Bilastine Tablets IP 40mg

Bepozal® 40

40

10 x10 Tablets

To be sold by retail on the prescription of Dermatologist only

1. Generic name
Bilastine 40mg Tablets

2. Qualitative and quantitative composition
Each film coated tablet contains:
Bilastine IP .....40 mg
Excipients ..... q.s.
Colour: Titanium Dioxide IP

3. Dosage form(s) and strength(s)
Bepozal 40 mg film coated tablet

4. Clinical particulars
4.1 Therapeutic Indications
For the treatment of Chronic Spontaneous Urticaria.

4.2 Posology & method of administration
Posology:

Chronic Spontaneous Urticaria	≥18 years	Bilastine 40 mg (One tablet) once daily

The tablet should be taken one hour before or two hours after intake of food of fruit juice.
Route of administration:
To be taken orally
The tablet is to be swallowed with water. It is recommended to take the daily dose in one single intake.

4.3 Contraindication
Hypersensitivity to the active substance or to any of the excipients

4.4 Special warnings & precaution for use
QTc prolonging drugs:
The concurrent use of bilastine with other QTc prolonging drugs is not recommended. Bilastine has been associated with QTc interval prolongation. Drugs that cause QT/QTc prolongation are suspected of increasing the risk of torsade de pointes.
Bilastine should not be used in patients with a history of QTc prolongation and/or torsade de pointes, including congenital long QT syndromes.

Renal impairment:
In patients with moderate or severe renal impairment co-administration 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, co-administration of Bilastine and P-glycoprotein inhibitors should be avoided in patients with moderate or severe renal impairment.

Paediatric use:
The safety and efficacy of Bilastine in children under 12 years of age have not been established. Bilastine should not be used in these age groups.

4.5 Drugs interactions
Ketoconazole and erythromycin: Concomitant administration of bilastine and ketoconazole or erythromycin 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 metabolized.
In a randomised, double-blind, placebo- and positive-controlled, 5-way crossover ECG assessment study in 30 healthy adult subjects, bilastine 20 mg/day administered alone for four days was associated with statistically significant positive mean differences from placebo in the QTcF interval at 1 and 3 h post-dosing on day 4, with a maximum mean difference from placebo of 4.0 ms (90% CI 1.20, 6.73) at 1 h, whereas

bilastine 20 mg/day and ketoconazole 400 mg administered concomitantly for four days produced statistically significant QTcF prolongation at all time points from 0.5-12 h, inclusive, on day 4 with a maximum mean difference from placebo of 10.0 ms (90% CI 6.49, 13.43) at 1 h. 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.

Diltiazem : Concomitant administration of Bilastine and diltiazem 60 mg increased Cmax 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.

Lorazepam: Concomitant intake of Bilastine and lorazepam 3 mg for 8 days did not potentiate the depressant CNS effects of lorazepam.

QTc-Prolonging Drugs: The concurrent use of Bilastine with other QTc prolonging drugs is not recommended.

Inhibitors of P-Glycoprotein: Plasma levels of bilastine can be increased by inhibitors of P-glycoprotein; the concomitant use of these drugs with bilastine is not recommended. Drugs that inhibit P-glycoprotein include, but are not limited to certain azole antifungal, macrolide antibiotics, and HIV protease inhibitors.

Drugs that Cause Electrolyte Depletion: The use of Bilastine with drugs that can cause electrolyte imbalance is not recommended.

Drug-Food Interactions: Food significantly reduces the oral bioavailability of bilastine by 30%. Plasma bilastine Cmax, AUC0-t, and AUC0-inf values were approximately 33%, 17%, and 18% lower, respectively, for subjects receiving Bilastine following a high-fat breakfast compared to Bilastine administered under fasted conditions. Plasma bilastine Cmax, AUC0-t, and AUC0-inf values were approximately 25%, 26%, and 25% lower, respectively, for subjects receiving Bilastine following a low-fat breakfast compared to bilastine administered under fasted conditions. The Phase 3 clinical trials were conducted under fasting conditions to ensure clinically appropriate exposure to bilastine.

Grapefruit Juice: Concomitant administration of Bilastine and grapefruit juice decreased bilastine bioavailability by approximately 30%. The degree of bioavailability decrease may vary between producers and types of fruit juice. 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.

4.6 Use in special populations
Paediatric (< 12 years of age)
The safety and efficacy of Bilastine in children under 12 years of age have not been established.

Adolescents (12 years to 17 years of age)
No pharmacokinetic data are available in adolescents (12 years to 17 years).

Geriatric patients
In general, it is recommended that caution should be exercised during the dose selection for an elderly patient, reflecting the greater frequency of decreased hepatic, renal, or cardiac function, and of concomitant disease or other drug therapy.

Gender
No statistically significant gender-related differences have been observed with regard to the pharmacokinetic parameters of bilastine.

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

Renal Insufficiency
In patients with moderate or severe renal impairment co-administration 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, co-administration of bilastine and P-glycoprotein inhibitors should be avoided in patients with moderate or severe renal impairment.

4.7 Effects on ability to drive & 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

Summary of safety profile in adults and adolescent patients.

The incidence of adverse events in patients suffering from allergic rhinoconjunctivitis or chronic idiopathic urticaria treated with 20 mg bilastine in clinical trials was comparable with the incidence in patients receiving placebo (12.7% versus 12.8%). The phase II and III clinical trials performed during the clinical development included 2525 patients treated with different doses of bilastine, of which 1697 received bilastine 20 mg. In these trials 1362 patients received placebo. The ADRs most commonly reported by patients receiving 20 mg bilastine for the indication of allergic rhinoconjunctivitis or chronic idiopathic urticaria were headache, somnolence, dizziness, and fatigue. These adverse events occurred with a comparable frequency in patients receiving placebo.

Tabulated summary of adverse reactions in adult and adolescent patients:

ADRs at least possibly related to bilastine and reported in more than 0.1% of the patients receiving 20 mg bilastine during the clinical development (N = 1697) are tabulated below.

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)

Rare, very rare and reactions with unknown frequency have not been included in the table.

System Organ Class		Bilastine 20 mg N = 1697	All Bilastine Doses N = 2525	Placebo N = 1362
Frequency	Adverse reaction			
Infections and infestations				
Uncommon	Oral herpes	2 (0.12%)	2 (0.08%)	0 (0.0%)
Metabolism and nutrition disorders				
Uncommon	Increased appetite	10 (0.59%)	10 (0.59%)	10 (0.59%)
Psychiatric disorders				
Uncommon	Anxiety	6 (0.35%)	8 (0.32%)	0 (0.0%)
	Insomnia	2 (0.12%)	4 (0.16%)	0 (0.0%)
Nervous system disorders				
Common	Somnolence	52 (3.06%)	82 (3.25%)	39 (2.86%)
	Headache	68 (4.01%)	90 (3.56%)	46 (3.38%)
Uncommon	Dizziness	14 (0.83%)	23 (0.91%)	8 (0.59%)
Ear and labyrinth disorders				
Uncommon	Tinnitus	2 (0.12%)	2 (0.08%)	0 (0.0%)
	Vertigo	3 (0.18%)	3 (0.12%)	0 (0.0%)
Cardiac disorders				
Uncommon	Right bundle branch block	4 (0.24%)	5 (0.20%)	3 (0.22%)
	Sinus arrhythmia	5 (0.30%)	5 (0.20%)	1 (0.07%)
	Electrocardiogram QT prolonged	9 (0.53%)	10 (0.40%)	5 (0.37%)
	Other ECG abnormalities	7 (0.41%)	11 (0.44%)	2 (0.15%)
Respiratory, thoracic and mediastinal disorders				
Uncommon	Dyspnoea	2 (0.12%)	2 (0.08%)	0 (0.0%)
	Nasal discomfort	2 (0.12%)	2 (0.08%)	0 (0.0%)
	Nasal dryness	3 (0.18%)	6 (0.24%)	4 (0.29%)
Gastrointestinal disorders				
Uncommon	Upper abdominal pain	11 (0.65%)	14 (0.55%)	6 (0.44%)
	Abdominal pain	5 (0.30%)	5 (0.20%)	4 (0.29%)
	Nausea	7 (0.41%)	10 (0.40%)	14 (1.03%)
	Stomach discomfort	3 (0.18%)	4 (0.16%)	0 (0.0%)
	Diarrhoea	4 (0.24%)	6 (0.24%)	3 (0.22%)
	Dry mouth	2 (0.12%)	6 (0.24%)	5 (0.37%)
	Dyspepsia	2 (0.12%)	4 (0.16%)	4 (0.29%)
	Gastritis	4 (0.24%)	4 (0.16%)	0 (0.0%)
Skin and subcutaneous tissue disorders				
Uncommon	Pruritus	2 (0.12%)	4 (0.16%)	2 (0.15%)
General disorders and administration site conditions				
Uncommon	Fatigue	14 (0.83%)	19 (0.75%)	18 (1.32%)
	Thirst	3 (0.18%)	4 (0.16%)	1 (0.07%)
	Improved pre existing condition	2 (0.12%)	2 (0.08%)	1 (0.07%)
	Pyrexia	2 (0.12%)	3 (0.12%)	1 (0.07%)
	Asthenia	3 (0.18%)	4 (0.16%)	5 (0.37%)

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

Adverse Drug Reaction Overview
The clinical safety of bilastine was evaluated in 10 Phase 2 and 3 studies performed in 2186 subjects with allergic rhinitis, or chronic spontaneous urticaria (CSU), where bilastine was used at doses ranging from 10– 40 mg over treatment periods of 2 – 4 weeks.
The most common treatment-emergent adverse reactions reported in the double-blind Phase 3 studies involving 931 subjects treated with bilastine 20 mg were related to the central nervous system **(headache, dizziness and somnolence) and the gastrointestinal system (abdominal pain upper).**

4.9 Overdose
Information regarding acute overdose of bilastine is retrieved from the experience of 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 healthy volunteer 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. 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 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 Pharmacodynamics
Studies in adult healthy subjects showed that bilastine inhibited the skin wheal and flare reactions induced with a histamine prick test for 24 hours, as well as the wheal and flare reactions in cold induced urticaria.
In an environmental chamber study, the onset of action of bilastine was demonstrated to be 1 hour after treatment administration and the effect lasted for 26 hours.
Bilastine at doses of up to 40 mg once daily did not affect psychomotor performance in clinical trials and did not affect driving performance in a standard driving test.

5.3 Pharmacokinetics
Absorption
Bilastine is rapidly absorbed after oral administration with a time to maximum plasma concentration of around 1.13 hours. No accumulation was observed in subjects treated with bilastine from 20 to 100 mg daily after 14 days. The absolute bioavailability of bilastine 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: MRP2, BCRP, BSEP, OATP1B3, OATP2B1, OAT1, OAT3, OCT2 and NTCP. Mild inhibition was detected for P-gp, OATP2B1 and OCT1, with an estimated IC50 ≥300 μM, much higher than the calculated clinical plasma Cmax. 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 is not significantly metabolized in humans (see Excretion). Bilastine does not induce or inhibit activity of CYP450 isoenzymes in in vitro and in vivo studies. Studies examining hepatic tissues (microsomes and hepatocytes) of human origin using different doses of bilastine demonstrated that there was little to no interaction with CYP isoenzymes.

Excretion
In a mass balance study performed in healthy 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. The mean

elimination half-life calculated in healthy volunteers in the population pharmacokinetic model was 14.5 h.

6. Non-clinical 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 antihistamine medication which is used in the treatment of allergic rhinoconjunctivitis and urticaria (hives). Bilastine is known chemically as 2-[4-(2-{4-[1-(2-ethoxyethyl)-1h-benzimidazol-2-yl] piperidin-1-yl} ethyl) phenyl]-2-methylpropanoic acid;2-[4-[2-[4-[1-(2-ethoxyethyl) benzimidazol-2-yl] piperidin-1-yl] ethyl] phenyl]-2-methylpropanoic acid. Its empirical formula is C28H37N3O3 and the molecular weight is 463.61168 g/mol.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf life

Refer pack

8.3 Packaging information

8.3 Packaging information
Each box contains 10x10 tablets in Alu-Alu blister pack.

8.4 Storage & handling instruction

Store below 30°C & Protect from light & moisture.

9. Patient counselling information

What is Bilastine 40 mg Tablet and what it is used for?
Bilastine 40 mg Tablet is an antihistamine. Bilastine is used for the treatment of Chronic Spontaneous Urticaria.

What you need to know before you take Bilastine 40 mg tablets?
Do not take Bilastine 40 mg Tablet:
If you have allergy to drug Bilastine or any of the other ingredients of this medicine.

Please discuss with your doctor if you are taking any of the following medicines before starting Bilastine Tablet:
- Ketoconazole
- Erythromycin
- Diltiazem
- Cyclosporine
- Ritonavir
- Rifampicin

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.

Bilastine 40 mg Tablet 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.

What are the possible side effects?
Like all medicines, this medicine can cause side effects, although not everybody gets them. Look undesirable effects section for possible side effects.

10. Manufactured by:
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
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12. Marketed by:
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4, Ground Floor, Print World Industrial,
Complex, Mankoli Village Road, Vehele,
Bhiwandi, Thane-421302.

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