

**The Ellipta® in asthma and chronic obstructive pulmonary disease: device characteristics and patient acceptability**

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## Abstract

Asthma and COPD are primarily treated with inhaled medication, but delivery of that medication to its site of action is problematic; patients' ability to use inhalers will affect therapeutic response. Multiple inhaler devices are available but they are variably easy to use with consequent effects on compliance, intentional or otherwise. The Ellipta device is a novel blister-strip dry powder inhaler with medium resistance and a consistent delivered dose across a range of inspiratory flow rates. The Ellipta has proven easy to use and is preferred by patients across several evaluations and compared to other inhaler devices. The Ellipta is used to administer multiple inhaled medications, all in single-daily-dose regimens, making it ideal for patients who struggle with complex inhaled therapy regimens.

## Introduction

Asthma and Chronic Obstructive Pulmonary Disease (COPD) are common airway diseases that result in significant morbidity and mortality worldwide. Asthma affects approximately 340 million people[1], resulting in 420,000 deaths in 2016 and 23.7m Disability Adjusted Life Years (DALYs). COPD is the fourth leading cause of death worldwide, accounting for 2.9m deaths in 2016 and 63.4m DALYs[1]. Around 65 million people suffer with moderate to severe COPD[2] which causes significant morbidity and economic burden on top of the effect on mortality[3]. Both conditions are characterised by airway inflammation, airway narrowing and consequent increased respiratory effort.

As conditions of airway inflammation, both asthma and COPD are treated by administration of inhaled medication in order to directly target the site of pathology[3,4]. Current international guidelines place inhaled corticosteroids at the forefront of the therapeutic armamentarium for asthma. COPD is treated primarily by bronchodilation with long acting beta agonists and muscarinic antagonists but both anti-inflammatory and bronchodilator treatments are used for both conditions. Oral therapies including oral corticosteroids and xanthines are used, but are primarily restricted to severe or acute disease due to systemic side effects of most *per oram* therapy.

The mechanics of delivery of inhaled therapy remains a significant challenge in the respiratory field. Devices and systems must be able to deliver relevant medications, alone or in combination, via the variable anatomy of the upper and lower respiratory tract, to the bronchial epithelium. This must be done in as uniform a manner as possible, whilst avoiding deposition in the upper respiratory tract to limit side effects and systemic absorption. Simultaneously, devices must be easy and pleasant to use, otherwise patients will not use them however optimal their delivery characteristics. Published data demonstrates 31% of patients have correct inhaler technique and this has not improved over time[5], perhaps because healthcare professionals inhaler technique can be equally poor[6].

Pressurised metered dose inhalers were first introduced in 1956[7] followed by dry powder inhalers in the late 1960s. Types of DPI have changed significantly since they were first introduced in order to optimise drug delivery and ease of use. Currently available DPIs vary significantly in design features and usability characteristics. In this article we aim to review the Ellipta® device in terms of device elements and patient usage.

## The Ellipta device

### Design features

The Ellipta is a breath-actuated blister strip dry powder inhaler, produced by GlaxoSmithKline plc. (Brentford, UK). The Ellipta device is currently used to deliver Fluticasone Fuorate (FF), Vilanterol (VI) and Umeclidinium (UMEC) in the following preparations: as FF alone (Arnuity®[8]), FF/VI (Relvar®/Revinty®/Breo®[9]), VI/UMEC (Anoro®[10]) and as UMEC alone (Incruse®[11]). Combinations of all three compounds within a single device are currently being tested with results to date being positive[12]. The combination inhalers contain separate blister strips for each medication, with parallel opening of blisters with a single priming action. The Ellipta device provides 30 doses in a single-use device. All preparations are intended for once daily administration, and therefore each device contains 30 days treatment[9–11]. The Ellipta device is licensed for use in people 12 years of age and over. There is no data available for its safe use in a paediatric population.

Actuation of the Ellipta device is kept simple with a three step actuation procedure: open the cover, inhale from the mouthpiece and re-close the cover. The device is primed by the opening of the lid, which uncovers the mouthpiece and the device is breath-actuated [13]. The simplicity of use belies a carefully engineered mechanism (figure 1) capable of reliable actuation at low flow rates . The device features a dose counter on the front surface to assist the patient with device replacement once empty. The counter is partly red once fewer than ten doses remain, and entirely red if it is primed after the final dose has been actuated. If a user primes the device by opening the lid (figure 2) and closes it again without inhaling then the dose is lost. The Ellipta® is a single use device, requires no cleaning and can be disposed of or recycled by pharmacies after use.



Figure 1. Internal structure of the Ellipta device. Image by Warwick Design Consultancy. Image ©GSK

### Specification

Aerosolisation of the contents of any DPI is dependent on sufficient flow being produced through the device. This is dependent on the patient generating a drop in pressure at the mouthpiece and the internal resistance of the inhaler. The Ellipta device is designed with a moderate resistance to patient inspiratory effort and has a typical specific resistance of  $0.027 \text{ kPa}^{0.5}(\text{L}/\text{min})^{-1}$  [14], resulting in a 3kPa pressure drop giving flow of 60L/min[13], and a 4.0kPa pressure drop giving flow of 74L/min[14]. Table 1 compares device resistances between the Ellipta and other DPIs. The inspiratory flow rate is an important inhalation profile parameter because of its direct influence on the dose delivery from most DPIs. The Ellipta device produces consistent dose delivery at flow rates over 30L/min[13,15] and this covers the inhalation rates across asthma and COPD disease severity, with even patients who suffer from very severe COPD able to generate an inspiratory effort of 41.6L/min whilst using the inhaler[15,16].

DPI	Device resistance [14] ( $\text{kPa}^{0.5}(\text{L}/\text{min})^{-1}$ )	Flow at 4.0kPa [14] (L/min)	Inhaler type	Dose Counter	Disease licences
Breezhaler	0.017	111	Capsule	N/A	COPD
Ellipta	0.027	74	Prefilled	Yes	Asthma, COPD
Accuhaler	0.027	72	Prefilled	Yes	Asthma, COPD
Genuair	0.031	64	Prefilled	Yes	COPD
NEXThaler	0.036	54	Prefilled	Yes	Asthma, COPD
Turbohaler Pulmicort	0.039	54	Prefilled	Yes	Asthma, COPD
Handihaler	0.058	37	Capsule	N/A	COPD

### Aerosol Characteristics

The particle size and fine particle fraction of the Ellipta inhalers vary by the medication delivered. Analysis using a next-generation impactor (NGI) at flow rates of 60L/min, the mean delivered dose (as % of the prescribed dose/blister content) is 81-94%. This drops to 71-97% when flow rates vary between 30-90L/min. The mean delivered dose increases with higher flow rates due to improved deagglomeration of the powdered medication. Mean fine particle mass ( $<5\mu\text{m}$ ) at 60L/min varied between 18.5% to 34.4% of blister content in ambient conditions[13].

In vitro evaluation of drug delivery using patient inhalation profiles captured in vivo demonstrates mean delivery of 77-90% of the blister content depending on the device contents[15]. This results in a pulmonary fraction (Ex-throat dose) of 22.0-42.5% and a fine particle dose of 18.8-37.2%, again depending on blister contents.

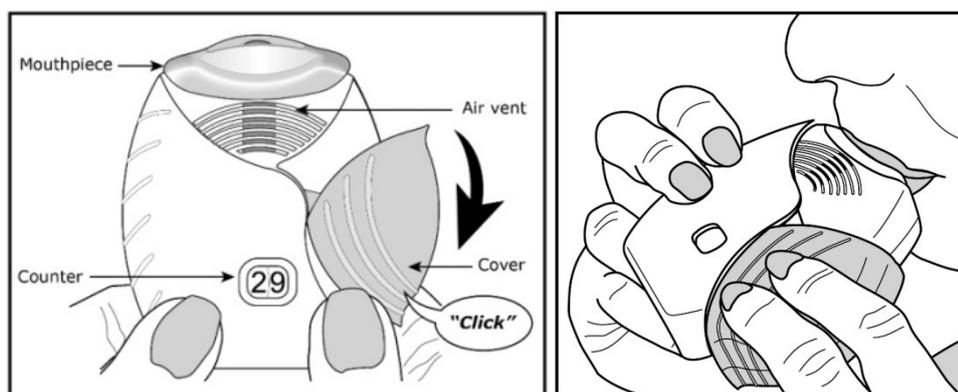


Figure 2. Priming and actuation of the Ellipta device, showing the key external features (Note a change in orientation does not affect device function). Image ©GSK.

### Ellipta and patients with airway disease

Optimising treatment effectiveness requires tailoring the drug-device combination for each individual patient, based on his/her individual characteristics, the disease and its severity, the characteristics of the device, and the skills of involved healthcare professionals. When prescribing any inhaled medication for the treatment of asthma and COPD, ease-of-use, patient preference and their satisfaction with the device must be taken into account. Studies have shown that adherence to inhaled therapies is generally poor[17] and this has been associated with complicated inhaler regimens, misplaced beliefs around side effects and a poor experience in using the device[18,19]. As a consequence the choice of inhaler should be, in part, based on ease-of-use and patient satisfaction as this can influence a person's adherence to their treatment and thus potentially alter their long-term outcome[18,19]. Furthermore correct inhaler technique is vital for efficient drug delivery. Tailored patient training, by a healthcare professional, is recommended by international guidelines for asthma and COPD management[3,4]. Critical inhaler errors can be defined as those that significantly impact the effectiveness of the drug delivery to the airways, for example failing to open the cover of the device, or exhaling directly into the mouthpiece. Without training and education, critical inhaler errors (which significantly impact the effectiveness of drug delivery) occur commonly in both asthma and COPD[20,21].

### Critical errors, time needed for instruction, ease-of-use and patient preference for Ellipta

Critical errors, time needed for instruction, ease-of-use and patient preference have recently been assessed in a randomised, open-label, multicentre crossover study in 729 patients with asthma or COPD[22]. Inhaler naïve patients were assigned to inhale Ellipta vs Diskus, metered dose inhaler (MDI), Turbuhaler, Handihaler or Breezhaler. Patients were required to read the Patient Information Leaflet (PIL) before using the device with no other training. Critical errors were recorded by trained respiratory nurses. In addition, the subsequent number of instructions required before correct technique was observed, alongside ease-of-use rating and inhaler preference was reported. Critical errors were made by significantly fewer COPD patients using the Ellipta inhaler compared with all 5 other inhalers ( $p < 0.001$ , Figure 3). Significantly fewer asthma patients made a critical error when

using the Ellipta inhaler compared with the Turbuhaler ( $p < 0.001$ ), with non-significant differences with MDI and Accuhaler ( $p = 0.074$ ). Furthermore the majority of asthma and COPD patients made no errors using the Ellipta inhaler after only reading the PIL. Whereas the majority of patients required nurse instruction and training for the other inhalers before a correct technique was witnessed. In both asthma and COPD populations patients reported a significantly high ease-of-use rating compared with that for the other inhalers (very easy or easy to use;  $p < 0.001$ ). The Ellipta inhaler was also significantly preferred by a majority of patients compared with all other comparator devices ( $p < 0.001$ , Figure 4), with specific preference for the time taken to use, dose counter, comfort of the mouthpiece and ease of opening highlighted. The study protocol minimised bias for patient preference reporting by using standardised, uniform questionnaire assessments completed by patients after finishing all inhaler procedures. By also being performed across multiple centres the results reflect the opinions of a diverse population.

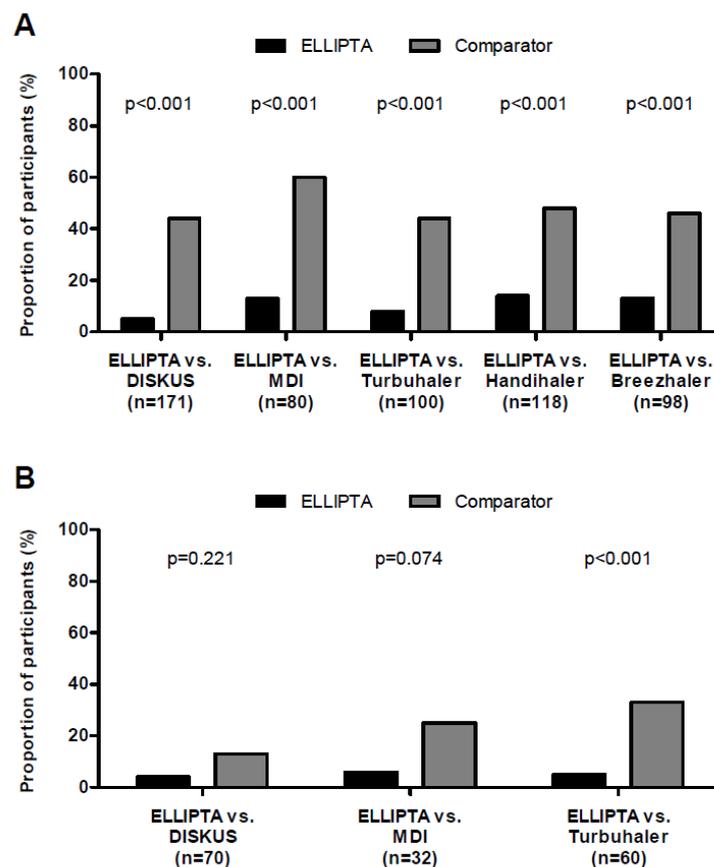


Figure 3. Percentage of patients with A – COPD, or B – Asthma making at least one critical error after reading the patient information leaflet. Reproduced from reference[22]

Patient preference has also been explored in a head-to-head, phase IIIb, randomised, open-label, crossover study between placebo Ellipta and Diskus DPI inhalers[23]. 287 COPD patients were randomised to either an Ellipta once daily or a Diskus twice daily inhaler regime for 1 week before crossover. Inhaler preference was explored based on dose-counter size, inhaler size, number of steps needed, comfort of mouthpiece, ease of opening and dosing regimen preference. A

significantly larger proportion of patients preferred the Ellipta inhaler over the Diskus for each of the selected attributes (all  $p < 0.001$ ). Preference was highest for the dose-counter size (68% vs 20%), number of steps needed to use the inhaler (67% vs 23%) and for the once daily dosing regimen (67% vs 23%).

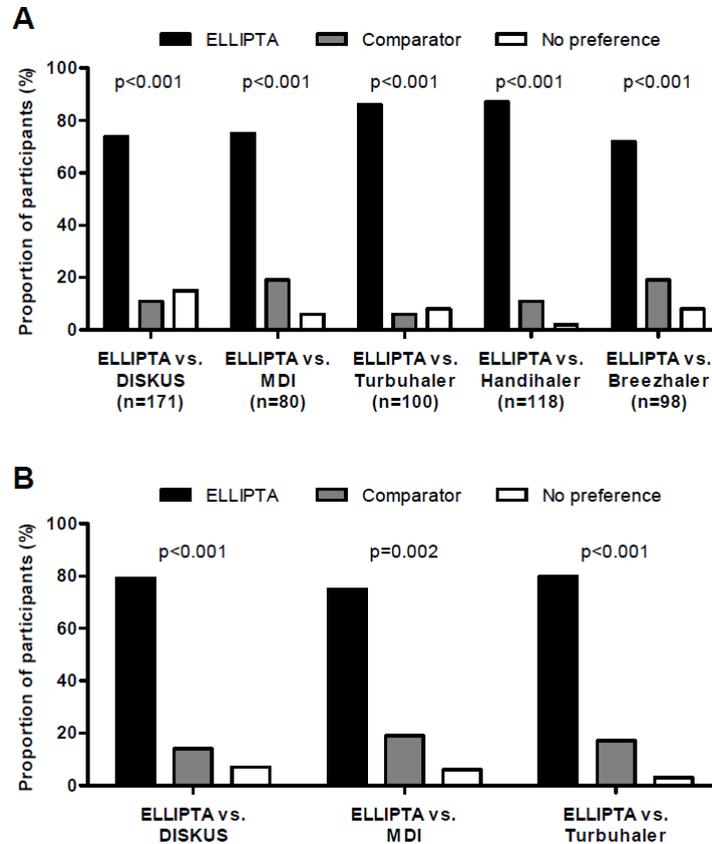


Figure 4. Device preferences reported by Van der Palen et al in A - COPD and B - Asthma. Reproduced from reference[22]

Qualitative assessment through the use of semi-structured interviews has been performed on 75 patients with asthma and COPD who had recently completed a phase IIIa clinical trial of the Ellipta inhaler[24]. Participants were asked about their satisfaction of the device and how they would rate the inhaler on a subjective 1-10 scale. Both asthma and COPD patients reported high levels of satisfaction with the Ellipta device, describing it as easy to use due to simple operation steps, good usability, clear dose counter and overall device ergonomics. Overall average performance scores were greater than 9 out of 10 and again interview participants preferred the Ellipta to other inhaler devices. The Ellipta also performs well in an elderly population, with the vast majority of patients  $\geq 65$  years of age finding it easy-to-use.[13,25]

## Conclusion

The Ellipta device is a patient friendly, easy-to-use device for delivering once daily dry powder therapy for asthma and COPD. It is a medium resistance inhaler that gives a consistent delivered dose over a wide range of inspiratory flow rates. The Ellipta compares favourably with other inhaler devices due to ease of use, handling and appearance. Simplicity of use for patients allows easier education by healthcare professions and greater confidence in reliable delivery of therapeutic compounds. It is an additional option in the complex decision making process in choosing the right inhaler device for the right patient.

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