

Seroflo (Salmeterol + Fluticasone propionate) Multi-haler Monograph

Introduction

Inhaled drug administration covers over 4000 years and traces its roots in India and the Middle East. The inhaled route has several well-recognised advantages over other routes of administration of drugs to the respiratory tract. By inhaling the drug the doses are directly delivered to their receptor sites in the lungs. Also, the amount of inhaled drug doses can be kept as small as possible. Therefore, undesirable side-effects can be minimised and drug response can be detected rapidly.

The introduction of the pressurised metered dose inhaler (pMDI) in 1956 was a milestone in asthma management. However, the drawbacks associated with pMDIs, like requirement of hand to lung co-ordination, cold Freon effect have led to the development of newer inhaler devices, such as dry powder inhalers (DPIs). DPIs offer the possibility of more predictable and less complicated drug delivery. Furthermore, because they contain no propellant or preservatives, they do not give rise to environmental concerns. Since 1987, there has been significant enhancement in the functionality and convenience of the device used in many DPI products developed. Early DPI devices, such as the Spinhaler and Rotahaler, had each dose stored in an individual capsule that the patient needed to load at the time of dosing. Many DPIs commercialised since 1987 are inherently discrete multi dose and require reduced patient manipulation and handling before dosing.

The Multi-Haler is an innovative discrete multi dose DPI designed to reduce the serious handling errors frequently reported with the common devices used by asthma and COPD patients.

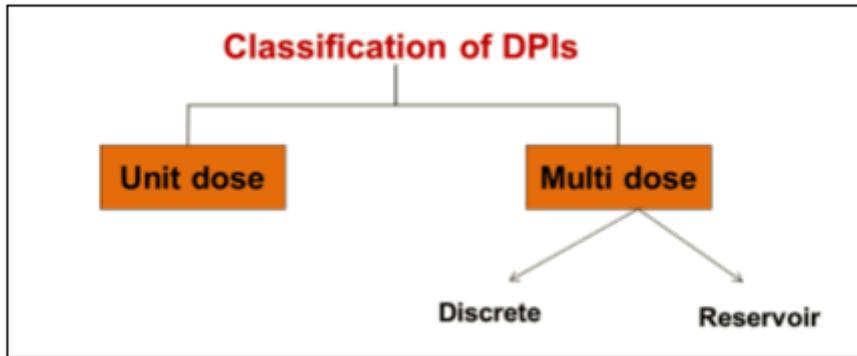
Dry Powder Inhalers

Dry Powder Inhalers (DPIs), as their name implies, dispense medication in a dry powder formulation. DPIs are breath-activated devices. The patient exhales out a full breath, seals lips around the mouthpiece, and then quickly breathes in the powder.⁽²⁾ The technique is different from the pressurized metered dose inhalers (pMDIs) as the DPIs do not require timing and coordination which is essential with pMDIs. DPIs are therefore, easy to use and are as effective as the pMDIs. DPIs can deliver bronchodilators as well as anti-inflammatory medications.

In DPIs the micronised drug is mixed with large carrier particles. The carrier material makes the powder less cohesive and better flowing and thus easier to handle during manufacturing processes. Lactose is the most commonly used carrier. During inhalation the small drug particles separate from their agglomerations or from the surfaces of carrier particles and deposit in the respiratory tract.⁽³⁾

► Classification of DPI

DPI devices can be divided into two major types⁽⁴⁾ on the basis of how the medication is contained:



► Unit Dose DPI

The transparent Rotahaler is a prototype of unit dose devices. It contains factory dispensed unit dose medication with the carrier, which has to be manually loaded into the device by the patient. The powder is released into the device by dividing or piercing the capsule prior to inhaling. The transparent Rotahaler was a major development in inhalation therapy due to its simple design and ease of use. The loading and recharging for every dose may be cumbersome which may impact adherence and hence is a disadvantage of the unit dose devices.

This is overcome by discrete multi dose DPIs, which are more convenient to use. Currently the trend is also moving away from unit dose DPIs towards multi dose DPI devices.

► Multiple-Dose DPI

The first multi dose DPIs were commercialized in Europe in 1988. Discrete multi dose DPIs, by definition, contains more than one dose of drug. There are two types of discrete multi dose DPI, reservoir and multi-unit dose devices.

The currently available multi dose DPIs can be further classified as Discrete-dose type and Reservoir type DPIs.

Multiple unit (Discrete) dose DPIs consist of multiple discrete factory dispensed doses in blisters or cartridges. Multi-unit dose DPIs utilise individually prepared and sealed doses of drug. Excipients such as lactose improve dose uniformity by increasing the mass of powder for each dose thereby improving the accuracy of dose metering and minimising the effect of inhalation flow-dependent dose emission. The sealed blisters offer a high degree of protection against environmental factors such as humidity and because the pre-metered doses of drug are factory prepared and separately packaged, dose uniformity is assured.

Multi dose (Reservoir) type DPI contains doses in bulk and the dose is dispensed by manipulation of the device prior to inhalation. Multi dose reservoir devices contain a bulk supply of drug from which individual doses are released with each actuation. These devices have several disadvantages as compared to the discrete-dose devices. They are susceptible to humidity and moisture. If a reservoir device gets wet or is dropped, the dose consistency for the entire inhaler may be adversely affected, unlike with a discrete-dose device, in which only one dose is lost.

Aspects Of Designing Inhalers

Preferences of physicians and patients form a very important parameter in designing any new device. Based upon patients and healthcare professionals' feedback, the characteristics in designing an 'ideal DPI'⁽⁵⁾ are as stated below.

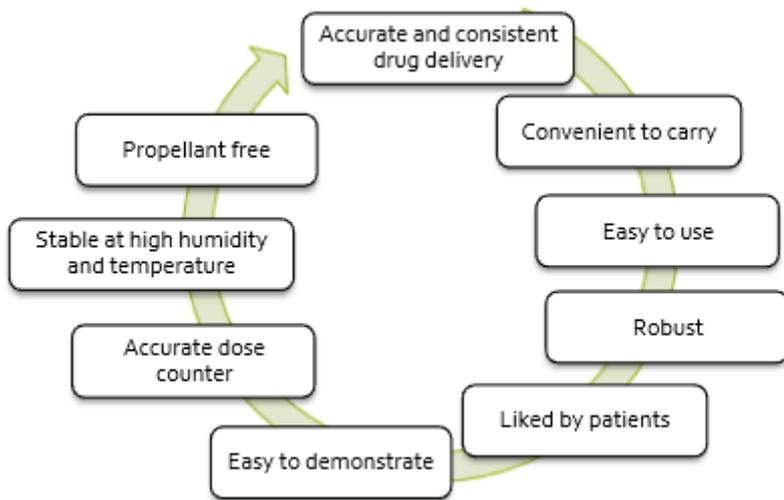
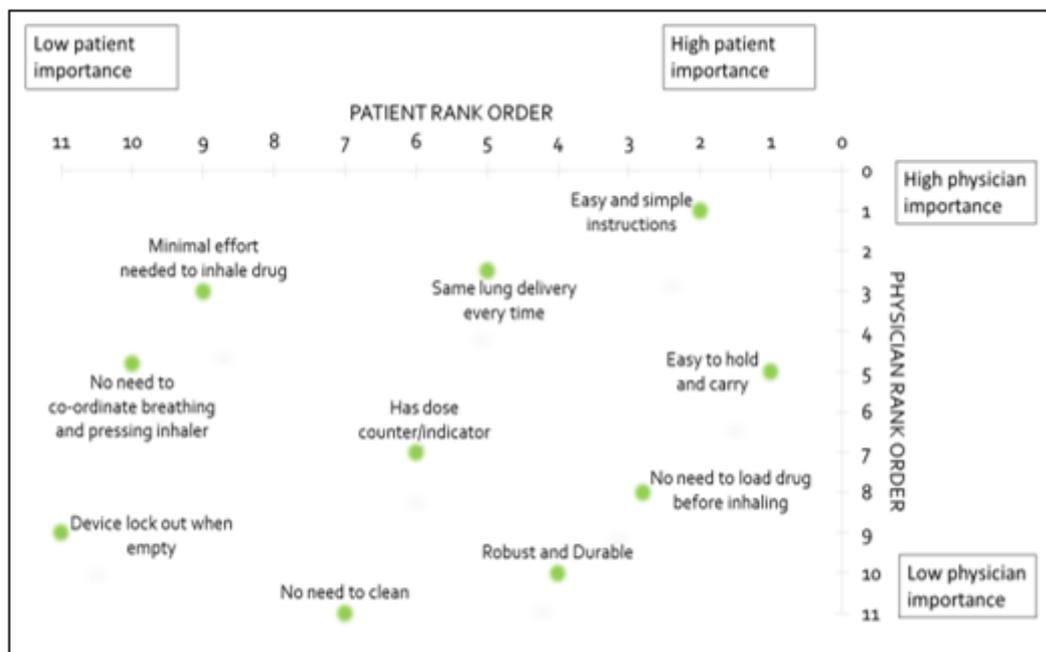


Figure 1: Ideal characteristics of a designing a DPI.

There are various aspects to designing an inhaler. Patients identify a long list of factors that influence their device preference,⁽⁶⁾ ranging from having a dose counter to the ease of carrying the inhaler in a pocket and simplicity of use. The Figure 2 summarizes patient and physician preferences to towards various aspects of inhaler design. “Easy and simple instructions” rank high among preference factors by both patients and physicians (Fig. 2). Factors determining the ease with which the device can be used ranked high amongst the various patient preferences e.g. Easy and simple instructions, easy to hold and carry and no need to load drug before inhaling.

Figure 2: Preference of patients and physicians for various aspects of inhaler design.⁽⁷⁾



The Multi-Haler has been designed considering all the above features (Figures 1 & 2).

Why A Discrete Multi Dose Dpi?



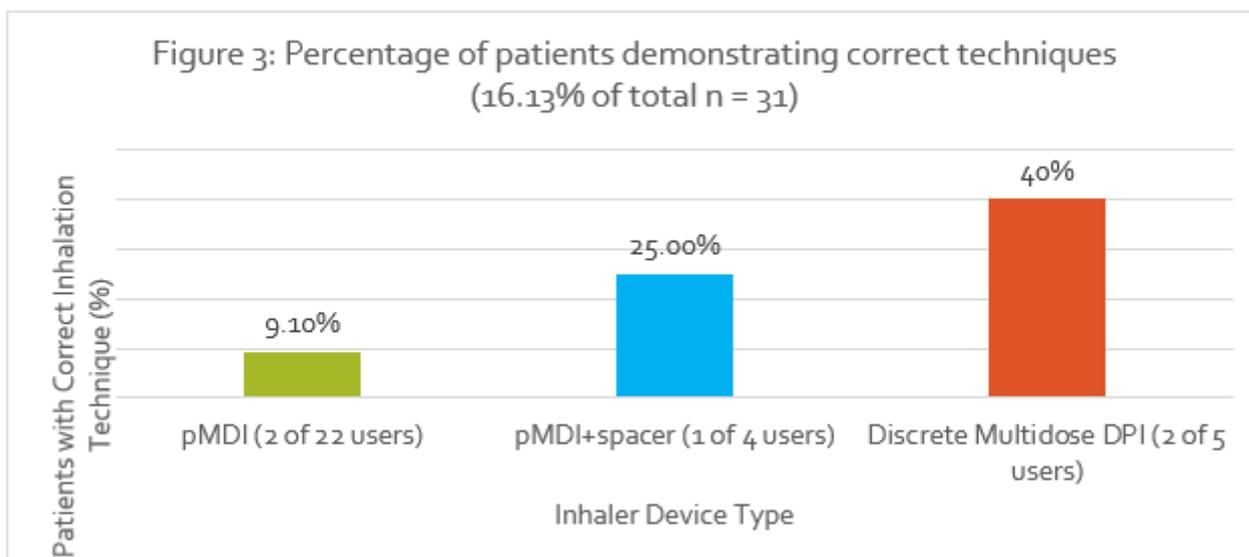
As the number of different types of DPIs on the market continues to increase the prescriber may experience some uncertainty in the selection of the optimal inhalation device for any given patient.⁽⁸⁾

► Reduced Patient Manipulation

Joule and Beauvois have defined manipulation as making people do things that they would not be inclined to do and that they will do thinking that they have made the decision by themselves.

Theoretically, patient education differs from patient manipulation by addressing the reflective intelligence of patients in full light and helping them make autonomous choices. For effective use of device, the patient must be able to manipulate the inhaler and be comfortable and enthusiastic about using it.

A DPI has some distinct advantages⁽⁹⁾ over pMDIs for the delivery of inhaled drugs. Both time and technique of inhaler use impact on clinical outcomes.⁽¹⁰⁾ Extensive training is required to achieve correct use of a pMDI. To deliver the drug effectively into the lung, the patient must actuate the pMDI as they start to inhale. This requires a high degree of ‘hand/lung’ co-ordination.⁽¹¹⁾ In a study by Jahedi *et al*, patients (n = 25) with asthma participated in qualitative semi-structured interviews and quantitative patient satisfaction and preference questionnaires (PASAPQ) were used to explore patients’ preferences, attitudes, perceptions about their inhalers and objective inhalation technique assessment was performed. Percentage of patients demonstrating correct techniques was higher in patients using discrete multi dose DPI when compared to pMDI or pMDI plus spacer (Figure 3). This indirectly reflects reduced patient adjustments made to use the device effectively i.e. reduced patient manipulation.



► Easy to Use

In a randomized, open label crossover study involving patients with asthma (n = 154), more individuals found the discrete multi dose DPI easier to use versus pMDI. (Figure 4)

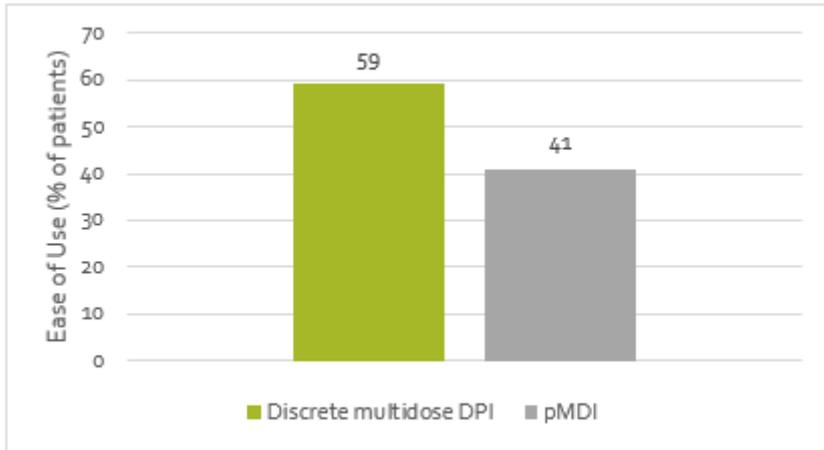


Figure 4: Ease of use of devices.

In an open-label, randomized, crossover DPI preference study which compared the discrete multi dose DPI and single unit dose DPI, the discrete multi dose DPI was preferred to the unit-dose DPI by 89% of subjects (n = 150) for ease of use.⁽¹³⁾

► Reduced Device Handling Errors and Steps

- Reduced number of steps makes the device easy to operate and learn. In a study done to evaluate the number of instructions that are necessary to minimize errors in patients (n = 216) using pMDIs and DPIs, the patients found multi dose DPI easy to operate and learn in one instruction which would imply ease to demonstration.
- pMDI (versus unit dose DPI 1st instruction) were associated with significant error percentage for device handling errors and required more number of instructions to train (Figure 5).
- Discrete multi dose DPI (48%) versus pMDI (3%) was associated with reduced device handling errors at first instruction (Figure 5).



Figure 5: Percentage of device handling errors after three consecutive instructions on proper inhaler technique.⁽¹⁴⁾ *P < 0.05, **P < 0.01, ***P < 0.001, ns = not significant. pMDI, pressurized metered dose inhaler

In a study presented at ATS 2016 International Conference, after reading the patient information leaflet, the proportion of participants who made atleast one critical error was significantly lower with the multidose inhaler compared with the other inhalers (p<0.001; figure 6).

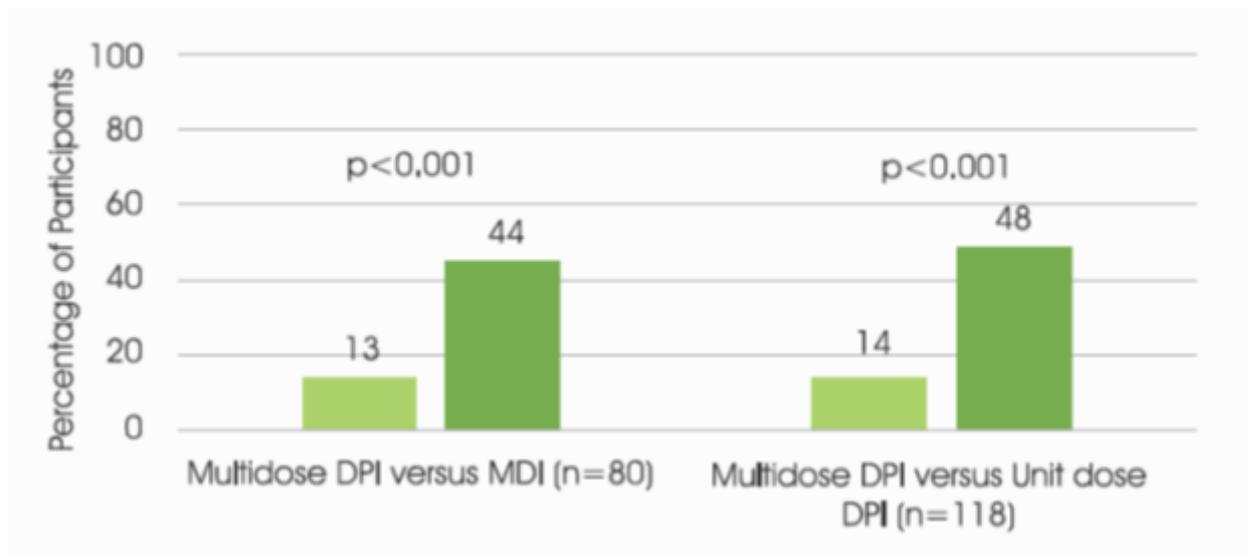


Figure 6. Proportion of participants who made atleast one critical error after reading patient information leaflet.

A critical error was defined as an error that is likely to result in no or minimal (i.e. significantly reduced) medication being inhaled.

A6811 presented at ATS 2016 International Conference. May 13-18, San Francisco, California.

► Preferred by Patients and Physicians

In a multi-center, comparative, cross-over, randomized study involving 419 patients with asthma or COPD, more patients were prescribed DPI (47.5%) as a preferred choice above the pMDI (32.5%).⁽¹⁵⁾

Seth *et al*¹⁸ did a randomized, open-label crossover study involving 154 asthma patients and significantly more patients preferred the discrete multi dose DPI than preferred the pMDI (Figure 7).

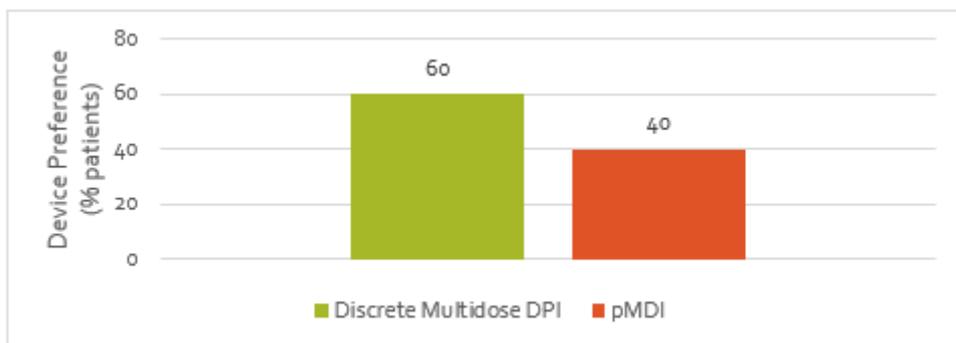


Figure 7: More patients preferred discrete multi dose DPI versus pMDI.

An open-label, randomized, cross over, non-drug interventional, crossover DPI preference study compared the discrete multi dose DPI and single unit dose DPI in which 150 subjects (≥ 40 years, both healthy volunteers and volunteers who had one or more recorded diagnoses, since health status was not assessed as part of study) were randomized to handle either of the DPIs until the point of inhalation, without receiving verbal or demonstrative instruction.

The discrete multi dose DPI was preferred to the unit-dose DPI¹³ by (Figure 8)

- 89% of subjects for ease of use,
- 63% of subjects ($P < 0.0001$) for ease of determining the number of doses remaining in the inhaler,
- 91% for lesser number of steps required,

- 93% for reduced time needed for handling the inhaler.

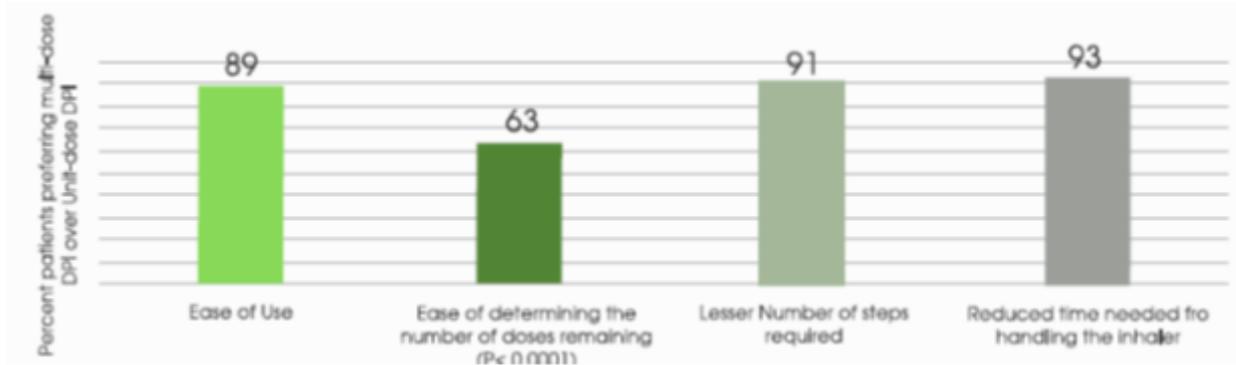


Figure 8. Reasons for patients (n=150) preferring multi-dose DPIs over unit-dose DPIs

Multi-Haler: An Advanced Multi Dose Dpi



- The Multi-Haler is a breath actuated multiple-dose dry powder inhaler device with an in-built dose counter.
- It is an extremely simple to use device consisting of just a single action.
- Rotating the dust cap positions the cartridge below the spike, which pierces one blister.
- The patient inhales the medication and brings the dust cap to its original position.
- The Multi-Haler has been designed as a medium resistance device and demonstrates minimal dependency on inspiratory flow rate.

► Parts of Multi-Haler

Delivering Benefits by Design

Multi-Haler has been ingeniously designed for ease of use. Figure 9 below shows the internal components of the Multi-Haler, each of which is manufactured to precise specifications.

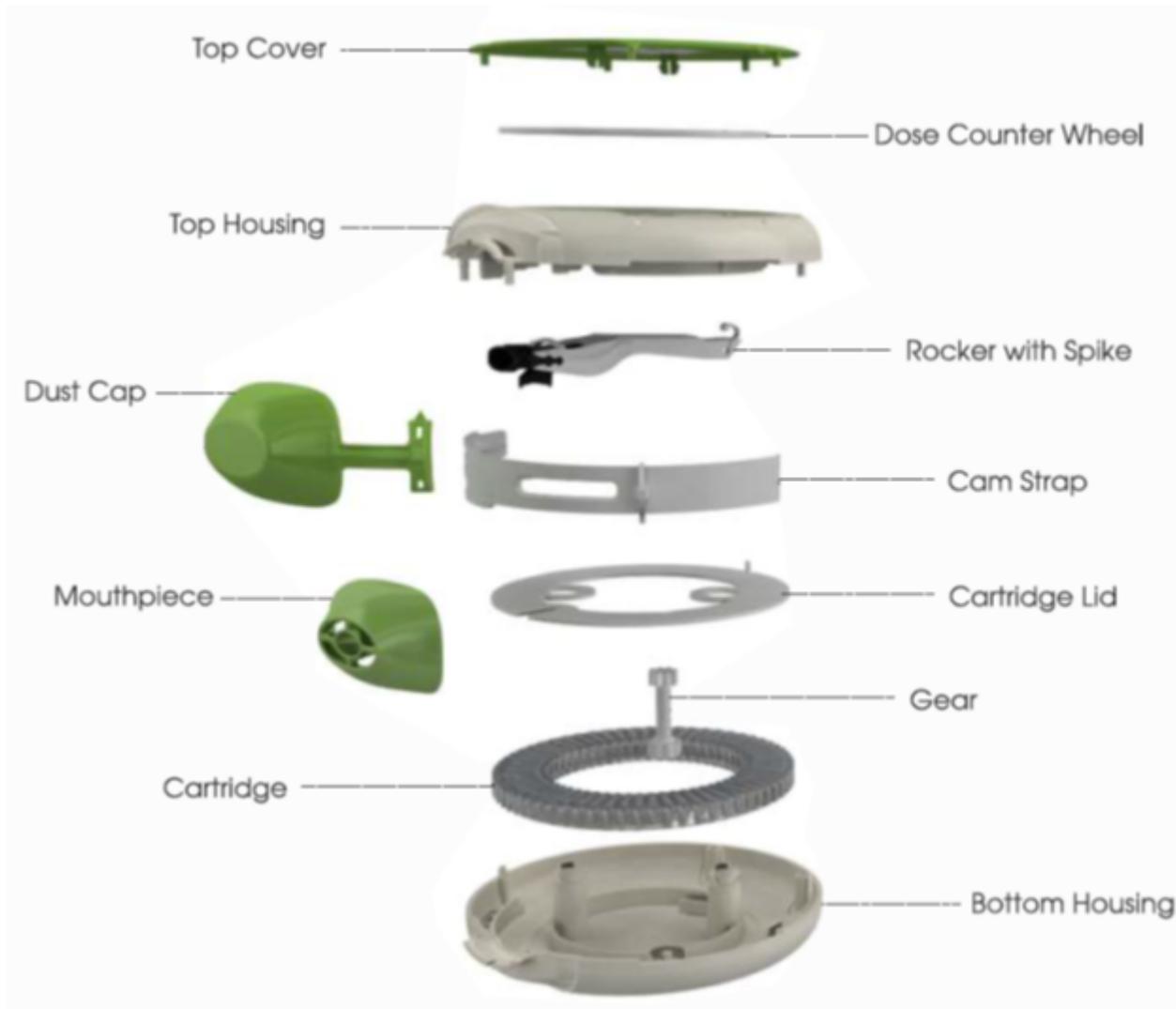


Figure 7: Parts of Multi-Haler.

Part	Function
Dose counter wheel	It has the dose counts inscribed on its surface. The dose counter wheel moves in anticlockwise direction and counts downwards from 60 till 0
Top housing	Holds dose counter along with the spike
Rocker with spike	As the rocker is pulled back the spike is forced down on the aluminium foil and tears it. It also acts like a conduit for air to enter into the capsule chamber for evacuation of drug particle.
The bottom housing	The bottom housing holds the cartridge, cartridge lid and the gear assembly.
Cartridge	Cartridge has 60 capsule chambers arranged adjacent to each other to form a circular ring. It holds the drug to deliver 60 single doses of medication.

Cartridge lid	Cartridge lid holds the cartridge in position and prevents vertical displacement. The lid has a slit whose width is just enough for the spike to pass through to tear the aluminium foil of one capsule chamber at a time. Gear translates the movement of slider to the movement of dose counter wheel such that each actuation results in the reduction of exactly one count.
Cam strap	The cam strap is attached to the slider from within such that it moves along with the slider guiding the spike downwards to rupture the aluminium foil of a single capsule chamber.
Mouthpiece	Mouthpiece is an ergonomically designed component around which the users seal their mouth to inhale through the Multi-Haler.
Mouthpiece cap	Mouthpiece cap prevents dust and moisture from entering the Multi-Haler.

► Working of Multi-Haler

On sliding the mouthpiece cover, the spike is moved into position over a blister and then punctures it. A patient inhales the dose and closes the dust cap. This motion causes the spike to retrieve from the empty blister.

► Mechanism of Operation

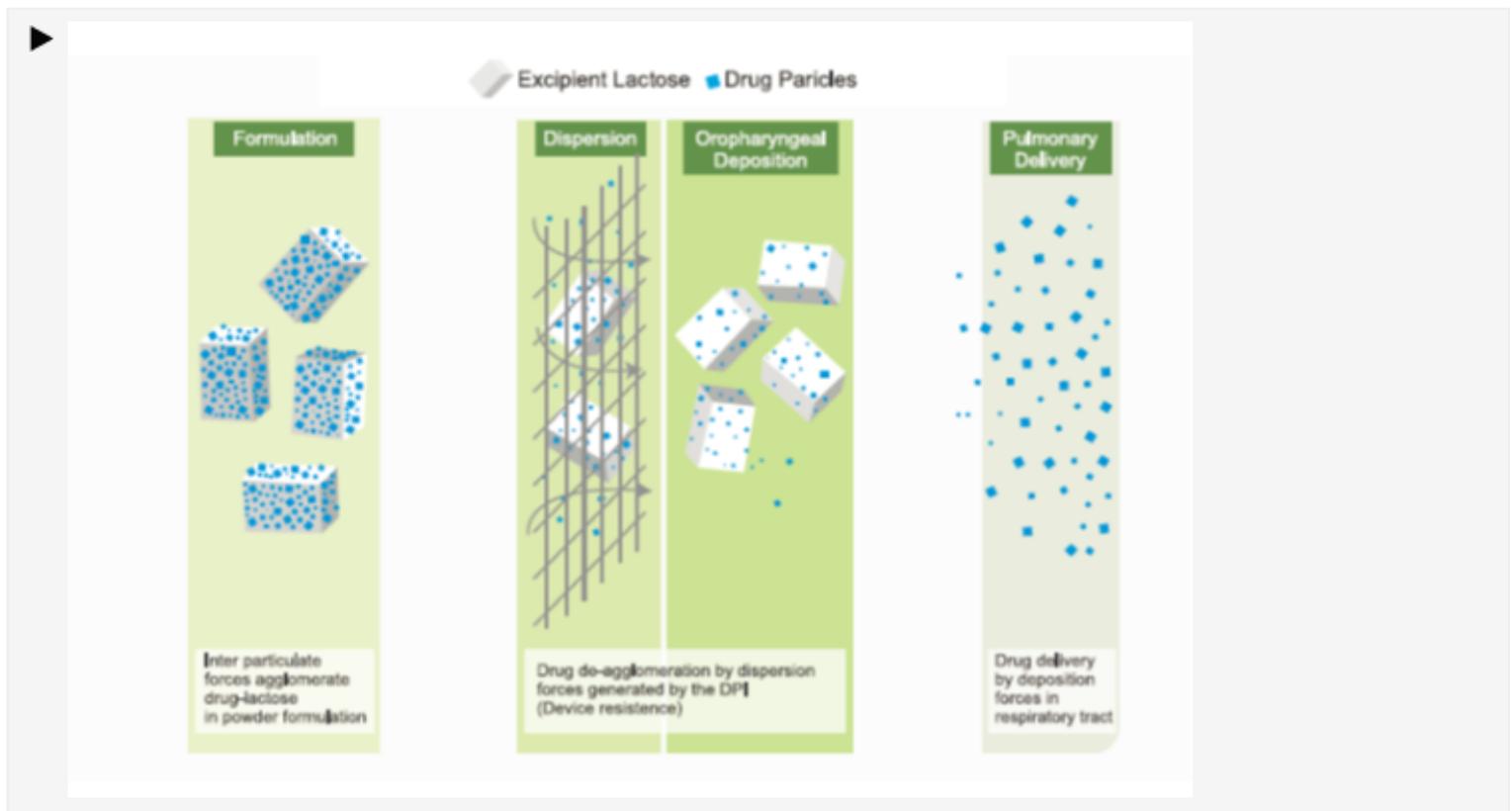


Figure 10: Principle of DPI Operation

Each DPI performance is affected by two main driving forces:⁽¹⁶⁾

- 1) The inspiratory flow generated by the patient, represents the only active force (a passive force for the device) able to produce the micro-dispersion of the powdered drug to inhale.
- 2) The turbulence produced inside the device, which uniquely depends by its inherent technical characteristics. (device resistance)

These factors affect the disaggregation of the powdered drug dose, the diameter of the particles to inhale, the consistency and the variability of the dose, substantially.

Multi-Haler: Designed To Perform

Multi-Haler: Technical Details

- Resistance
- *In-vitro* Analysis
- Stability
- Storage
- Consistent Dosing and In-use Life
- Robustness

► Resistance

When a patient inhales through a DPI, turbulent energy inside the device is created by the pressure drop that results from the interaction between the patient's inhalation flow and the internal design of the DPI, which translates into a resistance to airflow.

Since the turbulent energy is represented by the relationship,

$$\text{Resistance} = \frac{\text{Pressure Drop}}{\text{Patient's Inspiratory Rate}}$$

The above equation implies that the resistance of a device is inversely proportional to patient's inhalation flow. The resistance of a DPI is inherent characteristic and will not change. The higher the resistance of the DPI, the lower the flow required to generate an adequate dose and vice versa.

Multi-Haler is a medium resistance device.

DPI Device	Inspiratory Flow Rate (L/min)	Inspiratory Resistance L/min (kPa ^{0.5})
Multi-Haler 60 Dose Device	74.4	0.027
International discrete multi dose DPI	73.2	0.027

When using a medium-resistance DPI, both the disaggregation and the micro-dispersion of the powdered drug are relatively independent of the patient's inspiratory airflow. The relative independence is because the driving force depending on the intrinsic resistance of the DPI itself is able to produce the turbulence required for an effective drug micro-dispersion. Also, medium-resistance DPIs require a lower inhalation flow rate because the turbulence generated by the intrinsic resistance regimen operating inside these devices contribute substantially to the drug deagglomeration and to the effective production of particulate.⁽¹⁹⁾⁽²⁰⁾

► *In-vitro* Lung Deposition Data

The inspiratory airflow generated by the patient represents the only active force (a passive force for the device) able to produce the micro-dispersion of the powdered drug to inhale.

The extent of the patient's inspiratory airflow depends on the geometry of airways and lung conditions. During an inspiratory movement, the right balance between these two forces represents the critical factor which decides the true effectiveness of the couple "molecule-device".

Higher the airflow, higher the powder dispersion generating a fine particulate. However, at such a high airflow, higher losses via impaction in the proximal airways are incurred which in turn leads to a lower dose reaching peripheral airways.⁽²¹⁾ Vice versa, a lower airflow consents a deeper lung deposition of the powdered drug.

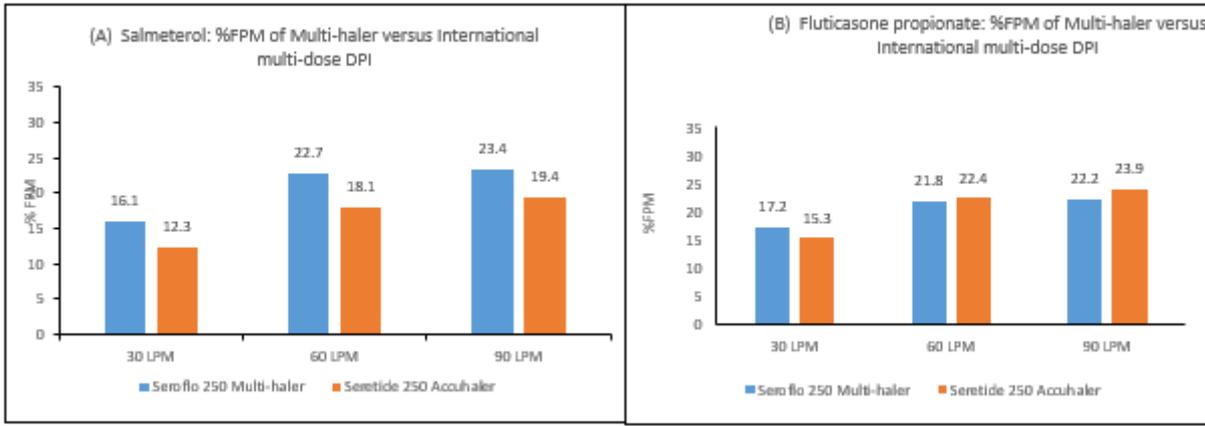


Figure 11: Percent Fine Particle Mass of (a) Salmeterol and (b) Fluticasone propionate in Multi-haler versus International discrete multi-dose DPI at variable flow rates

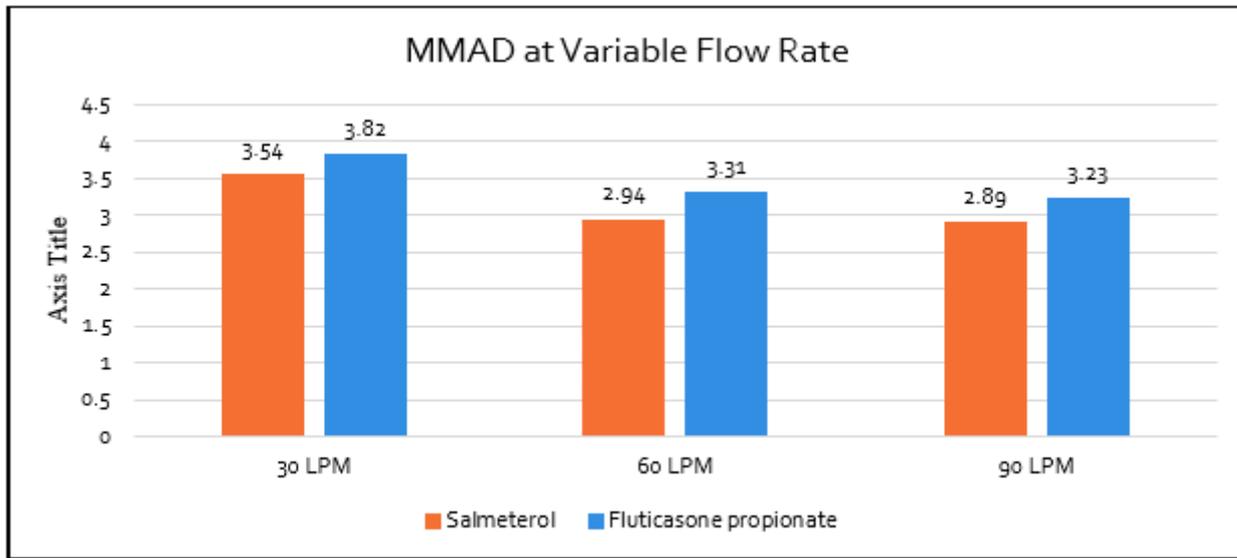


Figure 12: MMAD at variable flow rates.

Percent FPM is the % of delivered dose. The MMAD divides the aerosol size distribution in half. It is the diameter at which 50% of the particles of an aerosol by mass are larger and 50% are smaller. Example, if the MMAD is 3 µm, then by weight, 50% of the particles are >3 µm and 50% of the particles are <3 µm. (text missing, pl. check PDF)

The %FPM of salmeterol and fluticasone propionate of the Multi-haler were found to be comparable with internationally available discrete multi-dose DPIs (Figure 9 A &B). Also, the MMAD with Multi-Haler was found to be consistent with variable flow rates of 30, 60 and 90 LPM (Figures 10). Overall Multi-Haler 60 doses inhaler, in vitro, was shown to deliver a delivered dose closer within the respirable range (1-5 microns) at flow rates between 30 and 90 LPM. The 30 LPM is lower than the minimum >43 L/min peak inspiratory flow rate previously observed in asthma or COPD of all severities, through a moderate resistant DPI.⁽²²⁾

► Stability of Multi-Haler (ASS)

The Multi-Haler has been monitored for stability for performance at different Humidity and Temperature. Performance was analyzed by aerodynamic particle size distribution, delivered dose uniformity, Assay of related substances at

25°C/60% RH, 30°C/65% RH and 40°C/75% RH conditions.

The Multi-Haler was found to be stable with no significant change in all the above mentioned three conditions.

► Consistent Dosing and In-use Life

The delivered dose in the “in-use” life reflects the reproducibility and reliability of the device²⁴. *In vitro* dose delivery performance (Delivered dose) over 30 day Multi-Haler 60 doses inhaler life-time is depicted in the figure 11 below:

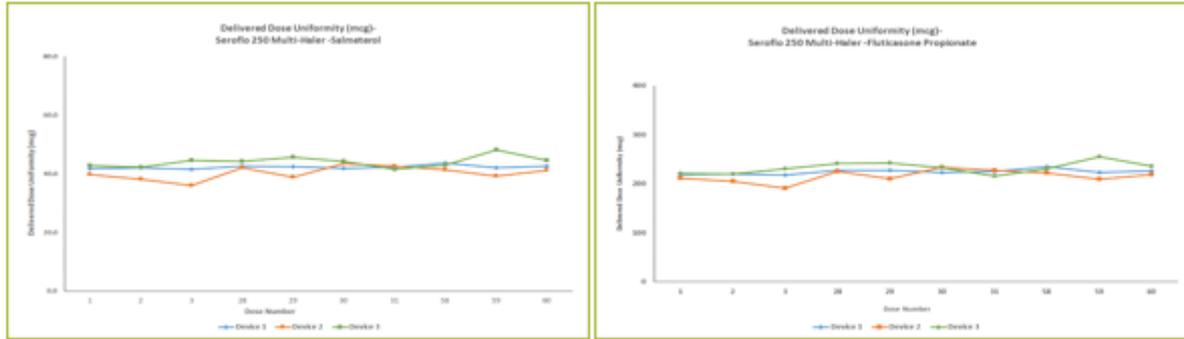


Figure 13: Delivered Dose Uniformity – Seroflo 250 Multi-Haler – a. Salmeterol b. Fluticasone Propionate.

The uniformity analysis was done at a flow rate of 60 L/min from three different devices of Seroflo 250 Multi-Haler.

► Robustness

The Multi-Haler devices were tested for robustness using drop test in which device was subjected to mimic device abuse scenarios. The Multi-Haler is a robust device and successfully withstood abuse scenarios.

Multi-Haler: Features

Unique design of Multi-Haler

- Patient convenience
- In-built dose counter
- Optimum 60 doses
- Discrete unit doses
- High performance
- Easy to demonstrate

► Patient Convenience

- Single action DPI: Reduced number of steps in device usage lead to reduced device handling time and reduced patient errors. These factors may lead to improved adherence and better clinical outcomes.
- Portable, compact and robust design, withstand extensive travel.
- Easy to use and convenient to carry.

► Dose Counter of Multi-Haler

Dose measuring mechanisms conferred to the product have to prevent double or incorrect dosing possible and that the patient should stop using the inhaler when the drug compartment is empty. A good dose counter is needed to address

these needs to indicate the number of doses left in the device.

The dose counter of the Multi-Haler helps to provide the user with confirmation that a dose has been delivered from the device after they have opened and closed the device. It helps patient to stay on track with their medication and also imparts need to refill. When the dose counter indicates red it indicates that it is time to refill the container.



Figure 14. Reading the dose counter of the new multi-haler (60 doses)

A dose counter also helps the doctor to check whether the patient is complying with the prescribed therapy.

Optimum 60 Doses

The Multi-Haler™ is designed to contain 60 doses, which provides an optimal 30 days therapy in the case of Seroflo Multi-Haler™. Studies have showed a positive effect of drug reminder packaging on adherence and clinical outcomes. Since the Multi-Haler™ is not designed to be refilled, it reduces additional steps and inconvenience to the patients, thus reducing the chances of errors.

► Discrete Unit Doses

In the case of Multi-Haler™ each individual dose is factory dispensed in a drug cartridge which is sealed with a moisture proof aluminium foil. This reduces the chances of exposure of the drug due to moisture.

In case the patient accidentally exhales into the device only one dose is lost, since the remaining doses are securely sealed.

If the patient forgets to inhale after sliding the mouthpiece cover the dose does not spill out, so there are no chances of overdosing or clogging of the device when the patient takes the next dose.

► High Performance

- High respirable fraction relatively independent of the flow rate
- Precise and consistent dosing
- Performance not affected by humidity or temperature

► Easy to Demonstrate

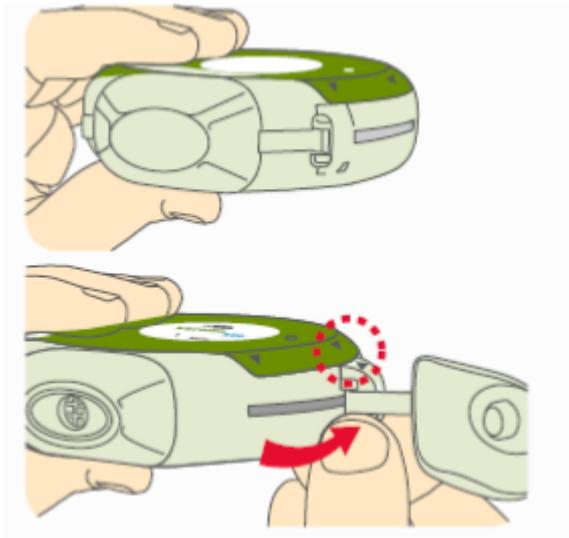
For a healthcare provider, Multi-Haler is an easy to teach device and from patient's perspective it is easy to learn and remember.

How To Use The Multi-Haler?

► Steps in Using Multi-Haler

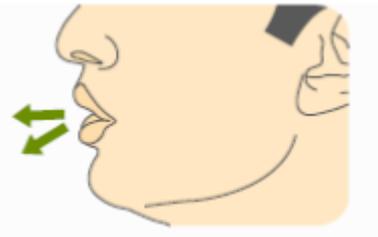
Step 1

Hold the multi-haler in one hand as shown in the picture below. With your other hand, open the mouthpiece cap and put your thumb on the slider and push it backwards. Continue pushing it till the arrow on the slider meets the arrow on the top cover. Ignore the click sound. The dose from the multi-haler is now ready to use.



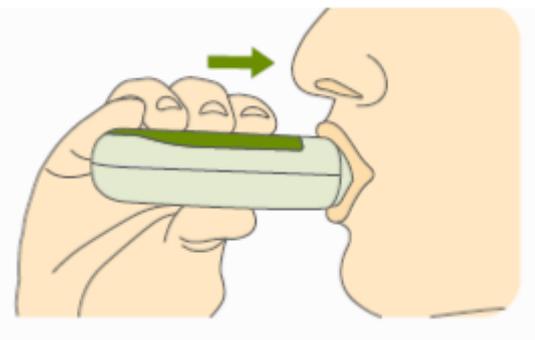
Step 2

Before taking a dose, breathe out fully as far as comfortable through your mouth, . never breathe out into the multi-halare mouthpiece.



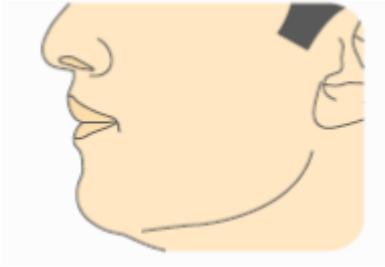
Step 3

Place the mouthpiece in your mouth and close your lips tightly around it. Sit or stand upright, keep your head straight, and breathe in through your mouth quickly and deeply.



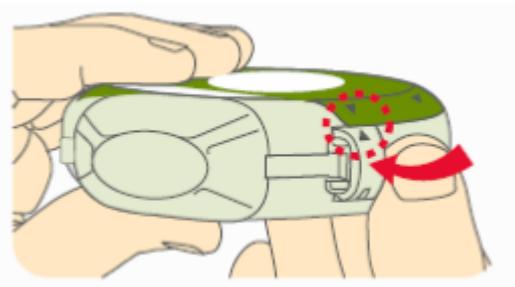
Step 4

Remove the Multi-Haler from your mouth and hold your breath for for about 10 seconds or for as long a sit is comfortable. Then breathe out slowly.



Step 5

Bring the slider back to its original position so that the arrow on the slider matches with the arrow on the top cover.



If another dose is required, repeat steps 1 to 5. Then close the mouthpiece cap and keep the multi-haler in the pouch provided.

After inhalation, rinse your mouth with water and spit it out. Do not swallow.

► Important

- Never breathe out into the Multi-Haler.
- Do not play around with the Multi-Haler or attempt to take the Multi-Haler apart.
- Always use the Multi-Haler in a level, horizontal position.
- Every time the mouthpiece cover is pushed back a dose is ready to be inhaled. Closing the mouthpiece with the cover without inhaling or playing with the mouthpiece cover will lead to wastage of the doses.
- After inhalation, rinse the mouth with water without swallowing.
- The Multi-Haler should NEVER be washed. It should always be kept dry.
- Keep out of reach of children.
- Discard the Multi-Haler when the dose indicator shows red line after 60 doses.

► How to Clean Your Seroflo Multi-Haler?

The outside of the mouthpiece may be wiped with a dry cloth or tissue. The Multi-Haler should NEVER be washed. It should always be kept dry.

► How to Store Your Seroflo Multi-Haler?

Store in a cool and dry place, away from direct heat or sunlight.

Glossary

- Labelled dose or nominal dose: The mass of drug that is available within the aerosol generator per actuation. This is the dose that is metered.

- Total emitted dose (TED) or delivered dose (DD): The mass of drug emitted per actuation that is actually available for inhalation at the mouth.
- Fine particle dose (FPD): The mass of particles <math><5 \mu</math> in size within the total emitted dose is FPD.
- Fine particle fraction (FPF): The percentage of particles in the fine-particle range.
- Fine particle mass (FPM): The total mass of the particles that are in the fine-particle range (less than 5μ).
- % Fine particle mass (FPM): It is the FPM expressed as the % of the delivered dose.
- Aerodynamic diameter: The diameter of a fictitious sphere of unit density (1 g.cm^{-3}) that has the same gravitational (settling) velocity in the same gas as the actual particle.
- Mass median aerodynamic diameter (MMAD): The MMAD divides the aerosol size distribution in half. It is the diameter at which 50% of the particles of an aerosol by mass are larger and 50% are smaller.
 - If the MMAD is $3 \mu\text{m}$, then by weight
 - >50% of the particles are $>3 \mu\text{m}$
 - >50% of the particles are $<3 \mu\text{m}$

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