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A Pharmacist's Guide to the Only FDA-Approved OTC Epinephrine Inhalation Aerosol Bronchodilator

The new Primatene® MIST, an epinephrine inhalation aerosol bronchodilator (0.125 mg L-epinephrine), is the only FDA-approved, over-the-counter (OTC) asthma medicine inhaler for the temporary relief of mild symptoms of intermittent asthma.^{1,2,3} Studies have demonstrated that it is safe and effective in patients with intermittent asthma when used as directed.² Pharmacists are ideally positioned to answer questions, educate patients, and offer support to patients who are interested in using the new and improved Primatene® MIST. During discussions, pharmacists can counsel patients on important points regarding safety, appropriate dosing, and use to guide them regarding treatments.

BACKGROUND AND HISTORY

A prior formulation of Primatene® MIST, approved by the FDA more than 50 years ago, used chlorofluorocarbon (CFC) propellant and was subsequently discontinued in 2011 as a part of the overall efforts of the Montreal Protocol of Substances that Deplete the Ozone Layer and the Clean Air Act of 1990 to phase out ozone-depleting CFC propellants.^{2,4,5} The new formulation of Primatene® MIST uses hydrofluoroalkane (HFA) as the propellant, and it was approved by the FDA for OTC use on November 7, 2018. The product was launched in December 2018.⁶ For the convenience of this guide, the new Primatene® MIST containing HFA will be referred to as Primatene® MIST HFA and the previous version will be referred to as Primatene® MIST CFC.

PRIMATENE® MIST

Primatene® MIST HFA is a metered-dose inhaler that is FDA approved for OTC use for the temporary relief of mild symptoms of intermittent asthma, such as wheezing, tightness of chest, and shortness of breath.^{1,6} It delivers 0.125 mg of L-epinephrine per spray and contains inactive ingredients such as dehydrated alcohol (1%), HFA 134a, polysorbate 80, and thymol.¹

There are several differences between Primatene® MIST CFC and the new Primatene® MIST HFA.² Both contain the same active ingredient, L-epinephrine; however, Primatene® MIST HFA contains a 43% lower dose of epinephrine than the previously marketed CFC version.² The efficacy remains comparable at the lower dose.² Further, because Primatene® MIST HFA is a suspension, the inhaler must be shaken prior to each use to ensure that the proper dose is administered.² Critical instructions and a dose indicator are provided directly on the inhaler.^{1,2} Primatene® MIST HFA is approved for patients 12 years and older. The previous version was indicated for patients 4 years and older.²

SUMMARY OF CLINICAL STUDIES AND POSTMARKETING DATA FOR PRIMATENE® MIST

The efficacy and safety of Primatene® MIST HFA were established in a phase 3, randomized, double-blind, placebo- and active-controlled (Primatene® MIST CFC), parallel-group study of patients 12 years and older with stable asthma. Patients were randomized 4:1:1 to receive Primatene® MIST HFA 250 mcg (two 125-mcg inhalations), placebo, or Primatene® MIST CFC 440 mcg (two 220-mcg inhalations), respectively, 4 times daily. The duration of treatment was 3 months, followed by a 3-month safety extension period.²

The results demonstrated that Primatene® MIST HFA is safe and effective in relieving mild symptoms of intermittent asthma in adolescents and adults. The primary efficacy end point studied was the mean area under the curve (AUC) of the change in 1-second forced expiratory volume ($\Delta\%$ FEV1) from same-day, predose baseline to 6 hours post dose (AUC_{0-6hr} of $\Delta\%$ FEV1) at week 12. The results demonstrated significant bronchodilator efficacy of Primatene® MIST HFA compared with placebo, with a between-group difference of 27.83 AUC_{0-6hr} of $\Delta\%$ FEV1 (95% CI, 11.99-43.68; $P < .05$). The efficacy of Primatene® MIST HFA was comparable with that of Primatene® MIST CFC.²

With regard to safety of Primatene® MIST HFA, the most common adverse event reported was tremor, followed by chest discomfort. Postmarketing safety data of the previous CFC version were also evaluated during the FDA review of the new drug application for Primatene® MIST HFA. Based on the postmarketing data, which included 15 years of data (1997 to 2012) from the FDA's Adverse Event Reporting System, the FDA concluded that Primatene® MIST CFC was safely used in the OTC setting and no safety issues were identified.²

OPPORTUNITIES FOR PHARMACIST INTERVENTION

Because Primatene® MIST is once again available OTC, pharmacists play a crucial role in educating patients who are interested in using the product on important counseling points. Key counseling points are discussed in this section and summarized in the [FIGURE](#).¹

The new Primatene® MIST HFA is approved only for patients 12 years and older; thus, it should not be used in patients younger than 12 years. Primatene® MIST HFA should not be used unless patients have been diagnosed with intermittent asthma.^{1,6} Patients should be counseled that Primatene® MIST HFA is not a replacement for long-term maintenance medications and that they should not stop taking any asthma treatment prescribed by their doctor.⁶ Contraindications include concomitant use of monoamine oxidase inhibitors (MAOIs) and for 2 weeks after stopping MAOIs.¹ Caution should be used if the patient is taking drugs that contain phenylephrine, pseudo-

FIGURE. KEY COUNSELING ON USING THE PRIMATENE® MIST INHALER¹

Activate

Before First Use Only

1. Shake.

2. Test spray into the air.

You must repeat both actions 4 times.

Dose

1 or 2 Inhalations

1. Shake, then spray into the air 1 time.

2. Inhale.

Wash

After Each Day of Use

1. Remove red cap and container.

2. Run water through mouthpiece for 30 seconds.

3. Shake off excess water.

Before first use	The patient will need to prime/activate the inhaler by removing the red cap, shaking the inhaler, and then spraying into the air. The patient should shake and then spray the inhaler a total of 4 separate times.
Each dose	- To take a dose, the patient must remove the red cap, shake the inhaler, and then spray into the air 1 time to activate it. - The patient should exhale completely, and then seal their lips around the mouthpiece opening. - Next, the patient should inhale deeply while pressing down on top of the inhaler, and then continue the deep breath. - The patient should hold their breath as long as possible and then exhale. - If, after 1 minute, their symptoms are not relieved, the patient may take a second inhalation by repeating the steps above. No more than 2 doses should be used at a time. - The patient must wait at least 4 hours between doses, and they should not use more than 8 inhalations within 24 hours.
After use	- The patient should wash the inhaler after each day of use. - To do so, the patient should remove the canister from the inhaler, and then run water through both ends of the mouthpiece for 30 seconds. - The inhaler should be dried overnight before the canister is put back into the inhaler.

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ephedrine, ephedrine, or other stimulants,¹ or if the patient has cardiovascular disease, hypertension, diabetes, thyroid disease, seizures, benign prostatic hyperplasia, a psychiatric disorder, or narrow-angle glaucoma.¹

Patients should be counseled that they must wait a minimum of 4 hours between doses and they should not use more than 8 inhalations within 24 hours. Patient must prime/activate their inhaler before first use and also must wash the inhaler after each day of use; however, a change in the color of the mouthpiece is expected over time. The dose indicator provides the number of sprays remaining in the inhaler. The remaining number of sprays updates after every 20 sprays. The inhaler should be replaced when there are 20 sprays left.¹

The Primatene® MIST HFA packaging contains an important **Asthma Alert** that should be highlighted. Because asthma may be life-threatening, patients should be advised to contact their doctor if any of the following occur: They are not better within 20 minutes of using Primatene® MIST HFA, their symptoms worsen, they require more than 8 inhalations in 24 hours, or they have more than 2 exacerbations in a week. These are all signs that their asthma may be getting worse. Patients should also contact their doctor if they experience any adverse events while taking Primatene® MIST HFA.¹

Primatene® MIST HFA should be stored at room temperature, between 15°C and 25°C (59°F-77°F).¹

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