Tuloplast

(Tulobuterol Patch-0.5/1/2 mg)
The First Transdermal Bronchodilator
## CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>Executive Summary</td>
<td></td>
</tr>
<tr>
<td>Pediatric Asthma</td>
<td></td>
</tr>
<tr>
<td>Epidemiology</td>
<td></td>
</tr>
<tr>
<td>Risk factors and Triggers</td>
<td></td>
</tr>
<tr>
<td>Pathophysiology</td>
<td></td>
</tr>
<tr>
<td>Goals of Childhood Asthma Management</td>
<td></td>
</tr>
<tr>
<td>Asthma Management: An Overview of GINA, Japanese and European Guidelines</td>
<td></td>
</tr>
<tr>
<td>Adherence: Key issue in Asthma</td>
<td></td>
</tr>
<tr>
<td>Limitations of Inhaled Therapy</td>
<td></td>
</tr>
<tr>
<td>Transdermal Drug Delivery System</td>
<td></td>
</tr>
<tr>
<td>Rationale for Tulobuterol Patch Formulation</td>
<td></td>
</tr>
<tr>
<td>Mechanism of Action</td>
<td></td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td></td>
</tr>
<tr>
<td>Dosage &amp; Administration</td>
<td></td>
</tr>
<tr>
<td>Clinical efficacy</td>
<td></td>
</tr>
<tr>
<td>Treatment Adherence</td>
<td></td>
</tr>
<tr>
<td>Positioning of Tuloplast in pediatric Asthma</td>
<td></td>
</tr>
<tr>
<td>Safety</td>
<td></td>
</tr>
<tr>
<td>Desensitization/tolerance</td>
<td></td>
</tr>
<tr>
<td>Pharmacological Studies supporting clinical Efficacy results</td>
<td></td>
</tr>
<tr>
<td>Salient Features</td>
<td></td>
</tr>
<tr>
<td>References</td>
<td></td>
</tr>
<tr>
<td>Tuloplast Pack Insert</td>
<td></td>
</tr>
</tbody>
</table>
Abbreviations

GINA: Global Initiative Against Asthma
CFC: ChlorofluoroCarbons
TDDS: Transdermal Drug Delivery System
LABA: Long Acting Beta-2 Agonist
SABA: Short Acting beta-2 Agonist
ICS: Inhalational Corticosteroids
SRT: Slow release Theophylline
SGRQ: St. George Respiratory Questionnaire
HRQoL: Health Related Quality of Life
LTRA: Leukotriene receptor Antagonist
Executive Summary

Inhalational therapy constitutes the cornerstone of treatment of pediatric asthma. The technical mastery in the adequate use of inhalation devices and aiding accessories is essential to obtain maximal efficacy of inhalation drugs which is compromised in pediatric population.

The tulobuterol patch was developed in Japan, and is the first bronchodilator available as an adhesive transdermal patch containing a β2-adrenergic agonist. The patch was designed for use as chronotherapy for nocturnal asthma when applied at bedtime, and is currently used in the long-term management of asthma in Japan, Korea, and China. The patch is applied to the skin once daily, continuously releases its active ingredient, and maintains effective serum tulobuterol concentrations for 24 hours.

Therefore, the tulobuterol patch provides long-acting β-agonist activity, despite tulobuterol being categorized pharmacokinetically as a short-acting β2-agonist. Because the tulobuterol patch requires only once-daily application, treatment adherence is excellent. Further, its clinical efficacy and safety in the treatment of pediatric asthma has been established since its launch in 1998.

Clinical trials have demonstrated the benefit of tulobuterol patch in pediatric asthma with respect to following parameters:

- Percentage Peak Expiratory flow rates in the morning and bedtime
- Percentage of respiratory Symptom free days
- Total Respiratory Symptom score
- Time to resolution of symptoms
- Treatment adherence
The Japanese Guidelines for childhood Asthma has classified tulobuterol patch as Long Acting Beta₂ Agonist and recommended the same from step 3 onwards. It is also DCGI approved for the treatment of Asthma without any co-morbidity in children older than 6 months of age.

This monograph, dedicated to tulobuterol patch, presents an up to date compilation of its various characteristic features & the comparative scientific data with conventional therapies in the management of pediatric asthma. We also discussed the safety and patient acceptability of the patch.

Dr. Sanjaykumar Navale;
M.B.B.S., M.D
Sr. Manager, Medical Services
Zuventus Healthcare Ltd.
Pediatric Asthma

Epidemiology\(^{[1,2,3]}\)

- The prevalence of Bronchial Asthma has increased continuously since the 1970s, and now affects an estimated 4 to 7% of the people worldwide.
- At the age of six to seven years, the prevalence ranges from 4 to 32%.
- Apart from being the leading cause of hospitalization for children, it is one of the most important chronic conditions causing elementary school absenteeism. Childhood Bronchial Asthma has multifactor causation. Geographical location, environmental, racial, as well as factors related to behaviors and life-styles are associated with the disease.
- The worst sufferer from indoor environment-induced asthma is children in low income urban families.
- India has an estimated 15-20 million asthmatics. In India, rough estimates indicate a prevalence of between 10 - 15% in 5-11 year old children. Mortality due to asthma is not comparable in size to the day-to-day effects of the disease.
- **According to National Family Health Survey-3, 2005-06**, prevalence is highest among those with less than five years of schooling (2,283 per 100,000 among women and 2,640 among men per 100,000), and among those with no education (1,914 among women per 100,000 and 2,440 among men per 100,000).

Early Childhood Risk Factors for Persistent Asthma\(^{[4]}\)

- Atopic dermatitis
- Allergic rhinitis
- Food allergy
- Inhalant allergen sensitization
- Food allergen sensitization
- Pneumonia
- Bronchiolitis requiring hospitalization
- Parental asthma
- Allergy
- Severe lower respiratory tract infection
- Wheezing apart from colds
- Male gender
- Low birth weight
- Environmental tobacco smoke exposure

Asthma Triggers

Figure 1: Triggers for Asthma
The pathologic changes linked to persistent airways inflammation and hyperresponsiveness underlie the chronic basis of asthma.

Figure 2: Pathophysiology of Asthma

Goals of childhood Asthma Management

- Regular school or day care attendance
- Full participation in physical exercise, athletics, and other recreational activities
- Maintain normal activity
- Prevent sleep disturbance
- Prevent chronic asthma symptoms
- Keep asthma exacerbations from becoming severe
- Maintain normal lung function
- Experience little to no adverse effects of treatment
## Asthma Management in Children

### Therapeutic Options

<table>
<thead>
<tr>
<th>Drug class</th>
<th>Generic name</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Short-acting beta agonists (SABAs)</strong></td>
<td>Albuterol, Albuterol sulfate</td>
</tr>
<tr>
<td></td>
<td>Albuterol sulfate /</td>
</tr>
<tr>
<td></td>
<td>Ipratropium bromide</td>
</tr>
<tr>
<td></td>
<td>Levalbuterol hydrochloride</td>
</tr>
<tr>
<td></td>
<td>Levalbuterol tartrate</td>
</tr>
<tr>
<td></td>
<td>Metaproterenol sulfate</td>
</tr>
<tr>
<td></td>
<td>Pirbuterol acetate</td>
</tr>
<tr>
<td></td>
<td>Terbutaline sulfate</td>
</tr>
<tr>
<td><strong>Long-acting beta agonists (LABAs)</strong></td>
<td>Aformoterol tartrate</td>
</tr>
<tr>
<td></td>
<td>Formoterol fumarate</td>
</tr>
<tr>
<td></td>
<td>Salmeterol xinafoate</td>
</tr>
<tr>
<td><strong>Inhaled corticosteroids (ICSs)</strong></td>
<td>Beclomethasone dipropionate</td>
</tr>
<tr>
<td></td>
<td>Budesonide</td>
</tr>
<tr>
<td></td>
<td>Ciclesonide</td>
</tr>
<tr>
<td></td>
<td>Flunisolide</td>
</tr>
<tr>
<td></td>
<td>Fluticasone propionate</td>
</tr>
<tr>
<td></td>
<td>Mometasone furoate</td>
</tr>
<tr>
<td></td>
<td>Triamcinolone acetonide</td>
</tr>
<tr>
<td><strong>LABA/ICS combination drugs</strong></td>
<td>Formoterol fumarate dihydrate /</td>
</tr>
<tr>
<td></td>
<td>Budesonide</td>
</tr>
<tr>
<td></td>
<td>Formoterol fumarate /</td>
</tr>
<tr>
<td></td>
<td>Mometasone Furoate</td>
</tr>
<tr>
<td></td>
<td>Salmeterol xinafoate / Fluticasone propionate</td>
</tr>
<tr>
<td><strong>Leukotriene receptor antagonists (LTRAs)</strong></td>
<td>Montelukast sodium</td>
</tr>
<tr>
<td></td>
<td>Zafirlukast</td>
</tr>
<tr>
<td></td>
<td>Zileuton</td>
</tr>
<tr>
<td><strong>Other anti-asthma medications</strong></td>
<td>Cromolyn sodium</td>
</tr>
<tr>
<td></td>
<td>Methylprednisolone</td>
</tr>
<tr>
<td></td>
<td>Omalizumab</td>
</tr>
<tr>
<td></td>
<td>Prednisolone sodium phosphate</td>
</tr>
<tr>
<td></td>
<td>Prednisone</td>
</tr>
</tbody>
</table>

Asthma Management in Children 6 years and older
GINA Guidelines 2015[^6]

Good control of asthma can be achieved in a majority of young children with a pharmacological intervention strategy. Other Key components of management include:

- Asthma education
- Skills training for inhaler devices
- Assessment of adherence
- Environmental control
- Regular monitoring
- Clinical Review
For children 6–11 years, theophylline is not recommended, and the preferred Step 3 treatment is medium dose ICS.

**Figure 3:** Stepwise approach to long-term management of asthma in adults, adolescents and children and children 6-11 years. **LABA recommended Step 3 onwards.**

**Japanese Guidelines of Pediatric Asthma 2014**

Table 1: Asthma Management in Children 6-15 years of age . **LABA recommended Step 3 onwards.**
Figure 4: Stepwise Approach to Asthma Treatment in Childhood Asthma
Asthma Management in Children < 5 years of age
GINA Guidelines 2015[6]

Figure 5: Stepwise approach to long-term management of asthma in children 5 years and younger
Japanese Guidelines 2014\textsuperscript{[7]}

The Japanese guidelines for childhood Asthma 2014 recommend use of LABA in step 3 and specifically mention about use of adhesive skin patch as LABA.

Table 2: Asthma Management in Children Under 2 years of age

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SABA As needed</td>
<td>LTRA and/or DSGC</td>
<td>ICS (medium dose)</td>
</tr>
<tr>
<td>Additional therapy</td>
<td>LTRA and/or DSGC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Table 3: Asthma Management in Children 2-5 years of age (LABA recommended from Step 3 onwards)

<table>
<thead>
<tr>
<th>Step 1</th>
<th>Step 2</th>
<th>Step 3</th>
<th>Step 4</th>
</tr>
</thead>
<tbody>
<tr>
<td>Basal therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>SABA as needed</td>
<td>LTRA and/or DSGC</td>
<td>ICS (medium dose)</td>
</tr>
<tr>
<td>Additional therapy</td>
<td>LTRA and/or DSGC</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>LTRA LABA or SFC</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Theophylline (consider)</td>
<td></td>
</tr>
</tbody>
</table>

Therapeutic issues of Delivery Devices in Children\textsuperscript{[9]}

\textit{Metered Dose Inhaler}

- Slow inhalation and co-ordination of actuation during inhalation may be difficult particularly in young children
- Patients may incorrectly stop inhalation at actuation
- Deposition of 50-80 percent of actuated dose in oropharynx

\textit{Dry Powder Inhaler}

- Rapid inhalation promotes greater deposition in larger central airways


**Spacer**
- May be bulky

**Face Mask**
- Reduces the delivery to lungs by 50%

**Nebulizer**
- Bulky, expensive, time consuming and output is dependent on device and operating parameters like fill volume and driving gas flow

**Management Issues with LABA in children < 5 years of age**
- Long-acting inhaled beta₂-agonist (LABA) salmeterol is not approved for use in children less than 4 years of age
- Long acting Inhaled formoterol is not approved for use in children less than 6 years of age
- Oral Salbutamol upper age limit is 2 years while the same is 2 years for slow release theophylline

So alongwith feasibility issues of use of LABA via inhalers, there is also regulatory constraint. Moreover, there remains an option for use of oral salbutamol in children upto 2 years of age. Oral salbutamol is ineffective in the treatment of paediatric asthma and is associated with an increased incidence of adverse events compared with inhaled formulation.\(^{[10]}\)
The inconvenience of inhaled treatment along with the cost and adverse effects leaves behind a mammoth task of proper counseling of patient and the parents.

Start the regime appropriate to the grade assessed and titrate upwards if control is not achieved.

<table>
<thead>
<tr>
<th>Grade 4</th>
<th>First Choice</th>
<th>Other Options</th>
</tr>
</thead>
<tbody>
<tr>
<td>Severe persistent</td>
<td>Medium to high dose inhaled steroid + LABA</td>
<td>***</td>
</tr>
<tr>
<td></td>
<td>If needed</td>
<td>Add oral steroid</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 3</th>
</tr>
</thead>
<tbody>
<tr>
<td>Moderate persistent</td>
</tr>
<tr>
<td></td>
</tr>
<tr>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild persistent</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Grade 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mild intermittent</td>
</tr>
</tbody>
</table>

* For children above 5 years only
** For children below 5 years
*** Evidence to date does not support using a third long-term control medication added to inhaled corticosteroids and long-acting inhaled β₂-agonists in order to avoid using systemic corticosteroid therapy.

**Figure 6:** Management of Asthma Indian Context
Adherence: A key Issue in Asthma\textsuperscript{[6,12]}

- Inhaled therapy constitutes the cornerstone of asthma treatment in children 5 years and younger. A pressurized metered dose inhaler (pMDI) with a valved spacer (with or without a face mask, depending on the child’s age) is the preferred delivery system.
- Approximately 50\% of adults and children on long-term therapy for asthma fail to take medications as directed at least part of the time.
- Some of the factors contributing to poor adherence include difficulties in using inhaler device, multiple dosing per day, misunderstanding of instructions, skills required for drug inhalation.
- Various studies have demonstrated increased illness, exacerbations, visits to the emergency department, morbidity, and mortality in asthma patients who are noncompliant or non-adherent to their treatment regimens.
- Most studies have documented relatively poor adherence to controller medications delivered by MDIs.
- Compliance was not significantly different in patients who used the combined inhalers.
- The way a spacer is used can markedly affect the amount of drug delivered:
  - Multiple actuations into the spacer before inhalation may markedly reduce the amount of drug inhaled.
  - Delay between actuating the pMDI into the spacer and inhalation may reduce the amount of drug available.
  - If a face mask is used it must be fitted tightly around the child’s mouth and nose, to avoid loss of drug.
  - Nebulizers, the only viable alternative delivery systems in children, are reserved for the minority of children who cannot be taught effective use of a spacer device.

Overall, use of inhalational therapy in children can lead to adherence issues because of their inability to comply appropriately with the instructions given for use of inhalation devices. Moreover, technical mastery in the adequate use of inhalation devices and aiding accessories is essential to obtain maximal efficacy of inhalation drugs.
Limitations of Inhaled Therapy\textsuperscript{[13]}

<table>
<thead>
<tr>
<th>Device Type</th>
<th>Limitations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metered dose inhaler</td>
<td>Coordination of breathing and actuation needed</td>
</tr>
<tr>
<td></td>
<td>Device actuation required</td>
</tr>
<tr>
<td></td>
<td>High pharyngeal deposition</td>
</tr>
<tr>
<td></td>
<td>Upper limit to unit dose content</td>
</tr>
<tr>
<td></td>
<td>Remaining doses difficult to determine</td>
</tr>
<tr>
<td></td>
<td>Potential for abuse</td>
</tr>
<tr>
<td></td>
<td>Not all medications available</td>
</tr>
<tr>
<td></td>
<td>Many use CFC propellants in USA</td>
</tr>
<tr>
<td>Holding chamber or spacer</td>
<td>Inhalation can be more complex for some patients</td>
</tr>
<tr>
<td></td>
<td>Can reduce dose available if not used properly</td>
</tr>
<tr>
<td></td>
<td>More expensive than MDI alone</td>
</tr>
<tr>
<td></td>
<td>Less portable than MDI alone</td>
</tr>
<tr>
<td>Dry powder inhaler</td>
<td>Requires moderate to high inspiratory flow</td>
</tr>
<tr>
<td></td>
<td>Some units are single dose</td>
</tr>
<tr>
<td></td>
<td>Can result in high pharyngeal deposition</td>
</tr>
<tr>
<td></td>
<td>Not all medications available</td>
</tr>
</tbody>
</table>

Transdermal Drug Delivery System (TDDS)\textsuperscript{[14]}

Transdermal drug delivery system is the topically administered medications in the form of patches which when applied to the skin deliver the drug, through the skin at a predetermined and controlled rate.

Controlled drug release can be achieved by transdermal drug delivery systems (TDDS) which can deliver the drug via the skin portal to systemic circulation at a predetermined rate over a prolonged period of time. For effective Transdermal drug delivery system, the drug should able to penetrate the skin easily and reach the target site. TDDS increase the patient compliance and reduces the load as compared to oral route.
Transdermal formulation maintain drug concentration within the therapeutic window for prolong period of time ensuring that drug levels neither fall below the minimum effective concentration nor exceed the maximum effective concentration.

**Figure 7:** Layers of Transdermal Patch

**Advantages of TDDS**

- Avoidance of first pass metabolism of drugs.
- Transdermal medication delivers a steady infusion of a drug over a prolonged period of time. Maintains stable or constant and controlled blood levels for longer period of time.
- Adverse effects or therapeutic failures frequently associated with intermittent dosing are avoided.
- Comfort via non-invasive, painless and simple application. The simplified medication regimen leads to improved patient compliance and inter & intra-patient variability.
- It increases the therapeutic value of many drugs via avoiding specific problems associated with the drug like GI irritation, lower absorption, decomposition due to ‘hepatic first pass’ effect.
- Comparable characteristics with intravenous infusion.
- This route is suitable for the administration of drugs having very short half life, narrow therapeutic window and poor oral availability.
- Flexibility of terminating the drug administration by simply removing the patch from the skin.
- Self administration is possible in these systems.

Disadvantages of TDDS

- The possibility of local irritation may develop at the site of application. Problems like Erythema, itching, and local edema can be caused by the drug, the adhesive, or other excipients in the patch formulation.
- The barrier function of the skin changes from one site to another on the same person, from person to person and with age.
Nocturnal worsening of asthma (nocturnal asthma), is a common and important problem for asthmatic patients. Nocturnal asthma is defined as variable exacerbation of the underlying asthma condition, which is associated with increased symptoms of airway hyper-responsiveness and/or worsening of lung function, and a need for medication. These changes are associated with circadian variations in lung function. Compared with the normal range of variation (5%–8%) of lung function in healthy subjects, nocturnal asthma exaggerates the changes in pulmonary function by >15%. This decrease in lung function in the early morning as a result of nocturnal asthma is known as the “morning dip”.

Dethlefsen et al. investigated approximately 3000 untreated asthma patients to determine the time of the day which asthma attacks are most frequent, and reported that the attacks occurred in clusters at around 4:00 am. Therefore, suppression of this morning dip can be expected to bring about an improvement in the patient's QOL and also reduce the burden on the caregiver in cases of childhood asthma.
Chronotherapy based on the circadian rhythm is needed in asthmatics to prevent this morning dip and to improve quality of life. The tulobuterol patch was initially developed to prevent the morning dip and to sustain drug efficacy over 24 hours (Figure 8).

Tulobuterol Patch was designed in accordance with the concept of chronotherapy: the blood drug concentration is controlled in such a manner that it is the highest during early morning, when the respiratory functions are most severely suppressed. This controlled release helps to reduce the systemic adverse reactions associated with excessive drug concentrations in the blood. [3]

Tulobuterol patch employs a technology that prolongs the duration of the drug's action to 24 h. This technology is the drug matrix system, which has been patented for the patch.

Figure 8: Concentration-time profiles for serum concentration of tulobuterol.
Notes: Dashed line indicates the ideal time profile of the serum concentration of tulobuterol on the basis of circadian pulmonary function (line). When the tulobuterol patch is applied before bedtime, the maximum concentration of tulobuterol is achieved during the morning dip (bold line).
To accomplish this, a matrix-type transdermal delivery system was used for formulation of the tulobuterol patch. The patch contains both crystallized and molecular forms of tulobuterol in an adhesive layer. It also includes a controlled drug release mechanism known as the drug matrix system (Figure 9).
Figure 10: Drug matrix system. [3]

Notes: The tulobuterol patch contains crystallized (closed rhombus) and molecular (open circle) forms of tulobuterol in an adhesive layer. When the patch is applied to the skin, molecular tulobuterol is gradually absorbed percutaneously. During application, the number of molecules in the patch is decreased. Subsequently, these molecules are supplied from the crystals.

- After the tulobuterol patch is applied to the skin, the molecular tulobuterol is gradually absorbed percutaneously.
- As the number of tulobuterol molecules in the patch decreases, additional molecules are supplied by dissociation of the tulobuterol crystals into a molecular and absorbable form.
This mechanism enables timed release of tulobuterol - the drug concentration peaks when the symptoms of asthma are at their worst.

Currently available oral β2-agonists- salbutamol, terbutaline, and bambuterol, reach peak levels in serum within 3 hours of administration, patients with asthma who take these medications before bedtime cannot achieve maximum bronchodilation when most needed during the morning dip.

In addition, oral β2-agonists often have clinically significant systemic adverse effects, such as tremor and palpitations, due to steep increases in plasma drug levels.

The tulobuterol patch provides gradual and continuous drug release, so reduces the risk of systemic adverse effects caused by high plasma drug concentrations.

**Mechanism of action**[^16]

Tulobuterol produces bronchodilation by directly stimulating β-2 receptors in airway smooth muscle. Occupation of β-2 receptors by tulobuterol results in the activation of the Gs-adenylyl cyclase-cAMP-PKA pathway, resulting in phosphorylative events leading to bronchial smooth muscle relaxation (Figure). There is a rapid decrease in airway resistance.
Figure 11: Cellular Mechanism of Action of Tulobuterol

Molecular actions of $\beta_2$ agonists to induce relaxation of airway smooth muscle cells. Activation of $\beta_2$ receptors results in activation of adenylyl cyclase (AC) via a stimulatory G protein ($G_s$), leading to an increase in intracellular cyclic AMP and activation of PKA. PKA phosphorylates a variety of target substrates, resulting in opening of $\text{Ca}^{2+}$-activated $K^+$ channels ($K_{\text{Ca}}$), thereby facilitating hyperpolarization, decreased phosphoinositide (PI) hydrolysis, increased $\text{Na}^+$/Ca$^{2+}$ exchange, increased $\text{Na}^+$.Ca$^{2+}$-ATPase activity, and decreased myosin light chain kinase (MLCK) activity. $\beta_2$ Receptors may also couple to $K_{\text{Ca}}$ via $G_s$. PDE, cyclic nucleotide phosphodiesterase.
Pharmacokinetics\cite{17}

Table 4: Pharmacokinetic parameters during application of Tulobuterol Patch

<table>
<thead>
<tr>
<th>Dose (No. of cases)</th>
<th>Drug administered</th>
<th>Cmax (ng/mL)</th>
<th>Tmax (hr)</th>
<th>T_{1/2} (hr)</th>
<th>AUC_{0-48hr} (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.)

Bioequivalence Study

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, C\text{max}) confirmed bioequivalence for both drugs.

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

The plasma concentration-time graph of tulobuterol patch against standardized preparation is depicted below.

![Figure 12: Plasma concentration-time graph of tulobuterol patch against standardized preparation](image-url)
Pharmacokinetics of Tulobuterol Patch in healthy male volunteers \[18\]

- When the 2 mg tulobuterol patch was administered, it was well absorbed, with an absorption lag-time of about four hours.
- Serum tulobuterol concentrations peaked at 9–12 hours and decreased gradually over the 24 hours. The maximum serum tulobuterol level was 1.4 ng/ml, which is higher than the target effective serum concentration of 1.0 ng/ml.
- The serum tulobuterol level was maintained in an effective range for a longer period after application of the patch.
- The mean % of drug absorbed during the application of a patch for 24 h was 82-90% after a single dose and 82-85% during repeated dosing.
- Mean urinary recovery of unchanged drug after application was 6%.
- According to the literature, the tulobuterol patch is suitable for preventing the morning dip because peak serum drug levels are achieved during the early morning.

Pharmacokinetics the tulobuterol patch in childhood asthma \[19\]

Similar pharmacokinetics was observed when used in children with asthma.

When subjects weighing, < 30 kg received a 1 mg tulobuterol patch and those weighing ≥ 30 kg received the 2 mg tulobuterol patch, the serum concentration of tulobuterol peaked 12 hours after application and remained at appropriate levels for 24 hours after application.

The peak plasma tulobuterol level was 1.33 ng/ml and the time taken to reach this level was 14 hours.

PEF was significantly improved after application of the tulobuterol patch and no side effects were reported.

Therefore, the tulobuterol patch is also suitable for use in children with asthma.
Dosage & Administration\textsuperscript{[17]}

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 children aged > 9 years: 2.0 mg

Although the timing of application for the tulobuterol patch is not clearly described and may depend on disease status, it will be most effective for treatment of asthma if applied in the evening or at bedtime.

\textbf{Figure 13:} Sites of application of Tulobuterol Transdermal Patch
Therapeutic Classification of anti asthma drugs \[20\]

<table>
<thead>
<tr>
<th>CLASSIFICATION</th>
<th>MEDICATION</th>
<th>DRUGS</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTROLLERS</td>
<td>1. Taken daily on a long-term basis</td>
<td>1. Inhaled corticosteroids</td>
</tr>
<tr>
<td></td>
<td>2. Prophylactic and preventive medication</td>
<td>2. Long-acting bronchodilators</td>
</tr>
<tr>
<td></td>
<td>3. Anti-allergic agents</td>
<td>3. Anti-allergic agents</td>
</tr>
<tr>
<td></td>
<td></td>
<td>[Leukotriene inhibitor, <em>Thromboxane A2 inhibitor</em>, Th2 cytokine inhibitor, Mast cell stabilizer, etc]</td>
</tr>
<tr>
<td>RELIEVERS</td>
<td>1. Taken on demand</td>
<td>1. Rapid-acting inhaled β2-agonists</td>
</tr>
<tr>
<td></td>
<td>2. Quick relief for the severe symptoms</td>
<td>2. Systemic glucocorticoids</td>
</tr>
<tr>
<td></td>
<td></td>
<td>3. Anti-cholinergics</td>
</tr>
<tr>
<td></td>
<td></td>
<td>4. Methylxanthines</td>
</tr>
</tbody>
</table>
Classification As Long-Acting Beta Agonists (LABA)\textsuperscript{[6,20,21,22]}

- Tulobuterol patch is a unique $\beta_2$ agonist drug preparation that allows transdermal delivery of tulobuterol through the drug matrix system, thereby avoiding the decrease in respiratory functions during the early morning hours (morning dip) seen in asthma patients receiving other formulations. This is because the patch prevents excessive increase in blood drug concentrations, while also reducing the incidence of systemic adverse reactions.
- The effect of the drug after once-daily application persists for over 24 h, and the formulation is designed such that, once the patch is applied at bedtime, the blood drug concentration reaches its peak in the early morning and the therapeutic effect is sustained for a prolonged period.
- The tulobuterol patch was found to exert an additive effect when combined with ICS in bronchial asthma patients therefore; the patch is positioned as a LABA in the Japanese Guidelines for Prevention and Management of Asthma
- The synergistic effects of ICS and LABAs are explained by the fact that inhaled steroids increase the expression of $\beta_2$ adrenergic receptors, while $\beta_2$ adrenergic agonists causes the down regulation of these receptors. On the other hand, the $\beta_2$ agonists activate the steroid receptors to potentiate the effect of the steroids. In addition, the tulobuterol patch may exert both local effects on the lungs and systemic effects.
- Yamaguchi \textit{et al.} investigated the effect of tulobuterol on the adhesive forces between blood eosinophils and human umbilical vein endothelial cells (HUVEC) in an \textit{in vitro} study. They reported that tulobuterol significantly inhibited the adhesion between eosinophils and HUVECs activated by IL-4 + TNF$\alpha$, IL-5, or formyl-methionyl-leucyl-
phenylalanine. Thus, tulobuterol can decrease the adhesion of blood eosinophils to endothelial cells.

These findings imply that the tulobuterol patch may possibly exert an anti-inflammatory effect.

Although ICS are widely used as first-line controllers in the long-term management of asthma, ICS alone are insufficient when treating patients with moderate to severe asthma. Such patients frequently experience the morning dip.

In the Global Initiative for Asthma, a global guideline for the treatment of asthma, LABAs are positioned as the first add-on controllers for ICS because they can significantly improve airflow obstruction and symptoms.

Use of LABAs as monotherapy is not recommended because these medications have no effects on airways inflammation in asthma and could mask underlying inflammation.

Therefore, LABAs should be used only in combination with ICS for the management of asthma.
Clinical Effects Of The Tulobuterol Patch In Children With Bronchial Asthma

Studies show that the combined use of the tulobuterol patch and an ICS is effective in the treatment of bronchial asthma in children. In addition, the tulobuterol patch has the advantage of being highly convenient to use in children of all ages.

Yoshihara et al. conducted a randomized, parallel-group, comparative study in 10 pediatric patients with severe asthma who were under ICS treatment. Once-daily application of tulobuterol patch showed an add-on effect equivalent to that of inhaled salmeterol (twice-daily inhalation). In addition, comparison of increasing the dose of the ICS vs. adding the tulobuterol patch to the ICS in 18 pediatric patients with severe asthma showed that combination of ICS plus Tulobuterol patch resulted in a significantly greater improvement in the PEF values and a significantly higher percentage of respiratory symptom-free days than increasing the ICS dose.

These results show that the tulobuterol patch is also useful for the long-term management of asthma in the pediatric population. Thus, the tulobuterol patch appears to be suitable for the treatment of asthma in almost all age groups, from infants aged ≥6 months to the elderly, and the combined application of this patch with an ICS plays an important role in the long-term management of asthma.

Effects of the tulobuterol patch on the treatment of acute asthma exacerbations in young children

Methods

➢ This study evaluated the effect of Tulobuterol Patch (TP) on the long-term management of asthma in young children. In this 1-year, randomized, multicenter, double-blind, placebo-
controlled study, children aged 0.5-3 years old with mild-to-moderate persistent asthma were treated with either TP or placebo patch.

- The parents/guardians applied the TP or placebo patch to their children after URTI symptoms appeared.
- Respiratory symptoms were recorded daily during the 1-year observation period.

Results

- Overall, 86 patients were enrolled and 80 were treated and analyzed in this study
- The time to symptom resolution was significantly shorter \((p = 0.001)\) and the total respiratory symptom score \((p = 0.0457)\) was significantly lower in the TP group than in the placebo group.

Conclusion:
In young children with mild-to-moderate asthma who had been treated with anti-inflammatory drugs, using the TP soon after the appearance of URTI symptoms led to quicker resolution of respiratory symptoms and lower respiratory symptom scores.

**Effects of Transdermal Tulobuterol in Pediatric Asthma Patients on Long-Term Leukotriene Receptor Antagonist Therapy: Results of a Randomized, Open-Label, Multicenter Clinical Trial in Japanese Children Aged 4-12 Years**

Methods

- Randomized, open-label, multicenter clinical trial wherein children aged 4-12 years on long-term LTRA therapy were treated with tulobuterol patches (1-2 mg daily) or oral sustained-release theophylline (usual dose, 4-5 mg/kg daily) for 4 weeks.
- LTRAs were continued throughout the trial.
- Outcomes included volume of peak expiratory flow (% PEF), fractional exhaled nitric oxide (FeNO), clinical symptoms and adverse events

Results
% PEF measured in the morning and before bedtime improved significantly in the tulobuterol group within 1 week of starting treatment, and continued to increase thereafter (Figure 14).

The magnitude of increase in % PEF measured in the morning and before bedtime in the theophylline group was much smaller than tulobuterol group while % PEF remained significantly lower than those in the tulobuterol patch group (Figure 14).

There were no marked changes in the Fractional Exhaled Nitric Oxide (FeNO) in either of the groups (Figure 15).

There were no drug-related adverse events in either group.

**Figure 14:** Changes in % peak expiratory flow (PEF) in the morning (A) and before bedtime (B).

*P < 0.05, **P < 0.001, and ***P < 0.001 vs run-in (Student’s one-sample test) or theophylline (Student’s two-sample test).

**Figure 15:** Changes in fractional exhaled nitric oxide (FeNO).
Conclusion
Short-term use of a transdermal β2 agonist is an effective therapy for pediatric asthma without inducing airway inflammation in children on long-term LTRA therapy.

**Efficacy and safety of tulobuterol patch versus oral salbutamol sulfate in children with mild or moderate acute attack of bronchial asthma: a comparative study** [26]

**Methods:**
- A total of 92 children with mild and moderate acute asthmatic attack were randomly divided into salbutamol group (n=46) and tulobuterol group (n=46)
- Both groups received routine treatment with antihistamine, selective leukotriene receptor antagonist and glucocorticoid.
- In addition, the salbutamol group was given slow-release capsules of salbutamol sulfate, and the tulobuterol group was treated with tulobuterol patch.

**Results:**
- The tulobuterol group had significantly lower symptom scores than the salbutamol group on third day of treatment
- On the fourteenth day of treatment, the tulobuterol group had a significantly lower cough score than the salbutamol group
- One child developed hand trembling in the salbutamol group, while no adverse event occurred in the tulobuterol group

**Conclusion:**
Compared with oral salbutamol sulfate, tulobuterol patch has a better therapeutic efficacy and a higher safety in children with mild or moderate acute asthmatic attack

**Pharmacokinetics and pharmacodynamics of the tulobuterol patch, HN-078, in childhood asthma** [27]

**Methods:**
- Single applications of HN-078 were applied transdermally in six children with asthma who had been admitted to a hospital
- Subjects weighing less than 30 kg received 1 mg of tulobuterol while subjects weighing 30 kg or above received 2 mg on the chest for 24 hours.
Results:

- Cmax of tulobuterol was determined to be 1.33 +/- 0.21 ng/mL, Tmax was 14.0 +/- 2.0 hours, and AUCO-t was 27.1 +/- 4.2 ng.hr/mL. These pharmacokinetic parameters per body surface area of children were nearly equivalent to those of adults obtained in other studies.
- Peak expiratory flow rate values obtained after application of HN-078 significantly increased in comparison to those obtained before application.
- No significant changes were observed in pulse rate or blood pressure, and no side effects were found with regard to the subjective symptoms and skin conditions.

Conclusion:

- The patch formulation of tulobuterol, HN-078, will be very useful for the treatment of pediatric asthma. It is especially significant that no side effects were observed.

Treatment Adherence\(^{[23]}\)

Treatment adherence is very important in the management of patients with chronic respiratory diseases. Treatment adherence - The % of patients who took the prescribed drug as instructed.

a) Although inhaled drugs play central roles in the treatment of chronic respiratory diseases, such as asthma and COPD, they are often associated with low treatment adherence.
b) Tamura and Ohta conducted a web-based survey (n=1470) on the treatment adherence to drugs used in asthma and COPD patients. Treatment adherence was significantly higher to the tulobuterol patch (84%) than that for any inhaled drug (31 to 64.6%).

- The complexity of the inhalation technique, difficulty in mastering the technique for using inhalers and insufficient inhalation rate
- The need for frequent administration of an inhaled drug

These are the reasons for the lower treatment adherence to inhaled drugs.

c) Further, the % of individuals who preferred once-daily administration was 83.2%.

d) Patient adherence to the use of the tulobuterol patch is high because of the ease of its application and the need for only once-daily administration.

**Positioning of Tulobuterol Patch in pediatric Asthma**[^6,7,8]

- GINA guidelines recommend LABA from step 3 in children 6-11 years and adolescents
In the Japanese guidelines for childhood asthma 2014, the tulobuterol patch is classified as LABA which is recommended to be used from Step 3.

The International Consensus on Pediatric Asthma 2012 published in European Journal of Allergy and Clinical Immunology recommends the use of LABA from Step 2 onwards.

Safety

1. Tulobuterol released from the patch did not accumulate during repeated transdermal application in healthy adults.
2. It was well tolerated, except for an increase in heart rate of 10–20 beats/min after 5 consecutive applications of a 4 mg patch.
3. No signs of tachyphylaxis after use for a year in adult patients.
4. No serious adverse events have been reported in patients with asthma
5. Mild adverse events reported as follows: itching, eruption, contact dermatitis, tremor, palpitation, numbness, increased serum creatinine phosphokinase, & abnormal hepatic function. These side effects resolved after stopping the patch.
6. Skin problems can be reduced by not applying the patch repeatedly to the same body site.

Desensitization/Tolerance\textsuperscript{[28]}

In the treatment of chronic respiratory diseases, it is important that long-term use of a drug is not associated with reduced efficacy; that is, that no tolerance is induced by its long-term use.

Concern related to the use of the tulobuterol patch is that continuous and repeated exposure to β-agonists leads to reduced relaxation of smooth muscle in the airways, referred to as desensitization to β-adrenoceptor agonists. However, Kume et al have reported that chronic exposure to low
concentrations of tulobuterol does not lead to desensitization of β-adrenoceptors on smooth muscle cells in the airways.

Neither a decrease in efficacy nor the development of tolerance was observed with the use of the tulobuterol patch, even after year-long use. Therefore; the tulobuterol patch is well tolerated and can be used for the long-term management of asthma in any age group.

**Pharmacological Studies Supporting the Clinical Efficacy Results**

**Promotes airway ciliary movement**\(^{[29]}\)

Study demonstrated that tulobuterol promotes airway ciliary movement, thereby enhancing airway clearance. This effect may underlie the improvement of expectoration and cough, which are the subjective symptoms of COPD. COPD patients have low flat diaphragms, and the consequent decrease in the contractility of the respiratory muscles may be associated with decreased respiratory functions and subjective symptoms in patients with COPD.

**Improves Diaphragm muscle contractility**\(^{[30]}\)

Shindoh *et al.* found that the increased contractility of the diaphragmatic muscle was maintained for 24 h after the application of the tulobuterol patch and that the patch suppressed the decrease in the contractility of the diaphragmatic muscle for 24 h. These findings suggest that the tulobuterol patch may increase the contractility of the weakened diaphragmatic muscle in asthma patients.

**Does not affect night sleep**\(^{[31]}\)
Burioka et al. assessed the effects of tulobuterol on the expression of the human clock gene *Per1* mRNA and confirmed that the drug does not affect its expression. This finding implies that the administration of tulobuterol at bedtime does not affect night sleep.
## Comparison of Tulobuterol Patch with other inhaled and oral Beta₂ Agonist with SRT [31,32,33,34,35]

<table>
<thead>
<tr>
<th>Drug Heading</th>
<th>Tuloplast (Tulobuterol Transdermal Patch)</th>
<th>Inhaled Salmeterol</th>
<th>Inhaled Formoterol</th>
<th>Oral Salbutamol</th>
<th>Oral Levosalbutamol</th>
<th>Oral Slow Release Theophylline(SRT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Category</td>
<td>LABA</td>
<td>LABA</td>
<td>LABA</td>
<td>SABA</td>
<td>SABA</td>
<td>Long acting Bronchodilator</td>
</tr>
<tr>
<td>Half life (hours)</td>
<td>0.5 mg: 7-15</td>
<td>1 mg: 8-12</td>
<td>2 mg: 7-15</td>
<td>5.5</td>
<td>10</td>
<td>5</td>
</tr>
<tr>
<td>Pediatric population</td>
<td>Approved for all except in children &lt; 6 months of age</td>
<td>Not approved for children &lt; 4 years of age</td>
<td>Not approved for children &lt; 6 years of age</td>
<td>Not approved for children &lt; 2 years of age</td>
<td>Not approved for children &lt; 6 years of age</td>
<td>Not approved for children &lt; 2 years of age</td>
</tr>
<tr>
<td>Geriatric population</td>
<td>Can be used but to start with a lower dose</td>
<td>No difference in efficacy and safety with younger population</td>
<td>No difference in efficacy and safety with younger population</td>
<td>Can be used but to start with a lower dose</td>
<td>Careful attention to dose reduction and frequent serum monitoring needed</td>
<td></td>
</tr>
<tr>
<td>Adverse Effects</td>
<td>Significantly lower risk compared to oral tablet Tremors: 0.9% Palpitation: 2.6%</td>
<td>Tremors, palpitations and tachycardia common</td>
<td>Tremors, palpitations and tachycardia common</td>
<td>Tremors: 10-20% Anxiety: 9-20% Headache, tachycardia, palpitations</td>
<td>Palpitations, tremors, tachycardia, headache common but lesser compared to salbutamol</td>
<td>Nausea, gastric irritation, palpitations, tachycardia, arrhythmias, convulsions, headache, CNS stimulation</td>
</tr>
<tr>
<td>Adherence (Tamura G et al)</td>
<td>84%</td>
<td></td>
<td>53-64%</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Convenience</td>
<td>Asthma: 79.3% very easy COPD: 73.2% very easy</td>
<td>Asthma: 42.7% very easy COPD: 32.1% very easy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Densensitization/ Tolerance</td>
<td>One year treatment with Tulobuterol TTS does not</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Prone to develop tolerance</td>
</tr>
</tbody>
</table>
| Source | Tuloplast Prescribing Information
FORADIL AEROLIZER. Available from: URL [http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020831s028lbl.pdf](http://www.accessdata.fda.gov/drugsatfda_docs/label/2012/020831s028lbl.pdf)
SALAPIN - Salbutamol Syrup 2mg/5ml. Available from: URL [https://www.medicines.org.uk/emc/medicine/24470](https://www.medicines.org.uk/emc/medicine/24470)
Tamura G, Ohta K. Adherence to treatment by patients with asthma or COPD: comparison between inhaled drugs and transdermal patch. Respir Med. 2007;101(9):1895-902

| Quality of Life | Improvement in total SGRQ score from baseline (-4.6) | No significant improvement as compared to Tulobuterol patch | Improvement in total SGRQ score from baseline (-2.5) | appear to cause tachyphylaxis |
## Salient Features

1. Tulobuterol is the world's first bronchodilator drug to be available as long-acting transdermal bronchodilator.

2. **Tuloplast** is a unique transdermal delivery system prepared using drug matrix technology, achieves continuous release of tulobuterol for 24 hours after the patch is applied to the skin.

3. Serum tulobuterol levels increases gradually and then remain at steady levels.

4. Similar pharmacokinetics was observed when used in children with asthma.

5. **Tuloplast** significantly contribute to the pharmacotherapy of asthma by countering the morning dip in respiratory function.

6. Several clinical trials confirm the efficacy of the **Tuloplast** in patients with pediatric asthma.

7. The safety of the tulobuterol patch when used in otherwise healthy adults, children with asthma, has been well established.

8. It is notable that adherence with treatment is far better in patients using the tulobuterol patch than in those on inhaled drugs.


10. **Tuloplast** might become a first choice in treatment, especially for children who are unable to inhale drugs reliably.
References

13. Device Selection and Outcomes of Aerosol Therapy: Evidence-Based Guidelines. American College of Chest Physicians/American College of Asthma, Allergy, and Immunology


Tuloplast Pack Insert

DESCRIPTION & COMPOSITION

Tulobuterol is a member of long acting β<sub>2</sub> receptor agonist family. Its chemical name is (RS) -2-tert-Butylamino-1- (2-chlorophenyl) ethanol and molecular formula is C<sub>12</sub> H<sub>18</sub> ClNO. Its structural formula is depicted below:

![Structural formula of Tulobuterol]

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&lt;sup&gt;2&lt;/sup&gt;</td>
<td>5 cm&lt;sup&gt;2&lt;/sup&gt;</td>
<td>10 cm&lt;sup&gt;2&lt;/sup&gt;</td>
</tr>
</tbody>
</table>

CLINICAL PHARMACOLOGY

Pharmacodynamics

Tulobuterol is a directly acting sympathomimetic and has selective β<sub>2</sub> receptor stimulating activity. Binding of Tulobuterol to β<sub>2</sub> 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, C\text{max}) confirmed bioequivalence for both drugs.
(The usual dose in adults is 2 mg per dose as Tulobuterol.)

**Pharmacokinetic parameters during application of Tulobuterol Patch**

<table>
<thead>
<tr>
<th>Dose (No. of cases)</th>
<th>Drug administered</th>
<th>C\text{max} (ng/mL)</th>
<th>Tmax (hr)</th>
<th>T\text{1/2} (hr)</th>
<th>AUC\text{0-48hr} (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>Incidence unknown</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypersensitivity (Caution)</td>
</tr>
<tr>
<td>Cardiovascular</td>
</tr>
<tr>
<td>Neuropsychiatric</td>
</tr>
<tr>
<td>Gastrointestinal</td>
</tr>
<tr>
<td>Hepatic</td>
</tr>
<tr>
<td>hematologic</td>
</tr>
<tr>
<td>Dermatologic</td>
</tr>
<tr>
<td>Other</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.