Pharmacokinetic data in children were obtained in a Phase II pharmacokinetic study including 31 children aged 4 to 11 years with allergic rhinoconjunctivitis or chronic urticaria, administered once daily with bilastine 10 mg orodispersible tablet. Pharmacokinetic analysis of plasma concentration data showed that the pediatric dose of bilastine 10 mg once daily results in systemic exposure equivalent to that seen after a 20 mg dose in adults and adolescents, being the mean AUC value 1014 ng* x hr/mL for children 6 to 11 years. These results were largely below the safety threshold based on data from 80 mg once daily dose in adults in accordance to the drug safety profile. These results confirmed the choice of bilastine 10 mg p.o. once daily as the appropriate therapeutic dose for the paediatric population in the age range 6 to 11 years with a body weight of at least 20 kg. 6- Recommended Dose.

5.3 Preclinical safety data
Non-clinical data with bilastine reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. In reproduction toxicity studies, effects of bilastine on the foetus (pre-and post-implantation loss in rats and incomplete ossification of cranial bones, sternebrae and limbs in rabbits) were only observed at maternal toxic doses. The exposure levels at the NOAELs are sufficiently in excess (> 30 fold) to the human exposure at the recommended therapeutic dose. In a lactation study, bilastine was identified in the milk of nursing rats administered a single oral dose (20 mg/kg). Concentrations of bilastine in milk were about half of those in maternal plasma. The relevance of those results for humans is unknown. In a fertility study in rats, bilastine administered orally up to 1000 mg/kg/day did not induce any effect on female and male reproductive organs. Mating, fertility and pregnancy indices were not affected. As seen in a distribution study in rats with determination of drug concentrations by autoradiography, bilastine does not accumulate in the CNS.

6- PHARMACEUTICAL PARTICULARS
6.1 Incompatibilities
Not applicable.
6.2 Shelf life
2 years
6.3 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.4 Nature and contents of container
The primary packaging for tablet is ALU/ALU blister packs with pack sizes of 10's, 20's and 30's
The primary packaging for oral solution in bottles of 30ml, 60ml, and 120ml.

6.5 Special precautions for disposal and other handling
Any unused product or waste material should be disposed of in accordance with local requirements.

STORAGE CONDITIONS AND INSTRUCTIONS:
- **Dosage:** As directed by the physician.
- Store below 30°C in a dry place, protect from light.
- To be dispensed on the prescription of a registered medical practitioner only.
- Keep out of the reach of children.

- **خوراک:** ڈاکٹر کی ہدایت کے مطابق استعمال کریں۔
- دوا کو ۳۰ ڈگری سینٹی گریڈ سے کم درجہ حرارت پر روشنی سے بچا کر خشک جگہ پر رکھیں۔
- صرف رجسٹرڈ ڈاکٹر کے نسخے پر ہی فروخت کریں۔
- بچوں کی پہنچ سے دور رکھیں۔

Manufactured by:
Kaizen Pharmaceuticals (Pvt.) Ltd.
E-127-129, North Western Industrial Zone,
Bin Qasim, Karachi-75020, Pakistan.

Art No. 891

MYALLER
(Bilastine)

20mg Tablet & 2.5mg/ml Oral Solutions

مائیلر
(بلاسٹن)

۲۰ ملی گرام گولیاں اور
۲.۵ ملی گرام/ملی لیٹر
اورل سلوشن

Composition:

Myaller 20mg Tablet
Each tablet contains:
Bilastine 20mg

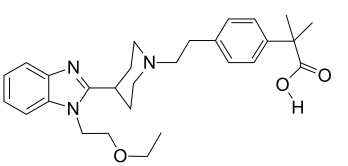
Myaller Oral Solution 2.5mg/ml
Each ml contains:
Bilastine 2.5mg

Product Description
Physical Properties

Chemical Name:
2-(4-(2-(4-(1-(2-ethoxyethyl)-1H-benzo[d]imidazol2-yl)piperidin-1-yl)ethyl)phenyl)-2-methylpropanoic acid

Molecular Weight
463.61 g/mol

Structural Formula



Clinical Particulars
4.1-Therapeutic indications
Symptomatic treatment of allergic rhino-conjunctivitis (seasonal and perennial) and urticaria.

4.2-Posology and method of administration
Pediatric population:
Children 6 to 11 years of age with a body weight of at least 20 kg 10 mg bilastine (4 ml of oral solution) once daily for the relief of symptoms of allergic rhino-conjunctivitis (seasonal allergic rhinitis and perennial allergic rhinitis) and urticaria.
The oral solution should be taken one hour before or two hours after intake of food or fruit juice.

Children under 6 years of age and under 20 kg
No recommendation on a posology can be made. Therefore, bilastine should not be used in this age group.

Adults: In adults and adolescents (over 12 years of age) the administration of bilastine 20 mg tablets is appropriate.

Method of administration
Oral

4.3- Precautions regarding use and dosage
Pediatric population
Efficacy and safety of bilastine in children under 2 years of age have not been established and there is little clinical experience in children aged 2 to 5 years, therefore bilastine should not be used in these age groups.

In patients with moderate or severe renal impairment coadministration of bilastine with P-glycoprotein inhibitors, such as e.g, ketoconazole, erythromycin, cyclosporine, ritonavir or diltiazem, may increase plasmatic levels of bilastine and therefore increase the risk of adverse effects of bilastine. Therefore, coadministration of bilastine and P-glycoprotein inhibitors should be avoided in patients with moderate or severe renal impairment.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially "sodium free".

4.4- Warnings and Precautions
Cardiovascular
MYALLER has been associated with QTc interval prolongation (see ACTION AND CLINICAL PHARMACOLOGY, Cardiac Electrophysiology). Drugs that cause QT/QTc prolongation are suspected of increasing the risk of torsade de pointes. Torsade de pointes is a polymorphic ventricular tachyarrhythmia. Generally, the risk of torsade de pointes increases with the magnitude of QT/QTc prolongation produced by the drug. Torsade de pointes may be asymptomatic or experienced by the patient as dizziness, palpitations, syncope, or seizures. If sustained, torsade de pointes can progress to ventricular fibrillation and sudden cardiac death. MYALLER should not be used in patients with a history of QTc prolongation and/or torsade de pointes, including congenital long QT syndromes (see CONTRAINDICATIONS). Particular care should be exercised when administering antihistamines, including MYALLER to patients who are suspected to be at an increased risk of experiencing torsade de pointes during treatment with a QTc-prolonging drug. This includes patients who have a history of cardiac arrhythmias; hypokalemia; hypomagnesaemia; significant bradycardia; family history of sudden cardiac death; concomitant use of other QT/QTc-prolonging drugs. When drugs that prolong the QTc interval are prescribed, healthcare professionals should counsel their patients concerning the nature and implications of the ECG changes, underlying diseases and disorders that are considered to represent risk factors, demonstrated and predicted drug-drug interactions, symptoms suggestive of arrhythmia, risk management strategies, and other information relevant to the use of the drug.

Hepatic
MYALLER has not been studied in subjects with hepatic impairment. Since bilastine is not metabolized and renal clearance is the major route of elimination, hepatic impairment is not expected to increase systemic exposure above the safety margin.

Renal
In subjects with moderate or severe renal impairment co-administration of bilastine with P-glycoprotein inhibitors, such as ketoconazole, erythromycin, cyclosporine, ritonavir or diltiazem, may increase plasma levels of bilastine and therefore increase the risk of adverse effects. Co-administration of bilastine and P-glycoprotein inhibitors should be avoided in subjects with moderate or severe renal impairment.

Special Populations
Pregnant Women
There are no adequate and well-controlled studies in pregnant women. Until such data become available, MYALLER should be avoided during pregnancy, unless advised otherwise by a physician. Animal studies do not indicate major direct or indirect harmful effects with respect to reproductive toxicity, parturition or postnatal development (see TOXICOLOGY). Twelve (12) pregnancies were reported during bilastine investigation. Follow-up was performed by the investigators through to the birth of newborns. Their observations indicated that there had been a normal outcome reported for every pregnancy, except one miscarriage due to an antiphospholipid syndrome (case history of repeated miscarriages) resulting in an induced abortion (voluntary).

Nursing Women
The excretion of bilastine in milk has not been studied in humans. Available pharmacokinetic data in animals have shown excretion of bilastine in milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with MYALLER should be made taking into account the benefit of breast-feeding to the child, the benefit of bilastine therapy to the mother, and these should be weighed against possible effects on the infant.

Pediatrics (< 12 years of age)
The safety and efficacy of MYALLER in children under 12 years of age has not been established.

Geriatrics (> 65 years of age)
No dosage adjustments are recommended in subjects over 65 years of age.
(see ACTION AND CLINICAL PHARMACOLOGY and DOSAGE AND ADMINISTRATION).

4.5- Interactions with other medicaments
Interaction studies have only been performed in adults and are summarised below.
Interaction with food: Food significantly reduces the oral bioavailability of bilastine 20 mg tablets by 30% and that of bilastine 2.5 mg/ml oral solution by 20%.

Interaction with grapefruit juice: concomitant intake of bilastine 20 mg and grapefruit juice decreased bilastine bioavailability by 30%. This effect may also apply to other fruit juices. The degree of bioavailability decrease may vary between producers and fruits. The mechanism for this interaction is an inhibition of OATP1A2, an uptake transporter for which bilastine is a substrate (see section 5.2). Medicinal products that are substrates or inhibitors of OATP1A2, such as ritonavir or rifampicin, may likewise have the potential to decrease plasma concentrations of bilastine.

Interaction with ketoconazole or erythromycin: Concomitant intake of bilastine 20 mg o.d and ketoconazole 400 mg o.d or erythromycin 500 mg t.i.d. increased bilastine AUC 2-fold and Cmax 2-3 fold. These changes can be explained by interaction with intestinal efflux transporters, since bilastine is a substrate for P-gp and not metabolised (see section 5.2). These changes do not appear to affect the safety profile of bilastine and ketoconazole or erythromycin, respectively. Other medicinal products that are substrates or inhibitors of P-gp, such as cyclosporine, may likewise have the potential to increase plasma concentrations of bilastine.

Interaction with diltiazem: Concomitant intake of bilastine 20 mg o.d. and diltiazem 60 mg o.d. increased Cmax of bilastine by 50%. This effect can be explained by interaction with intestinal efflux transporters (see section 5.2), and does not appear to affect the safety profile of bilastine.

Interaction with alcohol: The psychomotor performance after concomitant intake of alcohol and 20 mg o.d. bilastine was similar to that observed after intake of alcohol and placebo.

Interaction with lorazepam: Concomitant intake of bilastine 20 mg o.d. and lorazepam 3 mg o.d. for 8 days did not potentiate the depressant CNS effects of lorazepam.

Paediatric population
No interaction studies have been performed in children with bilastine oral solution. As there is no clinical experience regarding the interaction of bilastine with other medicinal products, food or fruit juices in children, the results obtained in adult interactions studies should be at present taken bilastine to children.
There are no clinical data in children to state whether changes to the AUC or Cmax due to interactions affect the safety profile of bilastine. into consideration when prescribing bilastine to children. There are no clinical data in children to state

whether changes to the AUC or Cmax due to interactions affect the safety profile of bilastine.

4.6- Pregnancy and lactation
Pregnancy
There are no or limited amount of data from the use of bilastine in pregnant women. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity, parturition or postnatal development. As a precautionary measure, it is preferable to avoid the use of bilastine during pregnancy.

Breastfeeding
The excretion of bilastine in milk has not been studied in humans. Available pharmacokinetic data in animals have shown excretion of bilastine in milk. A decision on whether to continue/discontinue breast-feeding or to discontinue/abstain from bilastine therapy must be made taking into account the benefit of breast-feeding for the child and the benefit of bilastine therapy for the mother.

4.7-Effects on Ability to Drive and Use Machines
A study performed in adults to assess the effects of bilastine on the ability to drive demonstrated that treatment with 20 mg did not affect the driving performance. However, as the individual response to the medicinal product may vary, patients should be advised not to drive or use machines until they have established their own response to bilastine.

4.8- Undesirable effects
• Cardiac disorders: Right bundle branch block, sinus arrhythmia.
• Ear and labyrinth disorders: Vertigo, tinnitus.
• Gastrointestinal disorders: Nausea, diarrhoea, dry mouth, thirst, dyspepsia, gastritis, upper abdominal pain, abdominal pain.
• General disorders and administration site conditions: Fatigue, asthenia, pyrexia.
• Infections and infestations: Oral herpes..
• Metabolism and nutrition disorders: Increased appetite.
• Nervous system disorders: Somnolence, headache, dizziness.
• Psychiatric disorders: Anxiety, insomnia.
• Respiratory, thoracic and mediastinal disorders: Nasal discomfort, nasal dryness, dyspnoea.
• Skin and subcutaneous tissue disorders: Pruritus.

4.9- Overdose and Treatment
Information regarding acute overdose is limited to experience from clinical trials conducted during the development of bilastine. After administration of bilastine at doses 10 to 11 times the therapeutic dose (220 mg (single dose); or 200 mg/day for 7 days) to healthy volunteers frequency of treatment emergent adverse events was two times higher than with placebo. The adverse reactions most frequently reported were dizziness, headache and nausea.

5- Pharmacodynamics and Pharmacokinetics
5.1- Pharmacodynamic properties
Pharmacotherapeutic group: Antihistamines for systemic use, it blocks the action of histamine and relieves hayfever symptoms, itchiness and hives.

Mechanism of action
Bilastine is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H1 receptors. The antihistaminic activity of bilastine has been documented in a variety of animal and human models. It shows moderate to high affinity for histamine H1-receptors and no affinity for muscarinic, serotonergic, dopaminergic and noradrenergic receptors. Bilastine has been demonstrated to have limited distribution to the brain following oral administration.

5.2- Pharmacokinetic properties
Absorption
Bilastine is rapidly absorbed after oral administration with a time to maximum plasma concentration of around 1.3 hours. No accumulation was observed.

The mean value of bilastine oral bioavailability is 61%.

Distribution
In vitro and in vivo studies have shown that bilastine is a substrate of P-gp (see section 4.5 " Interaction with ketoconazole, erythromycin and diltiazem") and OATP (see section 4.5 " Interaction with grapefruit juice"). Bilastine does not appear to be a substrate of the transporter BCRP or renal transporters OCT2, OAT1 and OAT3. Based on in vitro studies, bilastine is not expected to inhibit the following transporters in the systemic circulation: P-gp, MRP2, BCRP, BSEP, OATP1B1, OATP1B3, OATP2B1, OAT1, OAT3, OCT1, OCT2, and NTCP, since only mild inhibition was detected for P-gp, OATP2B1 and OCT1, with an estimated IC50 ≥ 300 µ M, much higher than the calculated clinical plasma Cmax and therefore these interactions will not be clinically relevant. However, based on these results inhibition by bilastine of transporters present in the intestinal mucosa, e.g. P-gp, cannot be excluded.

At therapeutic doses bilastine is 84-90% bound to plasma proteins.

Biotransformation
Bilastine did not induce or inhibit activity of CYP450 isoenzymes in in vitro studies.

Elimination
In a mass balance study performed in healthy adult volunteers, after administration of a single dose of 20 mg 14C-bilastine, almost 95% of the administered dose was recovered in urine (28.3%) and faeces (66.5%) as unchanged bilastine, confirming that bilastine is not significantly metabolized in humans. The mean elimination half-life calculated in healthy volunteers was 14.5 h.

Linearity
Bilastine presents linear pharmacokinetics in the dose range studied (5 to 220 mg), with a low interindividual variability.

Renal impairment
In a study in subjects with renal impairment the mean (SD) AUC0-∞ increased from 737.4 (± 260.8) ng x hr/mL in subjects without impairment (GFR: > 80 mL/min/1.73 m2) to: 967.4 (± 140.2) ng x hr/mL in subjects with mild impairment (GFR: 50-80 mL/min/1.73 m2), 1384.2 (± 263.23) ng x hr/mL in subjects with moderate impairment (GFR: 30 - <50 mL/min/1.73 m2), and 1708.5 (± 699.0) ng x hr/mL in subjects with severe impairment (GFR: < 30 mL/min/1.73 m2). Mean (SD) half-life of bilastine was 9.3 h (± 2.8) in subjects without impairment, 15.1 h (± 7.7) in subjects with mild impairment, 10.5 h (± 2.3) in subjects with moderate impairment and 18.4 h (± 11.4) in subjects with severe impairment. Urinary excretion of bilastine was essentially complete after 48 -72 h in all subjects. These pharmacokinetic changes are not expected to have a clinically relevant influence on the safety of bilastine, since bilastine plasma levels in patients with renal impairment are still within the safety range of bilastine.

Hepatic impairment
There are no pharmacokinetic data in subjects with hepatic impairment. Bilastine is not metabolized in human. Since the results of the renal impairment study indicate renal elimination to be a major contributor in the elimination, biliary excretion is expected to be only marginally involved in the elimination of bilastine. Changes in liver function are not expected to have a clinically relevant influence on bilastine pharmacokinetics.

Elderly
Only limited pharmacokinetic data are available in subjects older than 65 years. No statistically significant differences have been observed with regard to PK of bilastine in elderly aged over 65 years compared to adult population aged between 18 and 35 years.

Paediatric population
No pharmacokinetic data are available in adolescents (12 years to 17 years) as the extrapolation from adult data was deemed appropriate for this product.