Leaflet Bremax Syrup & Tabs.
Size: 220 x 140mm
Date: 10-07-2015, 27-06-2015
Ammara Commerial Printers (Pvt.) Ltd.

Subacute Toxicity
The maximum safe dose of tulobuterol was estimated to be 50 mg/kg in the rat.

Chronic Toxicity
In rats, the maximum safe dose of tulobuterol, orally, was 18 mg/kg/day for six months and 9 mg/kg/day for twelve months.

In dogs, the non-toxic dose level was 50 mg/kg/day.

CARCINOGENESIS, MUTAGENESIS AND IMPAIRMENT OF FERTILITY
Carcinogenicity
Potential tumorigenic effects of tulobuterol were evaluated in mice and rats by prolonged dietary administration in doses of 1, 3 and 9 mg/kg/day for two years. The highest dose used in these studies was greater than 100 times the recommended human dose (0.08 mg/kg/day).

Mice
No abnormal clinical signs were detected and longevity was not affected. Food consumption was not altered, but treated males gained less weight. Minor changes in differential leukocytes were reported.

The incidence of uterine smooth muscle tumors (leiomyoma, leiomyosarcoma) in mice receiving the highest dose of tulobuterol (9 mg/kg/day) was not statistically significant. The tendency for these treated females to develop lymphoreticular tumors was not greater than the background incidence in this strain of mice (Charles River CD-1).

Rats
Differences in clinical findings, mortality rates, food intake, and blood differentials were considered to be not related to treatment. Lower body weight gain was noted for both sexes receiving 9 mg/kg/day.

Long term administration resulted in the presence of leiomyomata in the ovary or ovarian suspensory ligament or smooth muscle hyperplasia at the hilus of the ovary in a few female rats receiving 9 mg/kg/day, and an increased incidence of ovarian cysts in treated females. These changes were considered to be related to the pharmacological activity of tulobuterol and have been reported for other sympathomimetic agents.

Mutagenicity
Studies on tulobuterol have been performed using bacterial and mammalian systems. These studies have provided no evidence of mutagenic potential for Tulobuterol.

Fertility, Reproduction and Teratogenicity
Fertility and reproductive function in rats were not affected by the administration of tulobuterol. The results of the administration, by gavage, of 0, 5, 20 and 40 mg/kg/day of tulobuterol to pregnant rabbits in the organogenesis period showed no significant differences in the successful pregnancy rates or the body weight increase in mothers and fetuses was not significantly different and there was no teratogenic effect.

STORAGE:
Protect from excessive heat, light and moisture.

HOW SUPPLIED
Tulobuterol Hydrochloride
1. Bremax 1 mg TABS: List # E388, pack size: 10X10S
2. Bremax 2 mg TABS: List # E390, pack size: 10X10S
3. Bremax Syrup: 1 mg / 5 ml, List # E 427, pack size: 60 ml

عمومی خوراک: بڑوں کے لیے
بریمیکس گولیاں ایک ملی گرام
دو گولیاں روزانہ دن میں دو مرتبہ

ابتدائی خوراک:
بڑوں اور بارہ سال سے بڑے بچوں میں ایک گولی روزانہ دن میں دو مرتبہ جو کہ سات سے دس دن بعد دو گولیاں روزانہ دن میں دو مرتبہ تک بڑھا سکتے ہیں۔ بشرطیکہ دوا کے غیر مناسب اثرات ظاہر نہ ہوں تاکہ دمہ سے بروقت اور بہتر شفا حاصل ہو سکے۔
مندرجہ بالا خوراک میں ڈاکٹر صاحبان مریض کی کیفیت کی مناسبت سے حسب ضرورت ردوبدل کر سکتے ہیں۔

بریمیکس گولیاں دو ملی گرام
ایک گولی روزانہ دن میں دو مرتبہ

ابتدائی خوراک:
بڑوں اور بارہ سال سے بڑے بچوں میں ۱/۴ گولی روزانہ دن میں دو مرتبہ جو کہ سات سے دس دن بعد ایک گولی روزانہ دن میں دو مرتبہ تک بڑھا سکتے ہیں۔ بشرطیکہ دوا کے غیر مناسب اثرات ظاہر نہ ہوں تاکہ دمہ سے بروقت اور بہتر شفا حاصل ہو سکے۔
مندرجہ بالا خوراک میں ڈاکٹر صاحبان مریض کی کیفیت کی مناسبت سے حسب ضرورت ردوبدل کر سکتے ہیں۔

بریمیکس سیرپ
بچوں کے لیے عمومی خوراک:
جسمانی وزن کے مطابق:
چالیس پاؤنڈ سے اسی پاؤنڈ یا تیئیس کلوگرام فی کلوگرام یومیہ حصے دو خوراکوں میں تقسیم کر کے دیں۔
عمر کے مطابق:
ایک سے چھ سال تک کے بچوں کے لیے:
۱/۴ سے ۱/۲ چائے کا چمچہ دن میں دو مرتبہ۔
چھ سے بارہ سال تک کے بچوں کے لیے:
۱/۲ سے ایک چائے کا چمچہ دن میں دو مرتبہ۔
بارہ سال سے بڑے بچوں کے لیے:
ایک سے دو چائے کے چمچے دن میں دو مرتبہ۔
عمر کے مطابق دی گئی مندرجہ بالا خوراک میں ڈاکٹر صاحبان مریض کی کیفیت کی مناسبت سے حسب ضرورت ردوبدل کر سکتے ہیں۔
دوا کو گرمی اور دھوپ سے بچائیں اور خشک جگہ پر رکھیں۔

Manufactured by:
Abbott Laboratories (Pakistan) Ltd.
Landhi, Karachi.

Abbott

01-027R5

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Bremax®
(Tulobuterol HCl)
Tablets

بریمیکس®
(ٹیولوبیٹرول ہائیڈروکلورائیڈ)
گولیاں

Bremax®
(Tulobuterol HCl)
Syrup

بریمیکس® سیرپ
(ٹیولوبیٹرول ہائیڈروکلورائیڈ)

DESCRIPTION
Tulobuterol is a synthetic beta 2-agonist with potent and prolonged bronchodilator activity of the sympathomimetic amine class related structurally and pharmacologically to epinephrine, isoproterenol, salbutamol (albuterol), metaproterenol, terbutaline, clorprenaline, carbuterol and procaterol.

Tulobuterol is an odorless and bitter tasting white crystalline powder. It is soluble in methanol, water, acetic acid, ethanol, chloroform, and 1,2-dichloroethane, only slightly soluble in acetone, isopropanol and dioxane and practically insoluble in benzene, ether, cyclohexane and isopropylether.

The chemical name for tulobuterol is alpha-o-chloro-[(tert-butylamino) methyl] benzyl alcohol. The molecular weight of the hydrochloride salt is 264.19 and the empirical formula is C12 H19Cl2NO.

Tulobuterol is available as tablets (1 mg and 2 mg) and syrup (1 mg/5 mL).

INDICATIONS
Tulobuterol is indicated for prophylaxis and control of bronchospasm in bronchial asthma, chronic bronchitis, asthmatic bronchitis, pulmonary emphysema, bronchiectasis, tracheobronchitis with emphysema and other bronchospastic disorders and conditions characterized by bronchoconstriction. Because oral tulobuterol is long acting, it is ideally suited for routine maintenance therapy in chronic asthma and chronic bronchitis. Tulobuterol has been shown in controlled single- and multiple-dose studies to be more effective than terbutaline and fenoterol and at least as effective as salbutamol (albuterol) in relieving bronchospasm associated with reversible obstructive airways disease such as asthma, and also chronic bronchitis and emphysema. Clinically significant improvement in pulmonary function, as demonstrated by an increase in FEV of 15% or more, occurred within 30 minutes after oral dosing with peak improvement occurring within two to three hours. In some patients, a therapeutic response was still apparent at 12 hours. Continued effectiveness was demonstrated over a one-year period.

DOSAGE AND ADMINISTRATION
As long-term clinical studies have demonstrated, tulobuterol continues to be efficacious and does not result in cumulative or toxic side effects. Due to the variability of the disease and the need for individualized dosage requirements, flexibility in dosing is indispensable.

The use of Long-Acting Beta Agonists is contraindicated without the use of an asthma controller medication such as inhaled corticosteroid.

Long-Acting Beta Agonists should be used for the shortest duration of time required to achieve control of asthma symptoms and discontinued, if possible, once asthma control is achieved. Patient should then be maintained on a long-term asthma controller medication (e.g. Corticosteroids).

Tablets
The usual oral adult dose of tulobuterol is one 2 mg tablet twice a day.
A convenient starting dose for children 12 years and over and adults is 1 mg twice a day, particularly for elderly patients and those with a history of sensitivity to beta-

adrenergic agents. Unless precluded by drug-related side effects, the patient may have the dose increased after seven to ten days to 2 mg twice a day, if necessary, to achieve a greater therapeutic response.

Although most patients can be maintained on a dose of 1 to 2 mg twice daily, the variability of patient response and severity of symptoms may require further adjustment of the dose, as with any bronchodilator treatment. Therefore, if necessary, the adult dose of tulobuterol may be increased to 6 mg a day in divided doses according to clinical response.

Syrup
Based on dose-ranging studies in children, the usual dose of tulobuterol syrup (1 mg/5 mL) for children is 40 to 80 mcg/kg/day in two divided doses.

In clinical studies in children, the effective dose has ranged from 20 to 100 mcg/kg/day.
This leads to the following recommendations on the basis of age:

For children aged one to six years, 0.25 tsp. (1.25 mL) to 0.5 tsp. (2.5 mL) BID;

For children aged six to twelve years, 0.5 tsp. (2.5 mL) to 1 tsp. (5 mL) BID;

For children aged over twelve years, 1 tsp. (5 mL) to 2 tsp. (10 mL) BID.

The above age recommended doses may have to be modified according to patient response.

CONTRAINDICATIONS
Administration of tulobuterol is contraindicated in patients with known hypersensitivity to sympathomimetic amines or any of the formulation components.

WARNINGS AND PRECAUTIONS
Long-Acting Beta Agonists should only be used long-term in patients whose asthma cannot be adequately controlled on asthma controller medications alone.

Tulobuterol should be used with caution in patients with diabetes mellitus, hypertension, hyperthyroidism, and seizure disorders.

Caution should be observed in patients with renal failure in view of the kidney being the principle route of elimination of the drug. Dosage may also require individualization in patients with impaired liver function as normally tulobuterol is extensively metabolized by the liver.

As with other sympathomimetic bronchodilator agents, tulobuterol should be administered cautiously to cardiac patients, especially those with associated arrhythmias, coronary insufficiency, or myocardial ischemia.

Clinical trials to study the effects of tulobuterol in combination treatment with theophylline or aerosol corticosteroids failed to demonstrate any deleterious effects. The concomitant systemic use of tulobuterol with other systemic sympathomimetic agents is not recommended, since their combined effect on the cardiovascular system may be deleterious to the patient.

Tulobuterol should not be prescribed together with beta-blocking agents. Although an intravenous injection of a cardio-selective beta-blocking agent can be given as a specific antidote for tulobuterol overdosage, these agents should be used with caution in patients with bronchospasm.

PREGNANCY AND LACTATION
Safety of this product for use during pregnancy has not been established. It is not known whether tulobuterol is excreted in human breast milk nor whether it has a harmful effect on the newborn. Therefore, as with any medication, the use of the drug in pregnancy, lactation, or women of childbearing potential requires that the expected therapeutic benefit of the drug be weighed against its possible hazards to the mother and child.

ADVERSE REACTIONS
The adverse reactions of tulobuterol are similar in nature to those of other sympathomimetic agents, however the incidence of certain cardiovascular effects is less with tulobuterol.

Dose-related finger tremor is common with these agents, but the effects tend to lessen with continued administration of the drug.

Oral formulations of tulobuterol, like other sympathomimetic agents, can also cause less frequent adverse reactions such as hypertension, palpitations, angina, tachycardia, vomiting, vertigo, central nervous system stimulation, insomnia and headache.

PHARMACOLOGIC PROPERTIES
The primary pharmacological action of beta-adrenergic drugs is to stimulate adenyl cyclase, the enzyme which catalyzes the formation of cyclic-3',5' adenosine monophosphate (cyclic AMP) from adenosine triphosphate (ATP). The cyclic AMP thus formed mediates the cellular response that results in bronchodilation. Tulobuterol, due to its highly selective action on beta-2 adrenoceptors, relaxes the bronchial smooth muscle and has been shown to be clinically successful in the symptomatic treatment of reversible obstructive airways disease (ROAD) such as bronchial asthma, and also in bronchitis and emphysema.

Some bronchodilators stimulate beta-1 (cardiac) receptors in addition to beta-2 receptors and may cause tachycardia, angina, and possibly arrhythmias in susceptible patients. Animal studies and in vitro experiments indicate that tulobuterol is more selective in its beta-2 agonist activity than other agents in this class and, therefore, should produce fewer cardiac side effects.

Studies in asthmatic patients have shown that intravenous tulobuterol caused less fluctuation in blood pressure than salbutamol (albuterol). Dose-dependent increases in pulse rate were observed after intravenous salbutamol (albuterol) but not after tulobuterol. Clinically significant improvement in pulmonary function was observed following tulobuterol but not after salbutamol (albuterol).

In vitro studies demonstrated that tulobuterol is a beta-2 adrenergic agonist exhibiting tissue selectivity causing relaxation of airway smooth muscle without causing atrial contractions. The potency of tulobuterol to stimulate beta-2 receptor activity was similar to salbutamol (albuterol).

Tulobuterol was effective when administered subcutaneously and by aerosol; it was more potent than clorprenaline, salbutamol (albuterol), and isoproterenol when administered orally.

Metabolism, Absorption, Distribution and Excretion
Clinical
The rationale for BID dosing is based on the following studies:

a. Single oral 2 mg doses of tulobuterol were rapidly absorbed and gave mean peak serum concentrations at approximately one hour post-dosing. The mean terminal half-life of the parent compound in plasma was 3.1 hours.

b. Oral doses of 14C-tulobuterol (4 mg free base) administered to human volunteers were well absorbed and after extensive metabolism, excreted mainly in urine. The rate of absorption was rapid and peak concentrations, ranging 3.5 to 5.8 ng/ml, of unchanged drug (10% plasma radioactivity) were observed within one hour of dosing. Radioactivity appeared to decline in a multi-exponential fashion, with a mean terminal half-life of 17 hours (± 5 S.D.). Metabolite profiles in plasma were very similar to those in urine at the corresponding time interval and thus contained some hydroxylated tulobuterol metabolites. The main metabolic pathway in humans was by ring-hydroxylation. Tulobuterol underwent extensive biotransformation and metabolites were excreted in the urine both unconjugated and in the form of sulphate conjugates. Unchanged drug after oral doses was identified as a minor radioactive component in urine and accounted for less than 5% of the excreted dose.

c. Following administration of a 2 mg or 4 mg oral dose of tulobuterol hydrochloride, the volume of distribution was determined to be 6.7 ± 3.4 L/kg, and 10.5 ± 4.7 L/kg, respectively. This relatively large volume of distribution, the possible enterohepatic recirculation, and the extended elimination half-lives of some of the metabolites may explain the long-acting properties of oral tulobuterol.

Other Studies of Special Interest Are the Following:

a. Oral doses of tulobuterol HCl of 2 mg were administered BID at 12 hour intervals to 18 normal volunteers for 14 days. The age range was 22 to 73 years. Accumulation factors were somewhat greater in the older subjects, in that Cmax ratio means were 1.5 for the oldest group and 1.0 for the youngest. Accumulation of tulobuterol was, therefore not marked but tended to be greater in the older group. In this respect, the pharmacokinetic behavior of tulobuterol in the elderly appears to be similar to that observed for many other drugs.

b. Serum concentration and urinary excretion were measured in 38 patients with chronic asthma and at least one of the following concurrent diseases: hypertension, diabetes mellitus, renal dysfunction, hepatic dysfunction. Patients were administered 2 mg tablets BID, at 12 hour intervals, for up to 14 days. It was concluded that the pharmacokinetics of tulobuterol were not affected by the concurrent disease status of these patients.

Parent Compound / Metabolites	Species (% urinary radioactivity)			
	Dog	Rat	Mouse	Man
Tulobuterol	3	2	3	4
4,5-dihydro-4,5-dihydroxytulobuterol	ND*	ND	ND	25
3,4-dihydro-3,4-dihydroxytulobuterol	3	<1	1	7
3-dihydroxytulobuterol	2	30	ND	11
4-dihydroxytulobuterol/ 5-hydroxytulobuterol	2	6	19	12
4-dihydro-5-methoxytulobuterol	2	12	6	4
* ND = None detectable				

c. The comparative metabolism of 14C-tulobuterol in animals and man is shown in the following table:

All species excreted small proportions of unchanged tulobuterol and the basic phenolic metabolites. Of the two dihydrodiols produced by man, the 3,4-diol was also detected in the animal species examined; whereas the 4,5-diol was not detected in any of these.

PRE-CLINICAL SAFETY DATA
Toxicology
Acute Toxicity
A comparison of the LD50 values for tulobuterol (p.o.) between young and adult animals is summarized in the following table:

		LD50 (95% C.L.*) Mg/kg	
Species	**Sex**	**Young**	**Adult**
Rat	Male	1050 (833.9 to 1322.1)	850 (756.2 to 955.4)
	Female	1025 (849.7 to 1236.5)	780 (650.3 to 935.5)
Rabbit	Male	635	563
	Female	772	525
Dog	Male	283	360
	Female		
* C.L. = Confidence Limits			