Control of Bronco-Spasm in Family Practice - Beyond Inhalation Therapy
Inhaled medications are the cornerstone of asthma/COPD therapy, but only be effective if used properly.
The effect of particle size on the site of preferential deposition in airways
The degree of lung disease influences the pattern of drug deposition within the lungs.

Several studies have shown that **central airway deposition** is enhanced as mucus plugging, turbulent airflow & airway obstruction increase.

Therefore, in the face of severe lung disease, **little or no drug** may deposit in the **lung peripheral airways**.

This is important for corticosteroids.

Corticosteroid receptors are also present throughout the airways and inflammation has been shown to exist in all regions of the lungs in asthma and COPD.

For these reasons, uniform distribution of an ICS throughout the airways, following inhalation, may be preferable.

Limitations of aerosol therapy

- Not all inhalation devices are appropriate for all patients.
- Based on a real-life setting, it has been reported that 76% of patients using a pMDI & 49–54% of those using a BA-pMDI make at least one error when using their inhaler.
- In addition, between 4 and 94% of patients using a DPI do not use it correctly and
- 25% have never received inhaler-technique training.

pMDI- Pressurized Metered Dose Inhaler, breath-actuated pMDIs (BA-pMDI), dry powder inhaler (DPI)  

• Studies have shown that a very high proportion of patients do not have the competence to use their device effectively, either because they have never been shown or because they have forgotten what they were taught.

• In addition, many of those who are able to demonstrate a good technique in the clinic will contrive to use the device ineffectively in routine use.
Cold Freon effect:

- The initial reaction to the cold blast of MDI propellant on the back of the throat
- Can often result in the patient aborting the inhalation process and hence receiving inconsistent delivery to the lungs.
Therapeutic Issues of Inhaler delivery devices

Metered Dose Inhaler
- More than 50% patients perform ≤ 5 out of 9 steps for correct use of inhaler
- Failure to co-ordinate actuation with inhalation and to hold breadth after inhalation
- Deposition of 50-80 percent of actuated dose in oropharynx

Dry Powder Inhaler
Rapid inhalation promotes greater deposition in larger central airways

Spacer can prove to be bulky

Face mask reduces the delivery to lungs by 50%

Nebulizer is bulky, expensive, time consuming and output is dependent on device and operating parameters


Myths Related to use of Inhalers

- Inhalers are habit forming
- Inhalers cause dryness of nose and mouth
- Inhalers affect the physical activities of a child
- Inhalers stunt the child growth
- Child becomes lethargy with the use of inhaler

Adherence: A key Issue in Asthma & COPD

According to the WHO, for inhaled therapy to be effective, the patient must use a device effectively and adhere to a regular treatment regimen.

- Approximately 50% of adults & children on long-term therapy for asthma fail to take medications as directed at least part of the time.

- Studies demonstrated: increased illness, exacerbations, visits to the emergency department, morbidity, & mortality in non-adherent asthma patients.

Factors Involved in Non-Adherence

<table>
<thead>
<tr>
<th>Medication Usage</th>
<th>Non-Medication Factors</th>
</tr>
</thead>
<tbody>
<tr>
<td>Difficulties associated with inhalers</td>
<td>Misunderstanding/lack of information</td>
</tr>
<tr>
<td>Complicated regimens</td>
<td>Inappropriate expectations</td>
</tr>
<tr>
<td>Fears about, or actual side effects</td>
<td>Underestimation of severity</td>
</tr>
<tr>
<td>Cost of medication</td>
<td>Attitudes toward ill health</td>
</tr>
<tr>
<td>Distance to pharmacies</td>
<td>Cultural factors</td>
</tr>
<tr>
<td></td>
<td>Poor communication</td>
</tr>
</tbody>
</table>
Fears about, or actual side effects

Poor Adherence

Uncontrolled Asthma

Unable To Inhale Drugs Reliably

Children & elderly

Complicated regimens

Drug doesn't reach to peripheral airway
## Results into Uncontrolled Asthma/COPD

<table>
<thead>
<tr>
<th>Study</th>
<th>Total Patients</th>
<th>Uncontrolled Asthma</th>
<th>Controlled Asthma</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHARIOT</td>
<td>1,009</td>
<td>18.1%</td>
<td>81.9%</td>
</tr>
<tr>
<td></td>
<td>(n=183)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fuhlbrigge</td>
<td>10,139</td>
<td>59.0%</td>
<td>41.0%</td>
</tr>
<tr>
<td></td>
<td>(n=5,982)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACCESS</td>
<td>2,238</td>
<td>42.0%</td>
<td>58.0%</td>
</tr>
<tr>
<td></td>
<td>(n=921)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIM</td>
<td>2,500</td>
<td>29.0%</td>
<td>71.0%</td>
</tr>
<tr>
<td></td>
<td>(n=725)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*CHARIOT*: Total of 1,009 patients with moderate to severe persistent asthma

*Fuhlbrigge et al*: Total of 10,139 patients with current asthma

*ACCESS*: Total of 2,238 patients with asthma

*AIM*: Total of 2,500 patients with asthma

What is the alternative for patients who are unable to inhale drugs reliably?
Circadian Rhythm & Asthma

The graph illustrates the variation of Cortisol and Melatonin levels throughout the day. Cortisol levels peak in the morning and decrease as the day progresses, while Melatonin levels rise from nighttime to early morning.
Night-time: an Asthmatic’s version of a perfect storm

- Bronchial asthma is a disease based on established circadian rhythm.
- Anti-inflammatory: Cortisol & Epinephrine reach a nadir during the night.
- Pro-inflammatory: Histamine & melatonin levels spike, increasing inflammation.
- Genetic component further exacerbates symptoms.
- “The pituitary gland tells the adrenal gland to produce cortisol, but there is a blunting of this response in nocturnal asthma.”

J Control Release. 2012 Nov 10;163(3):353-60
The symptoms of asthma worsen during midnight to early morning & therefore it is required to deliver the drug in such fashion that it will be effective during the time of asthma attacks.

**Chronotherapy** : drug delivery at a specific time as per the pathophysiological need of the disease, to improve patient compliance.

1. **TREATMENT ADHERENCE**: Very important in management of chronic respiratory diseases.  

INHALED DRUGS:  
- Often Associated With Low Treatment Adherence.  
- Difficulty In Mastering The Technique For Using Inhalers  
- Insufficient inhalation rate.  

2. **NO DRUG TOLERANCE OVER LONG TERM USE**  

3. **DRUG RESERVOIR-CONSISTENT DRUG DELIVERY**: For 24 hour efficacy  

4. **UNDISTURBED SLEEP**: 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. implying that tulobuterol at bedtime does not affect night sleep.

**Tulobuterol Patch Formulation**

- **Tulobuterol Patch:**
  - Designed in accordance with the concept of chronotherapy
  - The plasma drug concentration is controlled in such a manner that it is 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.
Developmental Rationale of Tuloplast

Concept 2: Lower excessive Cmax

Oral $\beta_2$ adrenoceptor agonist

Concept 1: Design Tmax

Morning dip

Respiratory function

Blood concentration

Treatment range

Start of application 20:00

4:00 12:00 20:00

Respiratory function

CRYSTAL RESERVOIR TECHNOLOGY: The tulobuterol patch delivery system prepared using crystal reservoir technology.

MORNING DIPS WELL CONTROLLED: It has been shown to significantly contribute to the pharmacotherapy of asthma by countering the morning dip in respiratory function.

IMPROVED QOL: Since single Patch a day provides therapeutically effective drug concentration via the systemic circulation, in Asthma & COPD, it improves patients’ QOL.

EXCELLENT TREATMENT ADHERENCE: Once-daily application makes Tulobuterol patch excellent in terms of treatment adherence and convenience.

LONG TERM MANAGEMENT: Transdermal delivery provides consistent relief thus suitable for the long-term management of chronic respiratory diseases like Asthma & COPD. (No decrease in efficacy or tolerance observed with tulobuterol patch, even after year-long use.)
Technology of Tuloplast Patch

It is composed of three distinctive layers:

1) **Backing film**: The innermost layer of non-woven laminate & a polyester. Easily applied on the skin, causes minimal discomfort. creates minimum moisture, while contents are gradually transmitted to the skin.

![Diagram of Tuloplast Patch]

2. **Drug matrix**: middle layer composed of polyisobutylene rubber. It has efficient rate of adhesion that can provide & sustain the effectiveness of the drug. It allows the content of the patch to penetrate in the skin layer.

3. **Liner**: The outermost layer. The surface of the liner is made of silicone & modified polyester. It protects the drug matrix & helps sustain the drug’s efficiency rate. Lengthen the therapeutic effect.
MAINTAINS SERUM CONCENTRATION WITHIN THERAPEUTIC RANGE FOR 24 HOURS
Pharmacokinetics of Tuloplast

Analysis of pharmacokinetic parameters confirmed bioequivalence for both drugs.
# Pharmacokinetics

<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$_{0\rightarrow48\text{hr}}$ (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>
Tulobuterol Plasma Concentration Curve
Patch versus oral tablets

Allergology International Vol 61, No2, 2012
Tulobuterol Patch
Long Term Effect on PEF

Increase in the morning PEF values after treatment with 1 mg or 2mg tulobuterol patch. **p < 0.01, p < 0.05.
Place of Tuloplast in Asthma Therapy: GINA 2015

Place of Tuloplast in Pediatric Asthma Therapy: Japanese Guidelines 2014

- Use of LABA is recommended to be used from Step 3 onwards
- Tulobuterol patch specifically mentioned to be used in children less than 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>SABA As needed</td>
<td>LTRA and/or DSCG</td>
<td>ICS (medium dose)</td>
<td>ICS (high dose) possibly add LTRA</td>
</tr>
<tr>
<td>Additional therapy</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LTRA and/or DSCG</td>
<td>ICS (low dose)</td>
<td>LTRA LABA (p.o. or adhesive skin patch)</td>
<td>LABA (p.o. or adhesive skin patch) Theophylline (maintain at 5-10 mg/mL in blood conc.) can be considered</td>
</tr>
</tbody>
</table>

Classified as LABA

<table>
<thead>
<tr>
<th>Drug</th>
<th>Inhaler (mcg)</th>
<th>Solution for Nebulizer (mg/ml)</th>
<th>Oral</th>
<th>Vials for Injection (mg)</th>
<th>Duration of Action (hours)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Beta₂-agonists</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Short-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fenoterol</td>
<td>100-200 (MDI)</td>
<td>1</td>
<td>0.05% (Syrup)</td>
<td></td>
<td>4-6</td>
</tr>
<tr>
<td>Levalbuterol</td>
<td>45-90 (MDI)</td>
<td>0.21, 0.42</td>
<td></td>
<td></td>
<td>6-8</td>
</tr>
<tr>
<td>Salbutamol (albuterol)</td>
<td>100, 200 (MDI &amp; DPI)</td>
<td>5</td>
<td>5 mg (Pill), 0.024% (Syrup)</td>
<td>0.1, 0.5</td>
<td>4-6</td>
</tr>
<tr>
<td>Terbutaline</td>
<td>400, 500 (DPI)</td>
<td></td>
<td>2.5, 5 mg (Pill)</td>
<td></td>
<td>4-6</td>
</tr>
<tr>
<td>Long-acting</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Formoterol</td>
<td>4.5-12 (MDI &amp; DPI)</td>
<td>0.01‖</td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Arformoterol</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Indacaterol</td>
<td>75-300 (DPI)</td>
<td></td>
<td></td>
<td></td>
<td>24</td>
</tr>
<tr>
<td>Salmeterol</td>
<td>25-50 (MDI &amp; DPI)</td>
<td></td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>Tulobuterol</td>
<td></td>
<td></td>
<td>2 mg (transdermal)</td>
<td></td>
<td>24</td>
</tr>
</tbody>
</table>

Place of Tuloplast in COPD Therapy: GOLD 2015

Clinical Evidence In Pediatric patients
Tulobuterol patch versus oral salbutamol sulfate in Childhood Asthma

Methods:
- 92 children with mild and moderate acute asthmatic attack were randomly assigned to receive either Tulobuterol patch or oral salbutamol.
- Both groups received routine treatment with antihistamine, selective leukotriene receptor antagonist and glucocorticoid.
- Duration of the treatment - 14 days.

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.

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.
The Use of Patch Formulation of Tulobuterol (LABA) In The Treatment of Severe Pediatric Asthma

- Tulobuterol patch with ICS vs. Inhaled salmeterol plus ICS
- Randomized, prospective

<table>
<thead>
<tr>
<th>Variable</th>
<th>2</th>
<th>4</th>
<th>6</th>
<th>8</th>
<th>10</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Increase in morning PEF, ΔL/min</td>
<td>55.6 ± 9.6†</td>
<td>61.1 ± 9.9†</td>
<td>64.4 ± 9.6†</td>
<td>71.1 ± 9.9†</td>
<td>74.4 ± 10.7†</td>
<td>76.6 ± 10.5†</td>
</tr>
<tr>
<td>Chlorofluorocarbon–beclomethasone dipropionate, 800 μg, and tulobuterol patch, 2 mg</td>
<td>23.9 ± 8.7</td>
<td>31.1 ± 7.4</td>
<td>37.8 ± 9.2</td>
<td>41.1 ± 8.7</td>
<td>44.4 ± 8.3</td>
<td>46.7 ± 6.7</td>
</tr>
<tr>
<td>Chlorofluorocarbon–beclomethasone dipropionate, 800 μg and 400 μg</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Increase in symptom-free days, %</td>
<td>40.0 ± 9.4†</td>
<td>43.2 ± 7.7†</td>
<td>57.3 ± 11.7†</td>
<td>61.1 ± 9.5†</td>
<td>70.8 ± 4.8†</td>
<td>72.2 ± 6.3†</td>
</tr>
<tr>
<td>Chlorofluorocarbon–beclomethasone dipropionate, 800 μg, and tulobuterol patch, 2 mg</td>
<td>8.4 ± 3.0</td>
<td>11.1 ± 3.3</td>
<td>12.8 ± 2.4</td>
<td>19.0 ± 5.2</td>
<td>21.8 ± 3.2</td>
<td>25.3 ± 4.0</td>
</tr>
<tr>
<td>Chlorofluorocarbon–beclomethasone dipropionate, 800 μg and 400 μg</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

* The data are presented as mean ± SD. To make intragroup comparisons, we confirmed the dispersion of the 2 groups using the F test. The unpaired t test was used in cases of even dispersion and the Welch test in cases of uneven dispersion. P < .05 was considered statistically significant. † P < .001 (chlorofluorocarbon–beclomethasone dipropionate, 800 μg, and tulobuterol patch, 2 mg, vs chlorofluorocarbon–beclomethasone dipropionate, 800 μg and 400 μg; n = 9 for both groups).
Conclusion:

• In 18 pediatric patients it was found that adding tulobuterol patch to ICS resulted in significantly greater improvement in the PEF values and a significantly higher percentage of respiratory symptom-free days than increasing the dose of ICS.

• Tulobuterol patch useful for the long-term management of asthma in the pediatric population.

• The Tulobuterol patch & ICS combination significantly improved the quality of life, in a similar manner to the salmeterol inhalant, by controlling pulmonary functions and respiratory symptoms superior to increasing the dose of ICSs.

Tulobuterol patch plus LTRA vs. Oral Sustained release Theophylline plus LTRA

- Multicenter, Randomized, open label
- Duration-4 weeks, n=64
- Children(4-12 years) with pediatric asthma on long term LTRA therapy

Results:
- Thirty-three and 31 patients were treated with tulobuterol patches and theophylline, respectively.
- % PEF measured in the morning and before bedtime was significantly higher at all times in the treatment period compared with baseline in the tulobuterol patch group \((p < 0.001)\), and was significantly higher in the tulobuterol patch group compared with the theophylline group.
- FeNO was similar and unchanged from baseline in both groups.
- There were no drug-related adverse events in either group.

Tulobuterol patch elicited significantly greater improvements in % PEF measured in the morning & before bedtime compared with sustained-release theophylline in children on long-term LTRA therapy.

Effects were observed without worsening of Fractional Exhaled Nitric Oxide (FeNO) indicating that it does not exacerbate airway inflammation in children.

Short-term continuous use of a transdermal β2 agonist is an effective therapy for pediatric asthma without inducing airway inflammation.
Tulobuterol patch for acute asthma exacerbations in young children

- Tulobuterol patch (TP) Vs. Placebo patch
- Randomized, multicenter, double-blind, placebo-controlled
- 1 year duration, n=86
- Children aged 0.5-3 yrs old with mild-to-moderate persistent asthma
- 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.
- 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.

Usefulness of Tulobuterol patch in the long-term management of childhood asthma

- Assessed the effect of adding the Tulobuterol patch in severe childhood asthma cases in which morning dipping was observed despite treatment with a high-dose beclomethasone dipropionate (BDP) 800 μg.
- The results showed that adding Tulobuterol patch daily at 8:00 pm improved the asthma attack points & morning PEFR ($p<0.05$, $n=9$) significantly $>$ BDP (1200 μg) alone.
- Early improvement was observed, within several days, & the inhibition of morning dipping lasted until 12 wks later.
- Based on the results of this study the Tulobuterol patch has an additive effect with steroid inhalants, & it can be used in all age groups, including infants.
- Compliance is also good because of its convenience, & there are fewer side effects than with oral LABA.
- These findings suggest that this Tulobuterol patch is highly useful as a drug for the long-term management of childhood asthma.

Yoshihara, S. et al. Journal of Allergy and Clinical Immunology, Volume 113, Issue 2, S33.
Tulobuterol tape in children with cough variant asthma

- 106 patients with **cough variant asthma** (CVA), randomly divided into 2 groups. Both received inhaled corticosteroids,
- Treatment group - **Tulobuterol** patches. Control group - **Procaterol hydrochloride** tablets.
- **Results:**
  - For the Tulobuterol group, the symptom of cough was obviously alleviated. The time for relieving cough was significantly shorter than that in control group (P<0.05).
  - After the course of 2 weeks, the effective rate of treatment group & control group were 90.4% and 79.6%, respectively. There was significant difference between the 2 groups. (P<0.05).
  - After treatment, the FEV1 & PEF of treatment group were both improved significantly as compared with control group (P<0.05).
  - There was no significant difference between the Tulobuterol patches & the procaterol hydrochloride tablets in relieving airway hyperactivity (P<0.05).
  - The Tulobuterol patches had low adverse reaction rates & good compliance.
- **Conclusions:** The Tulobuterol patches show dramatic effect on CVA in children. It has a good compliance, safe and effective.

WEI Bing. *Journal of Applied Clinical Pediatrics*. 2011-09
Tulobuterol tape in children with cough variant asthma

• 100 children with mild to moderate cough variant asthma randomly divided into experimental & control group.
• Antihistamine & selective leukotrienes receptor antagonist were given in both groups.
• In addition, the experimental group - Tulobuterol tape at bedtime.

Results:
– After 14 days, the symptom scores were significantly decreased in experimental group than that in control group; the percentage of improvement in total symptom score was significantly different between two groups (P <0.05), Tulobuterol achieved clinical control.
– There was no significant difference in PEF scores between the 2 groups (P <0.05).

Conclusions: Tulobuterol tape is effective and safe for treatment of mild to moderate cough variant asthma.
Effects of Tulobuterol Patches on Bronchiolitis in Infants

- Compared Tulobuterol patches & nebulized salbutamol on bronchiolitis in infants.
- 60 infants with bronchiohtis were randomly divided into observation group (Tulobuterol patches) & control group. Duration-7 days treatment
- Tulobuterol patches group was given combined with nebulization ipratropium bromide & budesonide, whereas the control group was given inhalation of salbutamol, ipratropium bromide & budesonide.

Results:
- Nocturnal sleep was improved significantly in observation group ($Z =1.974,\ P < 0.05$).
- The tidal volume, TI/TE, TPTEF/TE and VPEF/VE were significantly improved after 7-d treatment in both groups ($P < 0.05$), but no significant differences were found on the first day of treatment between two groups ($P > 0.05$).
- The values of TPTEF/TE and VPEF/VE were significantly better in observation group than those in control group after 7-d treatment ($P < 0.05$).

Conclusion: Tulobuterol patches combined with nebulized ipratropium bromide and budesonide have a certain effect in treatment of bronchiohtis in infants showing faster effect, fewer adverse reactions and good compliance.

Tulobuterol tape in treatment of recurrent wheezing in infants & young children

- 62 infants & young children with recurrent wheezing randomly divided into treatment group (n=31) & control group (n=31).
- When wheezing was relieved, patients in treatment group were treated with budesonide suspension fluid inhalation combined with Tulobuterol tape for 12 wks, while those in control group were treated with budesonide suspension fluid inhalation only.
- Patients were followed up during the 2nd, 4th, 6th, 8th, 10th and 12th wk.
- **Results:** Thirty patients in treatment group and 29 patients in control group completed the treatment and follow up.
- The scoring of cough, frequency of wheezing, scoring of wheezing and scoring of combination use of drugs in treatment group were significantly lower than those in control group (P<0.01), & the frequency of respiratory tract infection in treatment group was significantly lower than that in control group (P<0.05).

**Conclusion:** Budesonide suspension fluid inhalation combined with Tulobuterol tape is more effective and safe than budesonide suspension fluid inhalation only in treatment of recurrent wheezing in infants and young children.
The clinical effects and nursing of 50 infantile asthma patients treated with Tulobuterol patch

- **Objective:** To investigate the clinical effects and nursing of infantile asthma patients treated with Tulobuterol patch.
- **Methods:** 96 infantile asthma patients were randomly divided into two groups, control group, 46 patients were given combined therapy (anti-infective, antivirus, antitussive, expectorant, etc) and routine care; treatment group, 50 patients in addition to the above addressed management, plus were given Tulobuterol patch (Amiaid patch) 0.5mg percutaneously before sleeping, and proper nursing, the clinical effects of the two groups were observed.
- **Results:** The clinical effects of the treatment group (cough, asthma, wheezing, wet rales were disappeared) were significantly better than the control group, the clinical effects of the two groups were significantly different (P=0.0006), after statistical processing.
- **Conclusion:** Tulobuterol patch has a remarkable effects on infantile asthma, it could shorten the course. Tulobuterol patch is safe and effective for infantile asthma without adverse drug reactions, and had the same clinical efficacy as terbutaline inhalation.

LI Jian. Practical Clinical Medicine. 2012-11
Tulobuterol Inhibits Rhinovirus infection

- Tulobuterol patch has been designed to yield sustained β-2 agonistic effects & has been used as LABA in Japan.
- LABAs reduce the frequency of exacerbations of bronchial asthma. However, inhibitory effects of LABAs on the replication of rhinovirus (RV), the major cause of exacerbations, have not been demonstrated.
- To examine the effects of Tulobuterol on RV replication and on the production of the replication-induced pro-inflammatory cytokines, human tracheal epithelial cells were infected with a major group RV, type 14 rhinovirus (RV14). Tulobuterol reduced the RV14 titers and RNA levels; the concentrations of cytokines, including interleukin (IL)-1β, IL-6, and IL-8, in the supernatants; and susceptibility to RV14 infection. Tulobuterol reduced the expression of intercellular adhesion molecule-1 (ICAM-1), the receptor for RV14, and the number of acidic endosomes in the cells in which RV14 RNA enters the cytoplasm.
- Tulobuterol inhibited the activation of nuclear factor kappa B (NF-κB) proteins in nuclear extracts. A selective β2-adrenergic receptor antagonist, ICI 118551 [erythro-dl-1-(7-methylindan-4-yloxy)-3-isopropylaminobutan-2-ol], reversed the inhibitory effects of tulobuterol on the RV14 titers and RNA levels, the susceptibility to RV14 infection, cytokine production, and ICAM-1 expression.
- Tulobuterol may inhibit RV replication by reducing ICAM-1 expression and acidic endosomes and modulate airway inflammation during RV replication.

1. PROMOTES CILIARY MOVEMENTS: One such study demonstrated that tulobuterol promotes airway ciliary movement, thereby enhancing airway clearance. This effect may improve expectoration and cough, which are the subjective symptoms of COPD. ¹

2. IMPROVED CONTRACTILITY OF DIAPHRAGMATIC MUSCLES: 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. Shindoh et al.,²,³ reported the significance of the systemic effects of the tulobuterol patch. They also found that the increased contractility of 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 observed in a mouse model of endotoxin-induced sepsis. Suggesting, tulobuterol patch may increase the contractility of the weakened diaphragmatic muscle in both asthma and COPD patients.

Other Clinical Studies in children
<table>
<thead>
<tr>
<th>SN</th>
<th>Author year</th>
<th>Test drug</th>
<th>Study Design</th>
<th>Duration of the treatment</th>
<th>N</th>
<th>Patients</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| 1  | Suxiang Z et al. 2006 | Tulobuterol patch (treatment group) vs control group.                       | Randomized, prospective | 5-7 days                  | 96 | Children with bronchiolitis                     | 1. Total effective rate of the treatment group was 93.75% (45/48), while the control group was 79.17% (38/48), there was significant difference between two groups  
2. Time to disappearance of signs & symptoms; chest X-ray recovery time and total course of disease was significantly shorter in treatment group  
3. The clinical effect of transdermal Tulobuterol Patches in treating children with bronchiolitis is exact, usage is convenient, compliance is high, and there are no obvious adverse reactions. [16] |
| 2  | Yi Chu et al.         | TP plus Antihistaminics plus LTRA (Experimental) vs Antihistaminics plus LTRA (control) | Randomized, prospective | 14 days                   | 100| Children with mild to moderate cough variant asthma | 1. After 14 days, the symptom scores were significantly decreased in experimental group than that in control group  
2. Tulobuterol tape is effective and safe for treatment of mild to moderate cough variant asthma. [17]                                                                                                 |
| 3  | Ya Ju ZHU et al. 2006 | Budesonide suspension fluid inhalation plus plus tulobuterol tape vs Budesonide suspension alone | Randomized, prospective | 12 weeks                  | 62 | Recurrent wheezing                              | 1. The scoring of cough, frequency of wheezing, scoring of wheezing was significantly lower than those in control group  
2. The frequency of respiratory tract infection in treatment group was significantly lower than that in control group [18]                                                                                   |
<table>
<thead>
<tr>
<th>Authors</th>
<th>Study Details</th>
<th>Study Duration</th>
<th>Sample Size</th>
<th>Disease</th>
<th>Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jian Li et al.</td>
<td>Conventional treatment both groups. Tulobuterol patch vs Terbutaline sulfate inhalation</td>
<td>Randomized, prospective</td>
<td>5 days</td>
<td>60</td>
<td>1. Tulobuterol patch is safe and effective for infantile asthma without adverse drug reactions, and had the same clinical efficacy as terbutaline inhalation [20]</td>
</tr>
</tbody>
</table>
| Yanhua Xi et al.  | Basic treatment plus tulobuterol Patch (Treatment group) vs Basic treatment plus terbutaline aerosol inhalation (control group) | Randomized, prospective | 7 days      | 150             | 1. The clinical cure rate was 80% in treatment group while 20% in control group with no significant difference from control group  
2. Tulobuterol patch has a definite therapeutic effect on pediatric capillary bronchitis, and also has little side effect and excellent medication compliance. [22] |
| Genglian Z et al. | Conventional treatment plus Inhaled albuterol and iptatropium vs Conventional treatment with tulobuterol patch | Randomized, prospective | 3-7 days    | 52              | 1. Effective rate of treatment group was 84.62%, which was more than effective rate of control group (53.5%)  
2. Tulobuterol patch in adjuvant treatment of bronchiolitis has obvious curative effect [23] |
Clinical Studies in Adult Asthma Patients
Transdermal Tulobuterol Added to Inhaled Corticosteroids in Asthma

Study Design:
Randomized, double-blind, double-dummy, parallel-group, multicenter trial

Methods:
Asthma patients requiring Inhaled SABAs despite treatment with ICS were randomized to receive tulobuterol tape 1 mg or 2 mg and corresponding placebo tape for 4 weeks (n=239)

Results:
- In both groups, daytime and night-time supplemental use of β2-agonists significantly decreased from baseline
- The number of rescue-free days and nights significantly increased from baseline in both groups

Transdermal Tulobuterol Added to ICS in Asthma Cont... 

Increase in morning PEF and evening PEF after administration of tulobuterol patch

**Significant difference between the point and baseline (P < 0.01).
†Significant difference between 1 mg treatment group (square) and 2 mg treatment group (circle) (P < 0.05)

Tulobuterol patch is a convenient and effective long-acting β2-agonist for the treatment of persistent asthma.

Effects of the Addition of Beta2-agonist Tulobuterol Patches to Inhaled Corticosteroid in Patients with Asthma

- 24 Asthma patients on ICS were randomized to receive either ICS alone or ICS plus Tulobuterol patch (TP) for 4 weeks

**Results**

Changes in % predicted value of morning peak expiratory flow (PEF) before to during the four-week treatment period in the tulobuterol patch and control group

**p < 0.01 vs (Pre 2 and Pre1)**

Percentage of sputum eosinophils decreased significantly from 12.7 ± 1.8% before treatment to 8.7 ± 0.9% after treatment

Effects of the Addition of Beta2-agonist Tulobuterol Patches to Inhaled Corticosteroid in Patients with Asthma

65 patients with asthma on ICS alone were randomized to receive additive treatments of either alone tulobuterol patch 2 mg/day (T) or pranlukast 450 mg/day (P) or oral slow release theophylline (SRT) 400 mg/day (U) for 4 weeks.

**Difference in %PEF from baseline to week 4 of treatment (Δ%PEF)**
- 1 of the 15 patients in the control (C) group
- 8 of the 17 patients in the pranlukast (P) group
- 7 of the 16 patients in SRT (U) group
- 13 of the 17 patients in the tulobuterol patch (T) group

FEV$_1$ significantly increased after treatment with TP as compared to treatment with SRT or pranulukast.

TP can be used as a long-term add-on controller for patients with asthma receiving ICS.

<table>
<thead>
<tr>
<th>Author. year</th>
<th>Study groups</th>
<th>Duration</th>
<th>N</th>
<th>Study Findings</th>
</tr>
</thead>
</table>
| Su N et al. 2007. | Tulobuterol tape vs Tulobuterol tablet                  | 233      | 4  weeks | Morning PEF, evening PEF, percentage change significantly increased in tulobuterol vs tablet group  
|              |                                                        |          |    | The incidence of palpitations and tremor in the tulobuterol tape group was significantly lower than in the tablet group |
| Nishiyama Q et al. 2006. | Tulobuterol patch 2 mg OD vs Inhaled salmeterol 50 mg BD | 54       | 4  weeks | The mean morning PEF and HRQoL score were significantly improved in both groups  
|              |                                                        |          |    | The tulobuterol patch may be useful as a controller medication in addition to ICS in moderate to severe asthma |
| Burioka N et al. 2005. | Transdermal tulobuterol chronotherapy                  | 13       |    | Application of the tulobuterol patch at nighttime increased significantly the 03:00 h group average PEF and 24 h mean PEF  
|              |                                                        |          |    | Tulobuterol chronotherapy significantly increased both the level and stability of airway function over 24 hours |
# Trial Summary: Adult Asthma

<table>
<thead>
<tr>
<th>Author. year</th>
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<th>Duration</th>
<th>N</th>
<th>Study Findings</th>
</tr>
</thead>
</table>
| Horiguchi T et al. 2004. | ICS and tulobuterol Transdermal Therapeutic System (TTS) OR Tulobuterol TTS without ICS | 1 year | 24  | ➢ PEF exhibited significant improvements at 6 months and 1 year in patients treated with or without inhalational steroids  
➤ One-year treatment with tulobuterol TTS did not appear to cause tachyphylaxis.  
➤ Tulobuterol TTS is considered quite beneficial in improving quality of life (QOL) |
| Kume H. 2002. | Tulobuterol patch 2 mg once daily | 8 weeks | 7   | ➢ The early morning reduction in PEF rate was suppressed with tulobuterol patch  
➤ The rescue use of inhaled Beta-agonists and symptom scores underwent significant reduction |
| Kato H. 2002. | Transdermal tulobuterol | Review   |     | ➢ Tulobuterol TTS is superior as compared to oral formulations of Beta2 agonists in terms of pharmacokinetic profile and clinical trial efficacy |
Clinical Evidence In COPD Patients
BAREC Study: Comparison between Tulobuterol Patch and inhaled Salmeterol in COPD

Methods:
- Multicenter, parallel-group, comparative study of the tulobuterol patch and inhaled salmeterol in 92 patients with stable COPD

Results:
- Improvements in the morning and evening PEF values in both groups, with no significant intergroup difference
- Both groups demonstrated significant improvement in FEV₁, FVC, PEF
- Significantly greater improvement of the St. George Respiratory Questionnaire (SGRQ) at 8 weeks after the start of treatment was observed in the tulobuterol patch group compared with the salmeterol group
- Treatment compliance was also significantly better in the tulobuterol patch group than in the salmeterol group

Once daily transdermal tulobuterol is as effective or better than inhaled salmeterol in the management of stable COPD, with significant effects on quality of life.

Superiority over Inhaled Salmeterol

**Methods:**
- 165 elderly patients with moderate to severe AECOPD were randomized to receive either tulobuterol patch 2 mg/day plus fluticasone propionate 250 micro g BD or Inhaled salmeterol/fluticasone 50/250 micro g BD

**Results:**
- Significant improvement in TP group as compared to inhaled salmeterol in terms of:
  - FEV$_1$, PEF, 6 min walking distance and symptom scores
  - Frequencies of rescue medication, waking-up suffocating at night and days of hospital stay

**Conclusion:**
- Tulobuterol patch is an effective and safe medication for the treatment of acute exacerbation of AECOPD

Yu-guang Li et al., Chinese Journal of Geriatrics; 2012; 31(8): 679-82
Morning PEF Improvement over 12-week treatment period with Tulobuterol Patch and inhaled salmeterol in Stable COPD
Evening PEF Improvement over 12-week treatment period with Tulobuterol Patch and inhaled salmeterol in Stable COPD
St George’s Respiratory Questionnaire score during 12 weeks of treatment with tulobuterol patch and inhaled salmeterol in stable COPD. *p < 0.05, p < 0.05 (Intergroup).
Adherence to prescribed medication in Asthma and COPD

“As directed by physicians”

- DPI-LABA (n = 523)
  - 53.7% taking as prescribed
  - 37.3% sometimes failing to take as prescribed
  - 8.6% often failing to take as prescribed
  - 0.4% always failing to take as prescribed
  - Results of Mann-Whitney U test vs TP-LABA* 1.2%

- MDI-SABA (n = 567)
  - 64.6% taking as prescribed
  - 27.3% sometimes failing to take as prescribed
  - 6.9% often failing to take as prescribed
  - Results of Mann-Whitney U test vs TP-LABA* 2.2%

- DPI-CS (n = 279)
  - 38.7% taking as prescribed
  - 44.8% sometimes failing to take as prescribed
  - 14.3% often failing to take as prescribed
  - Results of Mann-Whitney U test vs TP-LABA* 2.2%

- MDI-CS (n = 132)
  - 39.4% taking as prescribed
  - 40.2% sometimes failing to take as prescribed
  - 20.5% often failing to take as prescribed
  - Results of Mann-Whitney U test vs TP-LABA* 2.2%

- MDI-anticholinergic (n = 42)
  - 31.0% taking as prescribed
  - 52.4% sometimes failing to take as prescribed
  - 16.7% often failing to take as prescribed
  - Results of Mann-Whitney U test vs TP-LABA* 4.5%

- TP-LABA (n = 470)
  - 84.0% taking as prescribed
  - 7.9% sometimes failing to take as prescribed
  - 4.5% often failing to take as prescribed
  - 3.6% always failing to take as prescribed
  - Results of Mann-Whitney U test vs TP-LABA* 4.5%
Better treatment adherence to a transdermal tulobuterol patch than inhaled Salmeterol in COPD

Methods:
- 44 treatment-naïve elderly COPD patients were randomized to receive either tulobuterol patch 2 mg once daily or inhaled Salmeterol

Results:
- The overall adherence rate was 90.3 ± 1.6% for TP and 75.5 ± 2.9% for salmeterol
- 6 minute walking distance and Quality of Life were significantly increased from baseline in TP group but not in salmeterol group

Conclusion:
- Adherence levels were higher overall with TP than with inhaled salmeterol, and more stable across age groups and Mini-Mental State Examination (MMSE) levels
1. PROMOTES CILIARY MOVEMENTS: One such study demonstrated that tulobuterol promotes airway ciliary movement, thereby enhancing airway clearance. This effect may improve expectoration and cough, which are the subjective symptoms of COPD. ¹

2. IMPROVED CONTRACTILITY OF DIAPHRAGMATIC MUSCLES: 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. Shindoh et al.,²,³ reported the significance of the systemic effects of the tulobuterol patch. They also found that the increased contractility of 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 observed in a mouse model of endotoxin-induced sepsis. Suggesting, tulobuterol patch may increase the contractility of the weakened diaphragmatic muscle in both asthma and COPD patients.

Effects of tulobuterol Patch on dyspnea and respiratory function during exercise in patients with COPD

Methods:
- 13 COPD patients were treated with 2 mg transdermal tulobuterol once daily for 4 weeks

Results:
- The maximum Borg scale for dyspnea and the Borg scale slope (BSS) decreased significantly from baseline to the end of treatment
- The threshold load of dyspnea (TLD) increased slightly in the constant load test
- No significant difference in blood pressure and heart rate 4 weeks after administration of tulobuterol patch compared to baseline

Conclusion:
- Tulobuterol patch lead to significant improvement in self-assessed dyspnoea which may encourage patients to perform daily life activities or regular physical activity

With Tulobuterol patch, Drug reaches the peripheral airways through the systemic circulation after transdermal absorption, thereby maintaining “patency of peripheral airways” resulting in:

1. More effective expiration
2. Reduction of the residual volume.
3. Prevents pulmonary hyperinflation
4. Improves the exercise tolerance
5. Improves the patients’ QOL.

BAREC II Study: Additive effects of transdermal tulobuterol to inhaled tiotropium in patients with COPD

Methods:
103 patients with stable COPD were randomized to receive either inhaled tiotropium alone (Tio group) or both tulobuterol patch and inhaled tiotropium (Tio + Tulo group)

Results:
➢ In both groups, FEV1, FVC and dyspnea improved significantly after 8 weeks

➢ Significant Percentage change in Inspiratory Capacity and significant improvement in SGRQ score was observed only in Tio plus Tulo group

BAREC II Study: Additive effects of transdermal tulobuterol to inhaled tiotropium in patients with COPD

Effect of tulobuterol used in combination therapy on (A) morning and (B) evening peak expiratory flow (PF).

*P < 0.05, **P < 0.01 (Tio group versus Tio plus Tulo group)

Additional administration of transdermal tulobuterol to inhaled tiotropium in COPD produced significant benefits in dyspnea, SGRQ score and Pulmonary function without an increase in risk of adverse effects

BAREC II study
“Tulobuterol patch” as an add on to Tiotropium

- Tiotropium exerts its effects via muscarinic “M3 receptors”, while tulobuterol acts via the “β2 adrenergic receptors”.
- Activated muscarinic M3 receptors are found mainly in the “central airways”, thus Tiotropium affects central airways rather than the peripheral airways.
- Tulobuterol activates the β2 adrenergic receptors in the peripheral airways via the systemic circulation.

The combination of the two agents have complementary effects and improve the functions of both the peripheral and central airways.

104 patients
Asthma/COPD

Tulobuterol patch
2 mg OD

Salmeterol
50 micro g/inhalation
BD

- Better improvement of morning PEF was found with Tulobuterol Patch compared to Salmeterol inhalation
- SGRQ score improved from baseline in TP group
- Compliance was better in TP as compared to inhaled salmeterol group
- No technical complaints

Once daily transdermal Tulobuterol patch is as effective or better than the inhaled long-acting beta2 agonist Salmeterol in the management of moderate to severe asthma/COPD, with significant effect on quality of life.

Data on File
## Trial Summary: COPD

<table>
<thead>
<tr>
<th>Author. Year</th>
<th>Study groups</th>
<th>Duration</th>
<th>N</th>
<th>Study Findings</th>
</tr>
</thead>
</table>
| Abe T et al. 2011. | Inhaled Tiotropium plus TP (Tio plus Tulo) vs Inhaled Tiotropium alone (Tio) | 4 weeks each treatment (Crossover) | 16 | ➢ Tio plus Tulo was associated with significantly greater improvements than Tio in Impulse Oscillation (IOS)-assessed markers of resistance (R5 and R5-R20), reactance and reactance area, from baseline to week 4)  
➢ Tio plus Tulo significantly improved dyspnoea and SGRQ score from baseline as compared to Tio alone |
| Minami S et al. 2007. | Transdermal tulobuterol patch (TP) Vs SRT | 4 weeks each treatment (Crossover) | 16 | ➢ Patients receiving TP exhibited significant improvement in the number and ease of sputum expectorations, cough frequency score, wheezing severity score and SGRQ score compared with baseline  
➢ Treatment of COPD patients with TP is more effective than with theophylline |
Tulobuterol Patch: Clinically well Proven Adherence

- Internet based questionnaire study to evaluate treatment adherence and convenience in asthma & COPD (n=1470)

- 52.7% patients with asthma took inhaled drugs as indicated as against 86% patients with TP

- 54.7% patients with COPD took inhaled drugs as indicated as against 86.6% patients with TP

- 79.3% with asthma and 73.2% of those with COPD described TP as “very easy to use” with corresponding percentages being 42.7% and 32.1% for inhalers

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):1895–1902
INDICATIONS

For treatment of patients with Asthma and COPD
DOSAGE AND ADMINISTRATION:

Once daily, apply the tape to chest, back, or upper arm as below dosage regimen.

- Children 6 months to 3 years: 0.5 mg
- Children 3 to 9 years: 1.0 mg
- Adults & children -> 9 years: 2.0 mg

• Most effective if applied in the evening or at bedtime.
Sites Of Application of Tuloplast

- Left or Right Upper Arm
  - Side
  - OR
  - Front
  - OR
- Left or Right Side of Chest
  - Front
  - OR
- Left or Right Upper Back
  - Back
  - OR
  - Back
  - OR
- Left or Right Lower Back
  - Back
  - OR
USE IN SPECIAL POPULATIONS

• Pregnancy
  – 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.

• Lactation
  – If Tulobuterol is applied to nursing mothers, breast feeding should be avoided.
  – Transfer of Tulobuterol into milk has been reported in animal studies.

• Pediatric Use
  – The safety of Tulobuterol has not been established in infants less than 6 months of age.
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.
### Adverse Reactions

- **Clinically significant adverse reactions**
- **Anaphylactoid symptoms**: if patient is hypersensitive.
- **Serious decrease in serum potassium level**: reported with β2 agonist.

<table>
<thead>
<tr>
<th>Category</th>
<th>Description</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.
Tuloplast: Summary

1. World's first bronchodilator to be available as long-acting transdermal patch.
2. A unique TDS prepared using Drug matrix technology, achieves continuous release for 24 hr.
3. Serum levels increases gradually & maintain a steady state level.
4. Tuloplast counters the morning dip in respiratory function.
5. Several clinical trials confirm the efficacy of the Tuloplast in patients with asthma & COPD.
6. Drug reaches the peripheral airways via the systemic circulation, is useful for the long-term management of COPD.
7. The safety of the tulobuterol patch in asthma or COPD has been well established.
8. Tuloplast adherence is far better than in those on inhaled drugs.
9. Only once-daily application: useful for long-term management of COPD.
10. Potential to become a first choice in treatment, especially for children & elderly patients who are unable to inhale drugs reliably.
CRYSTAL RESERVOIR TECHNOLOGY: The tulobuterol patch delivery system prepared using crystal reservoir technology.

MORNING DIPS WELL CONTROLLED: It has been shown to significantly contribute to the pharmacotherapy of asthma by countering the morning dip in respiratory function.

IMPROVED QOL: Since single Patch a day provides therapeutically effective drug concentration via the systemic circulation, in Asthma & COPD, it improves patients’ QOL.

EXCELLENT TREATMENT ADHERENCE: Once-daily application makes Tulobuterol patch excellent in terms of treatment adherence and convenience.

LONG TERM MANAGEMENT: Transdermal delivery provides consistent relief thus suitable for the long-term management of chronic respiratory diseases like Asthma & COPD. (No decrease in efficacy or tolerance observed with tulobuterol patch, even after year-long use.)