98% and 89%–93% of those emitted from the median PIF [18]. Therefore, the dose delivered to the lung using Easyhaler® is not exclusively determined by patients' inhalation flow and dosing consistency is guaranteed across a wide range of inhalation flows, from 30 L/min to 60 L/min, as often reported for asthmatic children and COPD patients [20].

Dose emission studies using real-life patient inhalation profiles show that not all of the metered dose is emptied from some DPIs during inhalation [27]. This is due to insufficient inhaled flow and volume passing through the dosing cup of

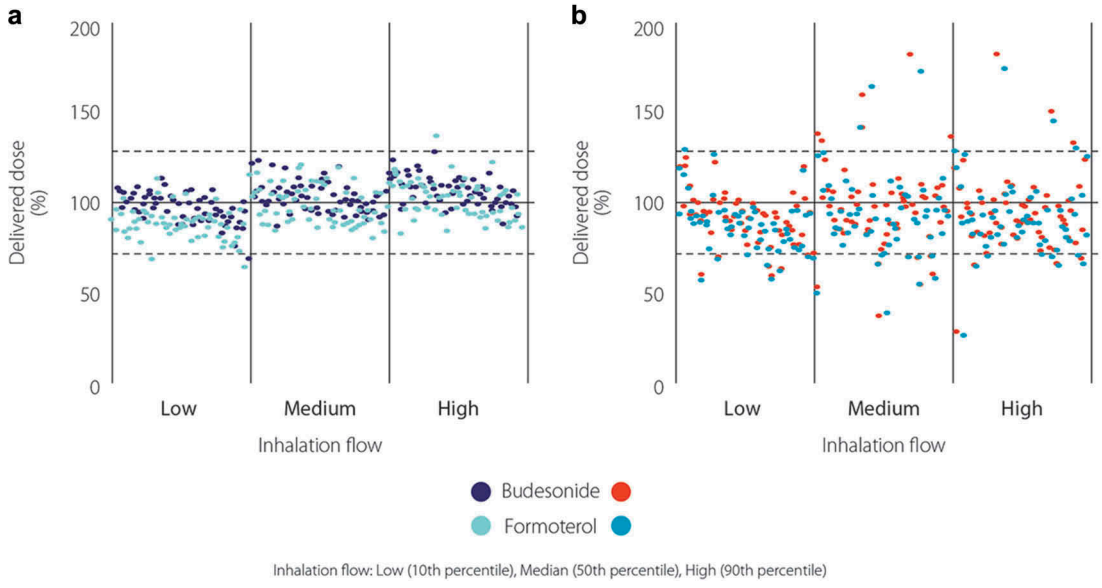


Figure 2. Comparison of two budesonide/formoterol DPIs 160/4.5 µg/dose, Easyhaler (a) and Turbuhaler (b) regarding the consistency of the delivered dose at different inhalation flow rates [Reproduced with permission from ref [18]].

the device. It has been shown that an inhaled volume of 750 ml is sufficient to empty all the metered dose from the dosing cup of the Easyhaler [28] and that the majority of patients, regardless of age and disease severity exceed this volume when they inhale through the Easyhaler [17,24]. The Easyhaler cross section, in Figure 3, reveals why only a small inhaled volume is required to deliver all the measured dose out of the dosing cup. This figure also shows the airtight reservoir, containing the inhaler's formulation, that protects the product from moisture such that dose delivery is unaffected by adverse storage conditions [26]. When the patient presses the top of the Easyhaler, a click is heard and the filled dosing cup rotates to place the metered dose at the inlet of the inhalation channel, next to the air intake vent. If the patient clicks twice or more, the unused powder falls to the chamber at the bottom of the device and will not be available for further dosing. Hence, only one dose is available for inhalation irrespective of the number of clicks/actuations.

Figure 3 shows that when the patient inhales through the Easyhaler, the inhaled air enters the device through the air inlet vent and is directed into the dosing cup where the metered dose is entrained into the inhaled airstream. Next, the airstream is lead to the aerosolization engine where the narrower flow channel leads to acceleration of the flow rate. Typical flow rates are 70 m/s in the aerosolization engine slowing down to 35 m/s at the exit according to computational fluid dynamics simulation [24]. This accelerated flow combined with wall collisions in the aerosolization engine produces a very efficient de-aggregation of the dose leading to a high and consistent FPD, which is only marginally affected by the patient's inhalation flow rate [24]. A PIF 30 L/min or higher is enough to efficiently disaggregate the dose in the Easyhaler® [17]. This PIF through the Easyhaler® can be easily achieved by both children with asthma and COPD patients [17]. Furthermore, the resistance in the Easyhaler contributes to a lower interpatient variability of PIF values and turbulent airflow energy [17] which leads to low inter- and intra-variation in the dose emission, with respect to the fine-particle delivery [20]. This aspect is extremely important from a clinical point of view since the valuable pharmaceutical performance of a device is given by the consistency between doses and the closeness to the labeled dose.

4.2. Equivalence between budesonide-formoterol Easyhaler and Turbuhaler

Budesonide-formoterol fumarate dihydrate is one of the most well documented of inhaled corticosteroids (ICS) + Long-acting β-agonists (LABAs) combinations currently on the market. This combination shows an increased anti-inflammatory activity and higher efficacy over time in achieving asthma control at a lower total dose of budesonide [29]. The rapid onset of action from formoterol could improve FEV_1 after 5 min from inhalation in asthmatic patients [30]. In MART (Maintenance and Reliever Therapy), for patients with asthma treatment administered by a single inhaler, formoterol quickly reduces symptoms and contributes to achieve asthma control [31]. Budesonide-formoterol Easyhaler® has been shown to be bioequivalent with the reference product budesonide-formoterol Turbuhaler® on both efficacy and safety [32,33]

4.3. Clinical effectiveness and safety

In real-life, the effectiveness of budesonide-formoterol Easyhaler® was evaluated in a post-authorization efficacy assessment study, enrolling 2200 asthmatic outpatients. The percentage of patients with well-controlled asthma (ACT score 20–25 points) increased from 46.6% at the first visit to 90.8% at the third visit, while the percentage of patients with poor control of asthma (ACT score less than 15 points) decreased from 14.9% to 1.2%. The adherence rate increased from 88% at the first visit to 95.3% at the third visit [34]. Tamasi and coworkers [35] have shown that, in a real-world setting, most patients with obstructive airway disease, asthma, COPD or

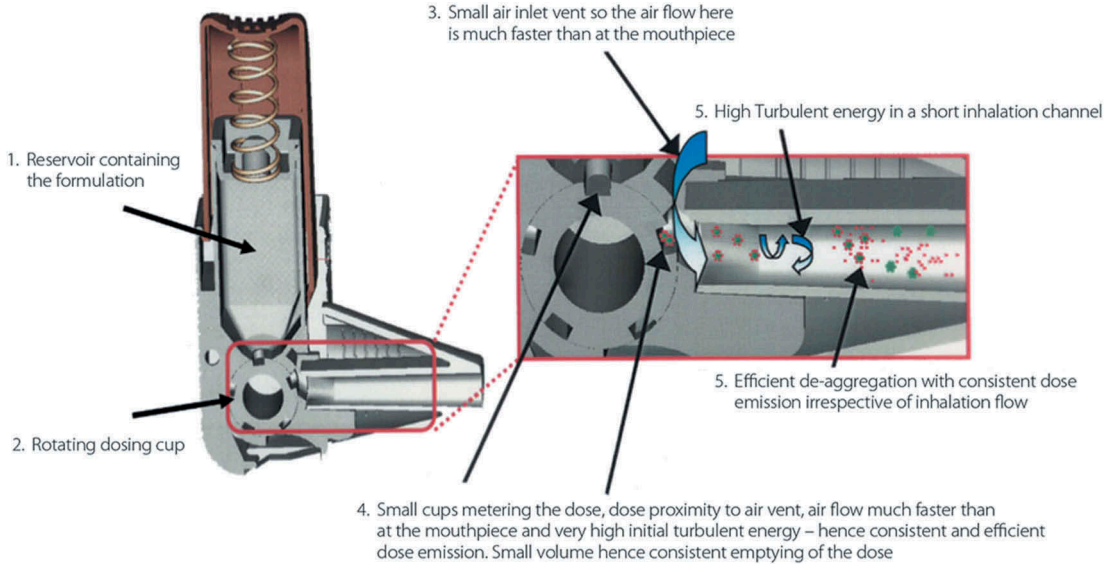


Figure 3. Easyhaler features for consistent dose emission. Cross-section of the Easyhaler® with a schematic design to explain how the fine-particle dose is generated during inhalation [Adapted from ref [20]].

ACO, treated with fixed combinations of inhaled bronchodilators and steroids, and switched from their current inhaler to the Easyhaler®, achieved a better control of the disease, after 3 months from the switching. Of note, most patients considered the Easyhaler® as portable, easy to learn and use and to keep clean device, during daily activities [35]. Both disease control and the quality of life improved, Easyhaler® was considered easy to use and most patients were satisfied with the device [35]. Other studies in real practice described Easyhaler® as easy to teach by clinicians and easy to use, and patients' satisfaction with the device was always high [36].

4.4. Switching device to improve adherence

Switching a patient from one inhaler to another should be accompanied by face-to-face consultation to minimize possible inhalation mistakes, due to technical differences among the various devices [37]. In Swedish primary care, adults with persistent asthma switched from budesonide/formoterol Turbuhaler® to budesonide/formoterol Easyhaler® and showed equivalent or better disease control after switching [38]. In real-life, Price et al. [39] compared clinical outcomes of patients (adults and children) who remained using the same inhaler or switched to Easyhaler®. They showed that 65.7% of patients who switched to Easyhaler® received a face-to-face consultation at the index prescription date, thus suggesting the feasibility of a correct training even in children. Compared to patients who maintained their same inhalers, patients who switched to Easyhaler® gained a higher overall asthma control (OR 1.26, 95% CI 1.05–1.52), and showed non-inferior risk domain asthma control -no asthma-related hospitalization, acute oral steroid use, or lower respiratory tract infection and exacerbation rate [39]. Although mean asthma-related health-care costs increased from baseline to outcome years in both groups, the costs of drugs (SABA) increased significantly more in patients who used other inhalers than in those who switched to Easyhaler® (mean difference £5.5/patient/year) and, consistently, consultation costs decreased significantly (mean difference £13.5/patient/year) [39]. Therefore, choosing the most appropriate inhaler for each patient is essential to achieve good clinical outcomes and optimize health-care resources. During switching, the patient should be involved and trained to avoid more frequent visits to the clinic for training and support and negative impacts on disease outcomes, resulting in higher short- and long-term health-care costs [40,41]. Furthermore, Muller et al. showed that Easyhaler was preferred by most patients and its use as simpler as and more effective than the use of a pMDI [42].

5. Conclusion

Guidelines for asthma and COPD consistently recommend that clinicians instruct patients in the use of their inhaler and regularly check the correctness of inhalation technique. However, it is not clear how this continuous training could be maintained. First of all, significant efforts are required to persuade patients about the importance of a correct inhalation procedure and adherence in face-to-face counseling before prescribing inhaled therapy.

The Easyhaler® is easy-to-use, and patients can be trained with reading the manufacturer's instructions. It has added design features, such as the protective case and dose counter that further facilitate its use, as confirmed by the proven patient acceptance. In addition, regardless of the age of patients and how the device is used, Easyhaler® provides a consistent and accurate drug delivery; this is valuable since any clinical change is related to asthma control rather than to wrong dosing. There is a misconception about DPI resistance because low inhalation flows through a DPI with high resistance are comparable to high inhalation flows through a DPI with low resistance. The internal resistance of budesonide-formoterol combination Easyhaler® is medium-high, as is that of budesonide-formoterol Turbuhaler hence inhalation flows achieved by patients through these two DPIs are relatively similar. This level of resistance in the Easyhaler and its internal design ensure complete deaggregation of the dose even at low peak inhalation flows (30 l/min and above). This inhalation flow can be achieved by children with asthma, adults with asthma and COPD patients regardless of the severity of their disease.

6. Expert opinion

Mistakes in the use of inhalers limit the clinical benefit, and so significant efforts are required to educate patients about the importance of a correct inhalation procedure and adherence. The easier the inhaler is to use, then the incidence of inhaler technique errors is reduced and the lesser the dose is affected by the patient's inhalation flow then the more consistent is the delivery of the emitted dose. Dry powder inhalers have different degrees of resistance such that when patients use one with a high resistance their inhalation flows are lower than when they use an inhaler with low resistance.

Among DPI currently available on the market, Easyhaler® is easy-to-use, and so patients can be trained with reading the manufacturer's instructions. Also, regardless of the age of patients and how the device is used, it provides a consistent and accurate drug delivery. The resistance of the budesonide-formoterol Easyhaler is classified as medium/high, which is similar to that of the budesonide-formoterol Turbuhaler. This means that inhalation flow rates through the budesonide-formoterol Easyhaler are similar to those through the budesonide-formoterol Turbuhaler. The degree of resistance in the Easyhaler contributes to a lower interpatient variability of peak inhalation flow and turbulent airflow energy which leads to the low inter- and intra-variation in the dose emission. In real-life, the effectiveness of budesonide-formoterol Easyhaler® has been evaluated in a post-authorization efficacy assessment study, enrolling 2200 asthmatic outpatients. The results of this study indicated that the percentage of patients with well-controlled asthma increased and even after three visits the majority of patients achieved asthma control. The majority of patients even considered the Easyhaler® as portable, easy to learn and use and to keep clean device, during daily activities; both disease control and the quality of life improved and patients were satisfied with the device.

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Declaration of interest

H Chrystyn has no shares in any pharmaceutical company. He has received sponsorship to carry out studies, together with Board Membership, consultant agreements, and honoraria for presentation, from several pharmaceutical companies that market inhaled products. These include Almirall, AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Innovata Biomed, Meda, Menarini, Mundipharma, Napp Pharmaceuticals, Nemera, NorPharma, Norvartis, Orion, Sanofi, Teva, Trudell Medical International, UCB and Zentiva. Research sponsorship has also been received from grant-awarding bodies (EPSRC and MRC). He is the owner of Inhalation Consultancy Ltd. He is also a consultant to Observational and Pragmatic Research Institute Pte Ltd.

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