**INDICATIONS AND USAGE**

The active component of SPIRIVA is tiotropium. The drug substance, tiotropium bromide is a non-chiral, quaternary ammonium compound. Tiotropium bromide is soluble in methanol.

**Pharmacokinetics**

- **Absorption:** The terminal half-life of the inhaled tiotropium is between 5 and 12 hours. Absorption was not influenced by the presence of food. Approximately 30% of the dose is absorbed after inhalation of the HandiHaler device.
- **Distribution:** Tiotropium bromide has a molecular weight of 394.44 and is a quaternary ammonium compound. The drug substance is non-chiral and is not significantly bound to plasma proteins. Over 99% of tiotropium is present in the lung compartment.
- **Metabolism:** Tiotropium is predominantly a site-specific effect. In vivo studies involving methacholine-induced bronchoconstriction in COPD patients revealed that the improvement in pulmonary function (FEV1) with SPIRIVA, which was maintained for 24 hours after administration, was associated with a decrease in the ratio of methacholine-induced bronchospasm.
- **Elimination:** The terminal elimination half-life of tiotropium in healthy volunteers is approximately 5 to 12 hours. Approximately 30% of the dose is absorbed after inhalation. Tiotropium is primarily excreted in the urine, leaving an unchanged fraction of about 5%.

**Special Populations:**

- **Renally-impaired Patients:** In COPD patients with moderate to severe renal impairment (CrCl <50 mL/min), the intravenous administration of tiotropium resulted in a doubling of the plasma concentrations (82% increase). The intravenous clearance of tiotropium was not significantly different in elderly patients (ages 65 and older) compared to younger patients. In COPD patients aged 70 years or older, the intravenous clearance of tiotropium was 37% lower.
- **Hepatically-impaired Patients:** Plasma concentrations were not significantly increased in patients with mild liver disease (Child-Pugh A) or severe liver disease (Child-Pugh B/C). However, the intravenous clearance of tiotropium was about 7% lower in patients with severe liver disease.
- **Pregnancy:** Tiotropium is not expected to influence the absorption of tiotropium for the same reasons that it is not expected to influence the absorption of other bronchodilators. Tiotropium is not expected to influence the absorption of tiotropium for the same reasons that it is not expected to influence the absorption of other bronchodilators.

**Clinical Laboratory Tests:**

- **Hematologic and Serum Chemistry:** Tiotropium did not result in any clinically relevant changes in these tests.
- **Immunology:** Tiotropium did not result in any clinically relevant changes in these tests.
- **Radiographic chest X-rays:** Tiotropium did not result in any clinically relevant changes in these tests.
- **Special Sensitivity Testing:** Tiotropium did not result in any clinically relevant changes in these tests.

**Precautions:**

- **Inhalation:** The active component of SPIRIVA is tiotropium. The drug substance, tiotropium bromide is a non-chiral, quaternary ammonium compound. Tiotropium bromide is soluble in methanol.
- **Special Populations:** In COPD patients with moderate to severe renal impairment (CrCl <50 mL/min), the intravenous administration of tiotropium resulted in a doubling of the plasma concentrations (82% increase). Tiotropium is primarily excreted in the urine, leaving an unchanged fraction of about 5%.

**CONTRAINDICATIONS:**

- **Hypersensitivity to any component of SPIRIVA**
- **Pregnancy or Lactation:** Tiotropium is not excreted in human breast milk. The safety and effectiveness of SPIRIVA HandiHaler in nursing women have not been established. Therefore, a decision should be made whether to discontinue breastfeeding or to discontinue the drug, taking into account the importance of the drug to the mother.

**ADVERSE REACTIONS:**

- **Respiratory System:** Tiotropium is a bronchodilator that is well tolerated in patients with COPD. In clinical trials, the most common adverse events reported were nasopharyngitis, cough, pharyngitis, and upper respiratory tract infection. Tiotropium is not expected to influence the absorption of tiotropium for the same reasons that it is not expected to influence the absorption of other bronchodilators.

**PHARMACODYNAMICS:**

- **Bronchodilator Activity:** Tiotropium is a bronchodilator that is well tolerated in patients with COPD. In clinical trials, the most common adverse events reported were nasopharyngitis, cough, pharyngitis, and upper respiratory tract infection. Tiotropium is not expected to influence the absorption of tiotropium for the same reasons that it is not expected to influence the absorption of other bronchodilators.

**ELECTROCARDIOGRAPHY:**

- **QTc Assessment:** Tiotropium is not expected to influence the absorption of tiotropium for the same reasons that it is not expected to influence the absorption of other bronchodilators. Tiotropium is not expected to influence the absorption of tiotropium for the same reasons that it is not expected to influence the absorption of other bronchodilators.

**INTERACTIONS:**

- **Drug Interactions:** Tiotropium is not expected to influence the absorption of tiotropium for the same reasons that it is not expected to influence the absorption of other bronchodilators. Tiotropium is not expected to influence the absorption of tiotropium for the same reasons that it is not expected to influence the absorption of other bronchodilators.

**HOW TO USE SPIRIVA:** Take your dose of SPIRIVA by 2:00 PM. To use SPIRIVA, simply open the blister pack and take your dose. Place your hand on your mouth before inhaling the capsule. Do not use the inhalation powder as an inhalation device.

**REMOVING THE SPIRIVA capsule from the blister pack:**

1. **Open:** The blister should be carefully opened to expose only one capsule at a time. Immediately before you open the blister pack, gently press the perforations of the blister pack against the edge of the blister pack. This will allow the capsule to enter the blister pack. Do not use the inhalation powder as an inhalation device.

2. **Remove:** Slip the capsule from the blister pack and avoid opening the blister pack further. Place the removed capsule into the inhalation device and dose your medication. Do not use the inhalation powder as an inhalation device.

3. **Close:** The blister pack should be closed and the blister pack should be discarded. Do not use the inhalation powder as an inhalation device.

**HOW TO USE THE SPIRIVA HandiHaler:**

1. **Open:** This is an inhalation device used to inhale the dry powder formulation within the capsule. The dry powder is delivered from the HandiHaler device.

2. **Insert:** The active component of SPIRIVA is tiotropium. The drug substance, tiotropium bromide is a non-chiral, quaternary ammonium compound. Tiotropium bromide is soluble in methanol.

3. **Inhale:** The terminal half-life of tiotropium in COPD patients is between 5 and 12 hours. Absorption was not influenced by the presence of food. Approximately 30% of the dose is absorbed after inhalation. Tiotropium is primarily excreted in the urine, leaving an unchanged fraction of about 5%.

4. **Place your hand on your mouth before inhaling the capsule. Do not use the inhalation powder as an inhalation device.**
To ensure you get the full dose of SPIRIVA, you must repeat steps 5 and 6 once again.

If you do not have the capsule blister after repeating the above steps please contact your pharmacist.

After you have finished taking your dose of SPIRIVA, open the blister card again. Tip out the used capsule and blister (Figure 4).

When you should see your HandiHaler again:

- Normally during a one-month period of use, the HandiHaler device does not need to be cleaned. However, if you have followed the same individual HandiHaler device for more than 1 month and you change HandiHaler models, it should be cleaned as described below.

- Open the dust cap and mouthpiece. Open the base by simply lifting up on the blue lever and pull the mouthpiece up and out of the device. Push up the piercing button to expose the powder (Figure 3).

- If the HandiHaler device is to be used for any length of time, open the mouthpiece again. Tip out the used capsule that is in the mouthpiece (Figure 5).

- Close the mouthpiece and dust cap for storage of your HandiHaler device.

When should you see your HandiHaler capsule blister again? (See Table 1 below).

<table>
<thead>
<tr>
<th>Condition</th>
<th>Screening Dose</th>
<th>Maintenance Dose</th>
<th>Recommended Dose</th>
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<tbody>
<tr>
<td>1 capsule/day</td>
<td>1 capsule/day</td>
<td>2 capsules/day</td>
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<td>3 capsules/day</td>
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<td>4 capsules/day</td>
<td>5 capsules/day</td>
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If you see any changes indicating that the SPIRIVA device may not be functioning properly, such as difficulty in measuring deposited doses or an increased inhalation effort, please discontinue use of SPIRIVA and contact your pharmacist for additional information.

Tiotropium bromide has been demonstrated to be safe and effective in clinical trials with a large number of patients that obser-