For the use of a Registered Medical Practitioner or a Hospital or a Laboratory only

MASTOWELL

1. Generic Name

Bilastine Tablet 20 mg

2. Qualitative and quantitative composition

Each film coated tablet contains:

Bilastine ……. 20 mg

Excipients…… q.s

Colour: Titanium Dioxide I.P.

The excipients used are Starch, Microcrystalline cellulose, Lactose, Polyvinyl pyrilidone, Sodium Starch Gloycolate, Colloidal Silicon Dioxide, Magnesium Stearate, Talcum, Super coat, Titanium dioxide.

3. Dosage form and strength

Dosage form: Film coated tablet

Strength: 20mg

4. CLINICAL PARTICULARS

4.1 Therapeutic Indication

For symptomatic treatment of allergic rhino-conjuctivitis (seasonal and perennial) and urticaria in adults.

4.2 Posology and Method of Administration

Posology

20 mg bilastine (1 tablet) once daily for the relief of symptoms of allergic rhinoconjunctivitis [SAR (seasonal) and PAR (perennial)] and urticarial in adults.

The tablet should be taken one hour before or two hours after intake of food or fruit juice.

Duration of treatment

For allergic rhino-conjunctivitis the treatment should be limited to the period of exposure to allergens. For seasonal allergic rhinitis treatment could be discontinued after the symptoms have resolved and reinitiated upon their reappearance. In perennial allergic rhinitis continued treatment may be proposed to the patients during the allergen exposure periods. For urticaria the duration of treatment depends on the type, duration and course of the complaints.

Special populations

Elderly

No dosage adjustments are required in elderly patients.

Renal impairment

Studies conducted in adults in special risk groups (renally impaired patients) indicate that it is not necessary to adjust the dose of bilastine in adults.

Hepatic impairment

There is no clinical experience in adult patients with hepatic impairment. However, since bilastine is not metabolized and is eliminated as unchanged in urine and faeces, hepatic impairment is not expected to increase systemic exposure above the safety margin in adult patients. Therefore, no dosage adjustment is required in adult patients with hepatic impairment.

Method of administration

Oral use.

The tablet is to be swallowed with water. It is recommended to take the daily dose in one single intake

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients.

4.4 Special Warnings and Precautions for Use

Paediatric 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.

4.5 Drugs Interactions

Interaction studies have only been performed in adults and are summarised below.

Interaction with food: Food significantly reduces the oral bioavailability of bilastine by 30%.

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. 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 C_{max} 2-3 fold. These changes can be explained by interaction with intestinal efflux transporters, since bilastine is substrate for P-gp and not metabolised. 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 C_{max} of bilastine by 50%. This effect can be explained by interaction with intestinal efflux transporters, 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 bilastine o.d. 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

Interaction studies have only been performed in adults. 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 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 Use in Special Populations (Such as Pregnant Women, Lactating Women, Paediatric Patients, Geriatric Patients Etc.)

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.

Breast-feeding:

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.

Fertility:

There are no or limited amount of clinical data. A study in rats did not indicate any negative effect on fertility.

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

The below adverse effects were determined based on data from the Bilastine clinical studies and frequencies are defined as: Frequencies are assigned as follows:

Very common (≥1/10)

Common (≥1/100 to <1/10)

Uncommon (≥1/1,000 to <1/100)

Rare (≥1/10,000 to <1/1,000)

Very rare (<1/10,000)

Not known (cannot be estimated from the available data)

Infections and infestations

Uncommon: Oral herpes

Metabolism and nutrition disorders

Uncommon: lncreased appetite

Psychiatric disorders

Uncommon: Anxiety, insomnia

Ear and labyrinth disorders

Uncommon: Tinnitus, vertigo

Cardiac disorders

Uncommon: Right bundle branch block, sinus arrhythmia, other ECG abnormal/ties, electrocardiogram QT prolonged

Nervous system disorders

Common: Somnolence, headache

Uncommon: Dizziness

Respiratory, thoracic and mediastinal disorders

Uncommon: Dyspnea, nasal discomfort, nasal dryness

Gastrointestinal disorders

Uncommon: Upper abdominal pain, nausea, stomach discomfort, diarrhea, dry mouth, dyspepsia and gastritis

Skin and subcutaneous tissue disorders

Uncommon: Pruritus

General disorders and administration site conditions

Uncommon: Fatigue, thirst, improved pre-existing condition, pyrexia and asthenia.

Investigations

Uncommon: Increased gamma-glutamyl transferase, alanine aminotransferase increased, aspartate aminotransferase increased, blood creatinine increased, blood triglycerides increased and increased weight

Frequency not known (cannot be estimated from the available data): Palpitations, tachycardia, hypersensitivity reactions (such as anaphylaxis, angioedema, dyspnoea, rash, localized oedema/local swelling, and erythema), and vomiting have been observed during the post-marketing period.

4.9 Overdose

Information regarding acute overdose of bilastine is retrieved from the experience of reported clinical trials conducted during the development and the post-marketing surveillance. In clinical trials, after administration of bilastine at doses 10 to 11 times the therapeutic dose (220

mg as single dose; or 200 mg/day for 7 days) to 26 adult healthy volunteer's frequency of treatment emergent adverse events was two times higher than with placebo. The adverse reactions most frequently reported were dizziness, headache and nausea. No serious adverse events and no significant prolongation in the QTc interval were reported. The information collected in the post-marketing surveillance is consistent with that reported in clinical trials.

Critical evaluation of bilastine's multiple dose (100 mg x 4 days) effect on ventricular repolarization by a "thorough QT/QTc cross-over study" involving 30 healthy adult volunteers did not show significant QTc prolongation.

In the event of overdose symptomatic and supportive treatment is recommended.

There is no known specific antidote to bilastine.

5. Pharmacological properties

5.1 Mechanism of Action

Bilastine is an antihistamine; its principal effects are mediated via selective inhibition of peripheral H1 receptors. The anti-histaminic activity of bilastine has been documented in a variety of animal and human models. It shows moderate Bilastine is a non-sedating, long-acting histamine antagonist with selective peripheral H1 receptor antagonist affinity and no affinity for muscarinic receptors.

Bilastine inhibited histamine-induced wheal and flare skin reactions for 24 hours following single doses of high affinity for histamine H,-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 Pharmacodynamic Properties

Pharmacotherapeutic group: Antihistamines for systemic use, other antihistamines for systemic use

ATC code R06AX29.

Bilastine is a non-sedating, long-acting histamine antagonist with selective peripheral H1 receptor antagonist affinity and no affinity for muscarinic receptors.

Bilastine inhibited histamine-induced wheal and flare skin reactions for 24 hours following single doses

5.3 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 and OATP. 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 $\geq$ 300 μM, 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.

6. Nonclinical properties

6.1 Animal Toxicology or Pharmacology

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.

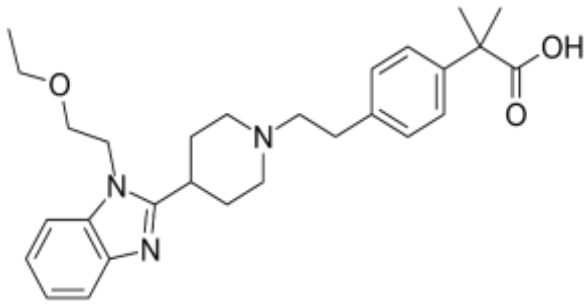
In a lactation study, bilastine was identified in the milk of nursing rats administered a single oral dose (20 mg/kg). Concentrations of bilastine in milk were about half of those in maternal plasma. The relevance of those results for humans is unknown.

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.

7. DESCRIPTION

Bilastine is a second-generation H1- antihistamine, indicated for the treatment of allergic rhinitis and chronic urticaria. Bilastine is known chemically as 2-[4-(2-{4-[1-(2-ethoxyethyl)-1H-benzimidazol-2-yl] piperidin-1-yl} ethyl) phenyl]-2-methylpropionic acid. The empirical formula is $C_{28}H_{37}N_3O_3$ and its molecular weight is 463.622 g/mol. The chemical structure of Bilastine is:



MASTOWELL is White coloured, round, biconvex, film coated tablets, plain on both side. The excipients used are Starch, Microcrystalline cellulose, Lactose, Polyvinyl pyrilidone, , Sodium Starch Gloycolate, Colloidal Silicon Dioxide, Magnesium Stearate, Talcum, Super coat, Titanium dioxide,

8. Pharmaceutical Particulars

8.1 Incompatibilities

None

8.2 Shelf-life

Do not use later than date of expiry

8.3 Packaging information

MASTOWELL is packed in Alu-Alu blister Pack of 10 tablets.

8.4 Storage and Handing Instructions

Store at a temperature not exceeding 30ºC, protected from light and moisture.

Keep out of reach of children.

9. PATIENT COUNSELLING INFORMATION

Package leaflet: Information for the user

MASTOWELL

Read all of this leaflet carefully before you start taking this medicine.

• Keep this leaflet. You may need to read it again.

• If you have any further questions, ask your doctor or pharmacist.

• This medicine has been prescribed for you. Do not pass it on to others. It may harm them, even if their symptoms are the same as yours.

• If any of the side effects gets troublesome or serious, or if you notice any side effects not listed in this leaflet, please tell your doctor or pharmacist. **In this leaflet:**

9.1. What MASTOWELL are and what they are used for

9.2. Before you take MASTOWELL

9.3. How to take MASTOWELL

9.4. Possible side effects

9.5. How to store MASTOWELL

9.6. Contents of the pack and other information

9.1. WHAT MASTOWELL IS AND WHAT IT IS USED FOR

MASTOWELL contains the active substance bilastine which is an antihistamine. MASTOWELL is used to relieve the symptoms of hay fever (sneezing, itchy, runny, blocked-up nose and red and watery eyes) and other forms of allergic rhinitis. It may also be used to treat itchy skin rashes (hives or urticaria).

9.2. BEFORE YOU TAKE MASTOWELL

Do not take MASTOWELL

if you are allergic to bilastine or any of the other ingredients of this medicine.

Warnings and precautions

Talk to your doctor or pharmacist before using MASTOWELL if you have moderate or severe renal impairment and in addition you are taking other medicines (see "Other medicines and MASTOWELL").

Children

Do not give this medicine to children under 12 years of age.

Do not exceed the recommended dose. If symptoms persist, consult your doctor.

Other medicines and MASTOWELL

Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines, including medicines obtained without a prescription.

In particular, please discuss with your doctor if you are taking any of the following medicines:

•Ketoconazole (an antifungal medicine)

•Erythromycin (an antibiotic)

•Diltiazem (to treat angina)

•Cyclosporine (to reduce the activity of your immune system, thus avoiding transplant rejection or reducing disease activity in autoimmune and allergic disorders, such as psoriasis, atopic dermatitis or rheumatoid arthritis)

•Ritonavir (to treat AIDS)

•Rifampicin (an antibiotic)

MASTOWELL with food, drink and alcohol

These tablets should not be taken with food or with grapefruit juice or other fruit juices, as this will decrease the effect of bilastine. To avoid this, you can:

•take the tablet and wait for one hour before taking food or fruit juice or

•if you have taken food or fruit juice, wait for two hours before taking the tablet.

Bilastine, at the recommended dose (20 mg), does not increase the drowsiness produced by alcohol.

Pregnancy, breast-feeding and fertility

There are no or limited amount of data from the use of bilastine in pregnant women and during breast-feeding and on the effects on fertility.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Ask your doctor or pharmacist for advice before taking any medicine.

Driving and using machines

It has been demonstrated that bilastine 20 mg does not affect the driving performance in adults. However the response from each patient to the medicine may be different. Therefore you should check how this medicine affects you, before driving or operating machinery.

9.3. HOW TO TAKE MASTOWELL

Always take this medicine exactly as your doctor or pharmacist have told you. Check with your doctor or pharmacist if you are not sure.

The recommended dose in adults, including the elderly and adolescents aged 12 years and over, is 1 tablet (20 mg) a day.

•The tablet is for oral use.

•The tablet must be taken one hour before or two hours after intake of food or fruit juice.

•Swallow your tablet with a glass of water.

•The score line is only here to help you break the tablet if you have difficulty swallowing it whole

Regarding the duration of treatment, your physician will determine the type of disease you are suffering from and will determine for how long you should take MASTOWELL.

Use in children

Other forms of this medicine - orodispersible tablets or oral solution - may be more suitable for children 6 to 11 years of age with a body weight of at least 20 kg ask your doctor or pharmacist.

Do not give this medicine to children under 6 years of age with a body weight below 20 kg since no sufficient data are available.

If you take more MASTOWELL than you should

If you, or anyone else, have taken too many MASTOWELL tablets, contact your doctor or pharmacist immediately or go to the emergency department of your nearest hospital. Please remember to take this medicine pack or this leaflet with you.

If you forget to take MASTOWELL

Do not take a double dose to make up for a forgotten dose.

If you forget to take your dose on time, take it as soon as possible, and then go back to your regular dosing schedule.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

9.4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Side effects that may be experienced in adults and adolescents are:

Common: may affect up to 1 in 10 people

- headache
- drowsiness

Uncommon: may affect up to 1 in 100 people

- abnormal ECG heart tracing
- blood tests which show changes in the way the liver is working
- dizziness
- stomach pain
- tiredness
- increased appetite
- irregular heartbeat
- increased weight
- nausea (the feeling of being sick)
- anxiety
- dry or uncomfortable nose
- belly pain
- diarrhoea
- gastritis (inflammation of the stomach wall)
- vertigo (a feeling of dizziness or spinning)
- feeling of weakness
- thirst
- dyspnoea (difficulty in breathing)
- dry mouth
- indigestion
- itching
- cold sores (oral herpes)
- fever
- tinnitus (ringing in the ears)
- difficulty in sleeping
- blood tests which show changes in the way kidney is working
- blood fats increased
- Frequency not known: cannot be estimated from the available data
- palpitations (feeling your heart beat)
- tachycardia (fast heart beat)
- allergic reactions the signs of which may include difficulty in breathing, dizziness, collapsing or losing consciousness, swelling of your face, lips, tongue or throat, and/or swelling and redness of the skin. If you notice any of these serious side effects, stop taking the medicine and seek urgent medical advice straight away.
- vomiting

9.5. HOW TO STORE MASTOWELL

Store at a temperature not exceeding 30ºC, protected from light and moisture.

Keep out of reach of children

9.6. CONTENS OF THE PACK AND OTHER INFORMATION

What MASTOWELL contains

•The active substance is bilastine. Each tablet contains 20 mg of bilastine

The excipients used are Starch, Microcrystalline cellulose, Lactose, Polyvinyl pyrilidone, Sodium Starch Gloycolate, Colloidal Silicon Dioxide, Magnesium Stearate, Talcum, Super coat, Titanium dioxide.

10. DETAILS OF MANUFACTURER

Synokem Pharmaceuticals Ltd

Plot No. 56-57, Sector 6A, I. I. E (SIDCUL), Ranipur (BHEL),

Haridwar – 249403(Uttarakhand).

11. DETAILS OF PERMISSION OR LICENCE NUMBER WITH DATE

Mfg Licence No.: 27/UA/2018 issued on 17.10.2019

12. DATE OF REVISION

Not Applicable

MARKETED BY

TORRENT PHARMACEUTICALS LTD.

IN/ MASTOWELL 20mg/AUG-20/01/PI