DESCRIPTION & COMPOSITION

Tulobuterol is a member of long acting \( \beta_2 \) receptor agonist family. Its chemical name is (RS) -2-tert-Butylamino-1- (2-chlorophenyl) ethanol and molecular formula is \( \text{C}_{12}\text{H}_{18}\text{ClNO} \). Its structural formula is depicted below:

\[
\text{\begin{tikzpicture}
\draw (0,0) circle (0.5cm);
\draw (-0.3,0.2) -- (-0.3,-0.2);
\draw (0.3,0.2) -- (0.3,-0.2);
\draw (-0.3,-0.2) -- (0.3,0.2);
\draw (0,-0.5) -- (0,0.5);
\draw (0,0) -- (0,-0.5);
\draw (0,0) -- (0.5,0);
\draw (0.5,0) -- (0.5,-0.5);
\draw (0.5,-0.5) -- (0,-0.5);
\draw (0.5,-0.5) -- (0.5,0);
\end{tikzpicture}}\]

Tulobuterol is a white crystal or crystalline powder without odor. It is very soluble in methanol, ethanol (95) or acetic acid (100) and practically insoluble in water. Tulobuterol is volatilized. Methanol solution (1→20) shows no optical rotation.

<table>
<thead>
<tr>
<th>Brand name</th>
<th>Tuloplast 0.5</th>
<th>Tuloplast 1</th>
<th>Tuloplast 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ingredient/contents</td>
<td>Tulobuterol 0.5 mg in each patch</td>
<td>Tulobuterol 1 mg in each patch</td>
<td>Tulobuterol 2 mg in each patch</td>
</tr>
<tr>
<td>Description</td>
<td>Square adhesive skin patch with rounded corners supporting a colorless translucent ointment on a white support and coating the surface of ointment with white liner</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Appearance/Size</td>
<td>2.5 cm(^2)</td>
<td>5 cm(^2)</td>
<td>10 cm(^2)</td>
</tr>
</tbody>
</table>
CLINICAL PHARMACOLOGY

Pharmacodynamics

Tulobuterol is a directly acting sympathomimetic and has selective β₂ receptor stimulating activity. Binding of Tulobuterol to β₂ receptor leads to activation of adenylate cyclase enzyme, conversion of ATP to cAMP and suppression of contraction of bronchial smooth muscles.

Pharmacokinetics

Bioequivalence testing

The concentration of Tulobuterol in plasma was measured (crossover method) after single transdermal application (chest, 24 hours) of Tulobuterol Patch 0.5 mg, 1 mg and 2 mg and standardized preparation corresponding to each standard to healthy adult males, and the statistical analysis of pharmacokinetic parameters (AUC, Cₘₐₓ) confirmed bioequivalence for both drugs.

(The usual dose in adults is 2 mg per dose as Tulobuterol.)

<table>
<thead>
<tr>
<th>Dose (No. of cases)</th>
<th>Drug administered</th>
<th>Cₘₐₓ (ng/mL)</th>
<th>Tₘₐₓ (hr)</th>
<th>T½ (hr)</th>
<th>AUC₀₋₄₈hr (ng•hr/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.5 mg [n=23]</td>
<td>Tulobuterol Patch 0.5 mg</td>
<td>0.48 ± 0.22</td>
<td>11.4 ± 4.1</td>
<td>11.1 ± 4.4</td>
<td>10.75 ± 7.65</td>
</tr>
<tr>
<td></td>
<td>Standardized preparation (adhesive skin patch 0.5 mg)</td>
<td>0.42 ± 0.20</td>
<td>15.4 ± 5.0</td>
<td>10.6 ± 4.2</td>
<td>10.67 ± 7.26</td>
</tr>
<tr>
<td>1 mg [n=24]</td>
<td>Tulobuterol Patch 1 mg</td>
<td>0.59 ± 0.32</td>
<td>9.1 ± 2.1</td>
<td>10.4 ± 1.9</td>
<td>11.09 ± 6.86</td>
</tr>
<tr>
<td></td>
<td>Standardized preparation (adhesive skin patch 1 mg)</td>
<td>0.56 ± 0.27</td>
<td>11.5 ± 3.7</td>
<td>9.7 ± 1.3</td>
<td>12.10 ± 7.35</td>
</tr>
<tr>
<td>2 mg [n=24]</td>
<td>Tulobuterol Patch 2 mg</td>
<td>1.29 ± 0.60</td>
<td>11.0 ± 2.7</td>
<td>11.0 ± 3.4</td>
<td>27.62 ± 18.77</td>
</tr>
<tr>
<td></td>
<td>Standardized preparation (adhesive skin patch 2 mg)</td>
<td>1.24 ± 0.63</td>
<td>14.5 ± 4.5</td>
<td>10.0 ± 4.5</td>
<td>29.65 ± 20.62</td>
</tr>
</tbody>
</table>

(Mean ± S.D.)

The plasma concentration-time graph of Tulobuterol Patch against standardized preparation is depicted below.
INDICATIONS

For treatment of patients with Asthma and COPD without co-morbidity

DOSAGE AND ADMINISTRATION

Once daily, apply the patch to chest, back, or upper arm as per the following dosage regimen.

• For children aged 6 months to 3 years: 0.5 mg
• For children aged 3 to 9 years: 1.0 mg
• For adults and children aged > 9 years: 2.0 mg

USE IN SPECIAL POPULATIONS

Pregnancy and Lactation

• Tulobuterol may be applied to pregnant women or women who may be pregnant only when medical benefits outweigh the risk. [The safety of Tulobuterol in pregnancy has not been established.]
• If Tulobuterol is applied to nursing mothers, breast feeding should be avoided. [Transfer of Tulobuterol into milk has been reported in animal studies (rat).]

Pediatric Use

• The safety of Tulobuterol has not been established in infants less than 6 months of age. [Few experience of use.]
• The safety of long term use of Tulobuterol has not been established in children. [Few experience of use.]

Elderly population
Since physiological function is generally weakened in elderly people, Tulobuterol should be carefully applied, e.g., by starting with lower dose.

**CONTRAINDICATIONS**

Should not be used in the patients with a history of hypersensitivity to components of this drug

**PRECAUTIONS**

**Careful Administration** (Tulobuterol should be applied with care in the following patients.)

1) Patients with hyperthyroidism [Symptoms may be aggravated.]
2) Patients with hypertension [Blood pressure may be increased.]
3) Patients with heart disorder [Palpitation or arrhythmia may occur.]
4) Patients with diabetes mellitus [Glucose metabolism and blood glucose may increase.]
5) Patients with atopic dermatitis [Pruritus or redness may appear on application site.]
6) Elderly patients [Preferable to start with lower dose]

**Important Precautions**

1) Anti-inflammatory drugs such as inhaled steroids are essential for long-term management of bronchial asthma. Tulobuterol should be applied concomitantly only if no improvement of symptoms is noted with steroids or concomitant treatment with inhaled steroids are considered appropriate according to the severity of patients’s condition. Since Tulobuterol is not an alternative anti-inflammatory drug such as inhaled steroids, careful instruction should be given to the patients, the patient's guardian or other appropriate designated person that the patients should not reduce or discontinue the inhaled steroids, etc without a physician advice and to use Tulobuterol alone even if the patients feel improvement of symptoms with the use of Tulobuterol.

2) Careful instruction should be given to the patients, the patient's guardian or other appropriate designated person that the patients should use other appropriate drugs such as short-acting beta-stimulator for acute attack occurred during application of Tulobuterol in the long-term management for the treatment of bronchial asthma. Further, if the doses of those drugs are increased or they become ineffective, careful instruction should be given to the patients, the patient's guardian or other appropriate designated person that the patients should visit medical institutions to receive treatment as soon as possible since asthma may not be adequately controlled. As this condition may be life-threatening, intensification of anti-inflammatory therapy should be pursued.

3) If Tulobuterol is ineffective even when properly used according to DOSAGE AND ADMINISTRATION (approximately one to two weeks as a guide), application should be
discontinued as Tulobuterol is considered inappropriate. In addition, proper instruction and adequate follow-up should be provided for pediatric use.

4) As continued use of Tulobuterol beyond the dose range may cause arrhythmia or occasionally cardiac arrest, caution should be given not to use beyond the dose limit.

### DRUG INTERACTIONS

<table>
<thead>
<tr>
<th>Drug</th>
<th>Clinical Symptoms</th>
<th>Mechanism</th>
</tr>
</thead>
<tbody>
<tr>
<td>Catecholamine drugs like adrenaline, isoproterenol, etc.</td>
<td>Arrhythmia or occasionally cardiac arrest.</td>
<td>Tulobuterol and catecholamine drugs both have a sympathomimetic effect</td>
</tr>
<tr>
<td>Xanthine derivatives: theophylline, aminophylline hydrate, diprophylline etc.</td>
<td>Arrhythmia due to hypokalemia may occur.</td>
<td>Tulobuterol and xanthine derivatives both have an effect of cellular uptake of potassium</td>
</tr>
<tr>
<td>Steroid drugs such as prednisolone, betamethasone, hydrocortisone, etc.</td>
<td>Arrhythmia due to hypokalemia may occur.</td>
<td>Steroids increase potassium excretion into urine.</td>
</tr>
<tr>
<td>Diuretics such as trichlormethiazide, furosemide, acetazolamide, etc.</td>
<td>Arrhythmia due to hypokalemia may occur.</td>
<td>Diuretics increase potassium excretion into urine.</td>
</tr>
</tbody>
</table>

### ADVERSE REACTIONS

**Clinically significant adverse reactions**

**Anaphylactoid symptoms**

Since anaphylactoid symptoms may occur, the patient should be closely observed. If any symptoms such as dyspnea, generalized flushing, angioedema and urticaria are noted, application should be discontinued and appropriate measures should be taken.

**Serious decrease in serum potassium level**
Serious decreased serum potassium has been reported with β2 stimulant. Since the serum potassium-lowering effect of β2 stimulant may increase with concomitant use of xanthine derivatives, steroids and diuretics, special caution should be given in patients with severe asthma. Furthermore, hypoxemia may enhance the effect of decreased serum potassium level on cardiac rhythm. In such case, serum potassium level should be monitored.

**Other Adverse Reactions**

<table>
<thead>
<tr>
<th>Category</th>
<th>Incidence unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity</td>
<td>Rash, pruritus, urticaria</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>Palpitations, facial flushing, arrhythmia, tachycardia</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
<td>Tremor, headache, insomnia, general feeling of malaise, dizziness, excitement, numbness, muscle spasms, heat sensation, feeling of stiffness</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>Nausea and vomiting, loss of appetite, diarrhea, stomach discomfort</td>
</tr>
<tr>
<td>Hepatic</td>
<td>AST (GOT) increased, ALT (GPT) rise</td>
</tr>
<tr>
<td>hematologic</td>
<td>Eosinophil count increased</td>
</tr>
<tr>
<td>Dermatologic</td>
<td>Application site pruritus, application site erythema, contact dermatitis, application site pain, application site discoloration</td>
</tr>
<tr>
<td>Other</td>
<td>CK (CPK) increased, decrease in serum potassium levels, chest pain, edema, dry mouth, muscle pain</td>
</tr>
</tbody>
</table>

Caution: If any symptoms are observed, application of Tulobuterol should be discontinued.

**PRECAUTIONS FOR APPLICATION**

- Before applying Tuloplast clean and dry the application site.
- Choose a new site each time to avoid cutaneous irritation.
- Place Tuloplast on an area that is out of reach of children who may peel it off.
- Tuloplast should not be used within the wound as animal studies (rat) showed an increase in the blood level when Tuloplast was applied on the compromised skin.

**PRECAUTION FOR HANDLING**

- **Precautions for use and storage**
  Provide Tuloplast in the inner package to the patients and instruct them to take it out from the inner package when used.

- **Safety study**
Among heat sealing packages used for each drug, those stored for 3 years under storage condition at 25°C and 60%RH met the standards of all test parameters including quantitative test.