For the use only of Registered Medical Practitioner

1. **Generic Name & Brand Name**
   Dextromethorphan Hydrobromide, Bilastine and Phenylephrine Hydrochloride Syrup
   Deletus® BL

2. **Qualitative and Quantitative Composition:**
   Each 5 ml contains:
   Dextromethorphan Hydrobromide I.P…...10 mg
   Bilastine I.P……...3.3 mg
   Phenylephrine Hydrochloride I.P……5 mg
   Flavoured Base……...q.s.
   Colour: Caramel USP-NF

3. **Dosage Form & strength**
   Refer section 1 & 2

4. **Clinical particulars**

4.1 Therapeutic indication

For relief of coughs and upper respiratory symptoms, including nasal congestion, associated with allergy or the common cold.

4.2 Posology and method of administration

Posology :

Pediatric - Children 6 to 11 years of age with a body weight of at least 20 kg – **5ml thrice daily for not more than 7 days.**

Adults and adolescents (over 12 years of age) - **10ml thrice daily.**

Method of administration: For oral administration only.

Method of Administration:

4.3 Contraindications

It is contraindicated in patients with known hypersensitivity or idiosyncrasy to any of its ingredients or to any other component of this product.
Dextromethorphan is contraindicated in the following patients:
- Dextromethorphan should not be given to subjects in, or at risk of developing respiratory failure.
- Should not be taken by patients with liver disease.
- Patients taking monoamine oxidase inhibitors (MAOIs) or within 14 days of stopping such treatment.
- Patients taking selective serotonin reuptake inhibitors (SSRI's).
- Not to be used in children under the age of 6 years.

Phenylephrine is contraindicated in the followings: Avoid in patients with cardiovascular disease, high blood pressure, diabetes mellitus, closed angle glaucoma, hyperthyroidism, prostatic

enlargement and phaeochromocytoma. Patients being treated with monoamine oxidase inhibitors or within 14 days of ceasing such treatment.

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.

Dextromethorphan

Patients suffering from chronic cough as occurs with smoking, asthma or patients suffering from an acute asthma attack, or where cough is accompanied by excessive secretions should be advised to consult a Healthcare Professional before use.

Causes of chronic cough should be excluded if symptoms are persistent. Any accompanying symptoms should be actively sought and appropriately investigated/ treated. Stop use and ask your healthcare professional if your cough lasts more than 7 days, comes back or is accompanied by a fever, rash or persistent headache. These could be signs of serious conditions.

Dextromethorphan should be used with caution in atopic children due to histamine release.

Use of dextromethorphan with alcohol or other CNS depressants may increase the effects on the CNS and cause toxicity in relatively smaller doses.

Do not take with any other cough and cold medicine.

<u>Drug dependence, tolerance and potential for abuse</u>

For all patients, prolonged use of this product may lead to drug dependence (addiction), even at therapeutic doses. The risks are increased in individuals with current or past history of substance misuse disorder (including alcohol misuse) or mental health disorder (e.g., major depression). Caution is particularly recommended for adolescents and young adults as well as in patients with a history of drug abuse or psychoactive substances.

<u>Drug withdrawal syndrome</u>

The drug withdrawal syndrome is characterised by some or all of the following: restlessness, lacrimation, rhinorrhoea, yawning, perspiration, chills, myalgia, mydriasis and palpitations. Other symptoms may also develop including irritability, agitation, anxiety, hyperkinesia, tremor, weakness, insomnia, anorexia, abdominal cramps, nausea, vomiting, diarrhoea, increased blood pressure, increased respiratory rate or heart rate.

Dextromethorphan is metabolised by hepatic cytochrome P450 2D6. The activity of this enzyme is genetically determined. About 10% of the general population are poor metabolisers of CYP2D6. Poor metabolisers and patients with concomitant use of CYP2D6 inhibitors may experience exaggerated and/or prolonged effects of dextromethorphan. Caution should therefore be exercised in patients who are slow metabolizers of CYP2D6 or use CYP2D6 inhibitors.

Serotonin Syndrome

Serotonergic effects, including the development of a potentially life-threatening serotonin syndrome, have been reported for dextromethorphan with concomitant administration of serotonergic agents, such as selective serotonin re-uptake inhibitors (SSRIs), drugs which impair metabolism of serotonin (including monoamine oxidase inhibitors (MAOIs)) and CYP2D6 inhibitors.

Serotonin syndrome may include mental-status changes, autonomic instability, neuromuscular abnormalities, and/or gastrointestinal symptoms. If serotonin syndrome is suspected, treatment with dextromethorphan should be discontinued.

Paediatric population

Serious adverse events may occur in children in case of overdose including neurological disorders. Caregivers should be advised not to exceed the recommended dose.

Phenylephrine

Exacerbation of Angina, Heart Failure, or Pulmonary Arterial Hypertension

Because of its pressor effects, phenylephrine hydrochloride can precipitate angina in patients with severe arteriosclerosis or history of angina, exacerbate underlying heart failure, and increase pulmonary arterial pressure.

Bradycardia

Phenylephrine hydrochloride can cause severe bradycardia and decreased cardiac output.

Risk in Patients with Autonomic Dysfunction

The pressor response to adrenergic drugs, including phenylephrine, can be increased in patients with autonomic dysfunction, as may occur with spinal cord injuries.

Skin and Subcutaneous Necrosis

Extravasation of phenylephrine can cause necrosis or sloughing of tissue.

Pressor Effect with Concomitant Oxytocic Drugs

Oxytocic drugs potentiate the pressor effect of sympathomimetic pressor amines including phenylephrine hydrochloride, with the potential for hemorrhagic stroke.

Allergic Reactions

This product contains sodium metabisulfite, a sulfite that may cause allergic-type reactions, including anaphylactic symptoms and life-threatening or less severe asthmatic episodes in certain susceptible people.

The overall prevalence of sulfite sensitivity in the general population is unknown and probably low. Sulfite sensitivity is seen more frequently in asthmatic than in nonasthmatic people.

Peripheral and Visceral Ischemia

Phenylephrine hydrochloride can cause excessive peripheral and visceral vasoconstriction and ischemia to vital organs, particularly in patients with extensive peripheral vascular disease.

Renal Toxicity

Phenylephrine hydrochloride can increase the need for renal replacement therapy in patients with septic shock. Monitor renal function.

Phenylephrine should be used with care in patients with cardiovascular disease, diabetes mellitus, closed angle glaucoma, prostatic enlargement and hypertension.

This medicine should be used with caution in patients with occlusive vascular disease including Raynaud's phenomenon. Do not take for longer than 7 days, unless your doctor agrees. If symptoms do not go away; consult with your doctor. Keep all medicines out of the reach of children.

Patients with rare hereditary problems of galactose intolerance, Lapp lactase deficiency or glucose-galactose malabsorption should not take this medicine.

Great care should be exercised in administering Phenylephrine Injection to patients with pre-existing cardiovascular disease such as ischaemic heart disease, arrhythmias, and occlusive vascular disease including arteriosclerosis, hypertension or aneurysms. Anginal pain may be precipitated in patients with angina pectoris.

Care is also required when given to patients with diabetes mellitus, or closed angle glaucoma.

Information for Patients:

Avoid alcohol and other CNS depressants while taking this product. Patients sensitive to antihistamines may experience moderate to severe drowsiness. Patients sensitive to sympathomimetic amines may notice mild CNS stimulation. Antihistamines may impair mental and physical abilities required for the performance of potentially hazardous tasks such as driving a vehicle or operating machinery. Patients should be warned accordingly.

Warning: Do not exceed the stated dose.

Keep all medicines out of the sight and reach of children.

Not to be given in children below 12 years of age for not more than 7 days.

4.5 Drug Interactions

Interaction studies have only been performed in adults and are summarized 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. 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 metabolized. 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, 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.

Pediatric 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 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.

Dextromethorphan

Not to be used in patients taking monoamine oxidase inhibitors or within 14 days of stopping treatment as there is a risk of serotonin syndrome (pyrexia, hypertension, arrhythmias) when MAOIs are taken in combination with dextromethorphan. (Severe and sometimes fatal reactions have been reported following administration of dextromethorphan to patients receiving MAOIs).

Dextromethorphan might exhibit additive CNS depressant effects when co-administered with alcohol, antihistamines, psychotropics, and other CNS depressant drugs.

CYP2D6 inhibitors

Dextromethorphan is metabolized by CYP2D6 and has an extensive first-pass metabolism. Concomitant use of potent CYP2D6 enzyme inhibitors can increase the dextromethorphan concentrations in the body to levels multifold higher than normal. This increases the patient's risk for toxic effects of dextromethorphan (agitation, confusion, tremor, insomnia, diarrhea and respiratory depression) and development of serotonin syndrome. Potent CYP2D6 enzyme inhibitors include fluoxetine, paroxetine, quinidine and terbinafine. In concomitant use with quinidine, plasma concentrations of dextromethorphan have increased up to 20-fold, which has increased the CNS adverse effects of the agent. Amiodarone, flecainide and propafenone, sertraline, bupropion, methadone, cinacalcet, haloperidol, perphenazine and thioridazine also have similar effects on the metabolism of dextromethorphan. If concomitant use of CYP2D6 inhibitors and dextromethorphan is necessary, the patient should be monitored and the dextromethorphan dose may need to be reduced.

Phenylephrine

It should not be given to patients being treated with monoamine oxidase inhibitors or within 14 days of stopping such treatment. It may enhance the effects of anticholinergic drugs such as tricyclic antidepressants. It may increase the possibility of arrhythmias in digitalized patients. It may enhance the cardiovascular effects of other sympathomimetic amines (e.g. decongestants).

This medicine should not be taken together with vasodilators, Beta-blockers or enzyme inducers such as alcohol.

Phenylephrine should be used with caution in combination with the following drugs as interactions have been reported:

Monoamine oxidase inhibitors (including moclobemide)	Hypertensive interactions occur between sympathomimetic amines such as phenylephrine and monoamine oxidase inhibitors (see contraindications).
Sympathomimetic amines	Concomitant use of phenylephrine with other sympathomimetic amines can increase the risk of cardiovascular side effects.
Beta-blockers and other antihypertensives (including debrisoquine, guanethidine, reserpine, methyldopa)	Phenylephrine may reduce the efficacy of beta-blocking drugs and antihypertensive drugs. The risk of hypertension and other cardiovascular side effects may be increased.
Tricyclic antidepressants (e.g. amitriptyline)	May increase the risk of cardiovascular side effects with phenylephrine.
Ergot alkaloids (ergotamine and methylsergide)	Increased risk of ergotism

Digoxin and cardiac glycosides	Increase the risk of irregular heartbeat or heart attack

Phenylephrine may interact with cyclopropane and halothane and other halogenated inhalational anaesthetics, to induce ventricular fibrillation. An increased risk of arrhythmias may also occur if phenylephrine injection is given to patients receiving cardiac glycosides, quinidine or tricyclic antidepressants.

Phenylephrine is a hypertensive agent and may consequently reverse the action of many antihypertensive drugs. Interactions of phenylephrine with alpha and beta receptor blocking drugs may be complex.

Drugs which have an effect on α1 adrenoceptors could potentiate (such as clonidine) or inhibit (such as doxazosin) the vasopressive action of phenylephrine.

Caution should be applied when administering atomoxetine concurrently, as there is potential for synergistic pharmacological effects.

Severe hypertension may occur following the use of phenylephrine and atropine or other antimuscarinics.

The pressor effects of phenylephrine may be slightly reduced by lithium carbonate.

The effects of phenylephrine may be potentiated by the use of monoamine oxidase inhibitors or reversible inhibitors of monoamine oxidase.

Interactions that Augment Pressor Effect

The increasing blood pressure effect of phenylephrine hydrochloride is increased in patients receiving: Monoamine oxidase inhibitors (MAOI), oxytocin and oxytocic drugs, tricyclic antidepressants, angiotensin, aldosterone, atropine, steroids, such as hydrocortisone, norepinephrine transporter inhibitors, such as atomoxetine, and ergot alkaloids, such as methylergonovine maleate.

Interactions that Antagonize the Pressor Effect

The increasing blood pressure effect of phenylephrine is decreased in patients receiving: α-adrenergic antagonists, phosphodiesterase type 5 inhibitors, mixed α- and β-receptor antagonists, calcium channel blockers, such as nifedipine, benzodiazepines, ace inhibitors, and centrally acting sympatholytic agents, such as reserpine, guanfacine.

4.6 Use in special populations (Pregnancy, Nursing woman, Pediatric use, Geriatric use)

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.

No animal studies or suitable, well-controlled human studies have been carried out. Several reports and literature references have concluded that dextromethorphan does not appear to incur any significant risk to the foetus, however, the use of this medicinal product is only accepted in the absence of safer therapeutic alternatives.

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.

It is unknown whether this medicinal product is excreted in human milk. A risk to the newborns/infants cannot be excluded. Therefore, as with all medicinal products, its use is not recommended during lactation.

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 bilastine did not affect 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

Dextromethorphan can impair cognitive function and can affect a patient's ability to drive safely.

Phenylephrine: No adverse effects known.

Thus, patients should be advised not to drive or operate machinery if affected by dizziness.

4.7 Undesirable effects

Bilastine

Summary of safety profile in paediatric population

During the clinical development the frequency, type and severity of adverse reactions in adolescents (12 years to 17 years) were the same as observed in adults. The information collected in this population (adolescents) during post-marketing surveillance has confirmed clinical trial findings. The percentage of children (2-11 years) which reported adverse events (AEs) after treatment with bilastine 10 mg for allergic rhinoconjunctivitis or chronic idiopathic urticaria in a 12-week controlled clinical trial was comparable with the percentage in the group receiving placebo (68.5% versus 67.5%). The related AEs most commonly reported by 291 children (2-11 years) receiving bilastine 10 mg (orodispersible tablet formulation) during clinical trials (#260 children exposed in the clinical safety study, 31 children exposed in the pharmacokinetic study) were headache, allergic conjunctivitis, rhinitis and abdominal pain. These related adverse events occurred with a comparable frequency in 249 patients receiving placebo.

Tabulated summary of adverse reactions in paedriatic population AEs at least possibly related to bilastine and reported in more than 0.1% of children (2-11 years) receiving bilastine during the clinical development 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 **Frequency**	**Adverse reaction**	**Bilastine 10 mg (n=291) #**	**Placebo (n=249)**
Infections and infestations			
Common	Rhinitis	3 (1.0 %)	3 (1.2 %)
Nervous system disorders			
Common	Headache	6 (2.1 %)	3 (1.2 %)
Uncommon	Dizziness	1 (0.3 %)	0 (0.0 %)
	Loss of consciousness	1 (0.3 %)	0 (0.0 %)
Eye disorders			
Common	Allergic conjunctivitis	4 (1.4 %)	5 (2.0 %)
Uncommon	Eye irritation	1 (0.3 %)	0 (0.0 %)
Gastrointestinal disorders			
Common	Abdominal pain / Upper abdominal pain	3 (1.0 %)	3 (1.2 %)
Uncommon	Diarrhoea	2 (0.7 %)	0 (0.0 %)
	Nausea	1 (0.3 %)	0 (0.0 %)
	Lip swelling	1 (0.3 %)	0 (0.0 %)
Skin and subcutaneous tissue disorders			
Uncommon	Eczema	1 (0.3 %)	0 (0.0 %)
	Urticaria	2 (0.7 %)	2 (0.8 %)
General disorders and administration site conditions			
Uncommon	Fatigue	2 (0.7 %)	0 (0.0 %)

#260 children exposed in the clinical safety study, 31 children exposed in the pharmacokinetic study

Description of selected adverse reactions in paediatric population

Headache, abdominal pain, allergic conjunctivitis and rhinitis were observed either in children treated with bilastine 10 mg or with placebo. The frequency reported was 2.1% vs. 1.2% for headache; 1.0% vs. 1.2% for abdominal pain; 1.4% vs. 2.0% for allergic conjunctivitis, and 1.0% vs. 1.2% for rhinitis.

Dextromethorphan

The following side effects may be associated with the use of dextromethorphan; occasional drowsiness, dizziness, excitation, mental confusion, convulsions, respiratory depression, vomiting, gastrointestinal disturbances (nausea and diarrhoea) and skin reactions including rash.

Adverse effects are rare; however the following side effects may be associated with dextromethorphan hydrobromide:

Gastrointestinal Disorders: Rare: Gastrointestinal upset.

Nervous System Disorders: Rare: Dizziness, drowsiness, mental confusion.

Immune System Disorders: Hypersensitivity.

Psychiatric disorders: Frequency unknown: Drug dependence.

General disorders and administration site conditions: Frequency unknown: drug withdrawal syndrome.

Phenylephrine

Sympathomimetic amines may cause convulsions, CNS stimulation, cardiac arrhythmia, respiratory difficulties, increased heart rate or blood pressure, hallucinations, tremors, nervousness, insomnia, pallor and dysuria.

The following adverse reactions associated with the use of phenylephrine hydrochloride were identified in the literature. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to estimate their frequency reliably or to establish a causal relationship to drug exposure.

Cardiac disorders: Bradycardia, AV block, ventricular extrasystoles, myocardial ischemia.

Gastrointestinal disorders: Nausea, vomiting.

General disorders and administrative site conditions: Chest pain, extravasation.

Immune system disorders: Sulfite sensitivity.

Nervous system disorders: Headache, nervousness, paresthesia, tremor.

Psychiatric disorders: Excitability.

Respiratory: Pulmonary edema, rales.

Skin and subcutaneous tissue disorders: Diaphoresis, pallor, piloerection, skin blanching, skin necrosis with extravasation.

Vascular disorders: Hypertensive crisis.

The following adverse events have been observed in clinical trials with phenylephrine and may therefore represent the most commonly occurring adverse events.

Psychiatric disorders: Nervousness, irritability, restlessness, and excitability.

Nervous system disorders: Headache, dizziness, insomnia, cerebral haemorrhage, paraesthesia.

Cardiac disorders: Increased blood pressure.

Gastrointestinal disorders: Nausea, diarrhoea. Not known: Vomiting, salivary hypersecretion.

Adverse reactions identified during post-marketing use are listed below. The frequency of these reactions is unknown but likely to be rare.

Eye disorders: Not known: Mydriasis, acute angle closure glaucoma. The most likely to occur in those with closed angle glaucoma.

Cardiac disorders: Not known: Pulmonary oedema, bradycardia, tachycardia, arrhythmia, angina pectoris, palpitations, cardiac arrest.

Vascular disorders: Not known: Hypotension, dizziness, syncope, flushing.

Respiratory, thoracic and mediastinal disorders: Not known: Dyspnoea.

Skin and subcutaneous disorders: Allergic reactions (e.g. rash, urticaria, allergic dermatitis). Hypersensitivity reactions – including that cross-sensitivity may occur with other sympathomimetics.

Renal and urinary disorders: Not known: Dysuria, urinary retention. This is most likely to occur in those with bladder outlet obstruction, such as prostatic hypertrophy.

Immune system disorders: Not known: Hypersensitivity, Metabolism and nutrition disorders, and metabolic disorders.

General disorders and administration site conditions (for injection): Not known: Extravasation, infusion site necrosis, hyperhidrosis.

Investigations: Not known: Increased blood pressure, abnormal blood glucose.

Phenylephrine is without significant stimulating effects on the central nervous system at usual doses.

Adverse effects may include tachycardia, cardiac arrhythmias, palpitations, hypertension, nausea, vomiting, headache and occasionally urinary retention in males.

4.8 Overdose

Bilastine

There are no data for overdose in children. Information regarding acute overdose of bilastine is retrieved from the experience of clinical trials conducted during the development in adults 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 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. No

serious adverse events and no significant prolongation in the QTc interval were reported. The information collected in the postmarketing surveillance is consistent with that reported in clinical trials. Critical evaluation of bilastine's multiple dose (100 mg x4 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.

Dextromethorphan
Symptoms and signs: Dextromethorphan overdose may be associated with nausea, vomiting, dystonia, agitation, confusion, somnolence, stupor, nystagmus, cardiotoxicity (tachycardia, abnormal ECG including QTc prolongation), ataxia, toxic psychosis with visual hallucinations, hyperexcitability. In the event of massive overdose the following symptoms may be observed: coma, respiratory depression, convulsions.
Management: Activated charcoal can be administered to asymptomatic patients who have ingested overdoses of dextromethorphan within the preceding hour. For patients who have ingested dextromethorphan and are sedated or comatose, naloxone, in the usual doses for treatment of opioid overdose, can be considered. Benzodiazepines for seizures and benzodiazepines and external cooling measures for hyperthermia from serotonin syndrome can be used.

Phenylephrine
Symptoms of overdosage include irritability, restlessness, palpitations, hypertension, and difficulty in micturition, nausea, vomiting, thirst and convulsions. In severe overdosage gastric lavage and aspiration should be performed. Symptomatic and supportive measures should be undertaken, particularly with regard to cardiovascular and respiratory systems. Convulsions should be controlled with intravenous diazepam. Chlorpromazine may be used to control marked excitement and hallucinations. Severe hypertension may need to be treated with an alpha-adrenoreceptor blocking drug, such as phentolamine. A beta blocker may be required to control cardiac arrhythmias.

5. Pharmacological properties

5.1 Mechanism of action

Mechanism of action

Bilastine

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.

Clinical efficacy The efficacy of bilastine has been studied in adults and adolescents. According to guidelines, the proved efficacy in adults and adolescents can be extrapolated to children, having demonstrated that the systemic exposure with 10 mg bilastine in children from 6 to 11 years with a body weight of at least 20 kg is equivalent to the exposure in adults with 20 mg bilastine. The extrapolation from adult and adolescent data is deemed appropriate for this product as the pathophysiology of allergic rhinoconjunctivitis and urticaria is the same for all age groups.

Dextromethorphan

Dextromethorphan is a non-opioid, antitussive drug. It exerts its antitussive activity by acting on the cough centre in the medulla oblongata, raising the threshold for the cough reflex. A single oral dose of 10-20 mg dextromethorphan produces its antitussive action within 1 hour and lasts for at least 4 hours. It has no analgesic properties and little sedative activity.

Phenylephrine

Phenylephrine hydrochloride is a sympathomimetic agent with mainly direct effects on adrenergic receptors. It has predominantly alpha adrenergic activity and is without stimulating effects on the central nervous system. The sympathomimetic effect of phenylephrine produces vasoconstriction which in turn relieves nasal congestion.

5.2 Pharmacodynamic Properties

Bilastine

Pharmacotherapeutic group: Antihistamines for systemic use; Other antihistamines for systemic use. ATC code: R06AX29.

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5.3 Pharmacokinetic properties

Bilastine

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 Pgp and OATP. 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.

Dextromethorphan

Dextromethorphan hydrobromide is well absorbed from the gastrointestinal tract. Dextromethorphan undergoes rapid and extensive first-pass metabolism in the liver after oral administration. Genetically controlled O-demethylation (CYD2D6) is the main determinant of dextromethorphan pharmacokinetics in human volunteers. It appears that there are distinct phenotypes for this oxidation process resulting in highly variable pharmacokinetics between subjects. Unmetabolised dextromethorphan, together with the three demethylated morphinan metabolites dextrorphan (also known as 3-hydroxy-N-methylmorphinan), 3- hydroxymorphinan and 3-methoxymorphinan have been identified as conjugated products in the urine. Dextrorphan, which also has antitussive action, is the main metabolite. In some individuals metabolism proceeds more slowly and unchanged dextromethorphan predominates in the blood and urine.

Phenylephrine

Phenylephrine is readily absorbed after oral administration but is subject to extensive presystemic metabolism, much of which occurs in the enterocytes. As a consequence, systemic bioavailability is only about 40%. Following oral administration, peak plasma concentrations are achieved in 1-2 hours. The mean plasma half-life is in the range 2-3 hours. Penetration into the brain appears to be minimal. Following absorption, the drug is extensively metabolised in the liver. Both phenylephrine and its metabolites are excreted in the urine. The volume of distribution is between 200 and 500 litres, but there are no data on the extent of plasma protein binding.

6. Nonclinical properties

Bilastine

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.

Dextromethorphan

Acute oral toxicity studies conducted with Dextromethorphan report the following LD50 values (mg/kg): mouse, 210 and rat, 116. Acute subcutaneous toxicity with Dextromethorphan reports the LD50 value (mg/kg): mouse, 112. Acute intravenous toxicity with Dextromethorphan reports the LD50 value (mg/kg): rat, 16.3. Repeat dose toxicity studies conducted in rats for 13 weeks duration at doses up to 100 mg/kg and 27 weeks at 10 mg/kg, and of 14 weeks in dogs by oral gavage at doses up to 4 mg/kg on five days per week. The only effect recorded was of reduced body weight gain in the rat 13-week study at the highest dose.

Phenylephrine

Phenylephrine has been used to induce cardiac myocyte hypertrophy in cultures of rat neonatal mycocytes at doses of 100 μM and 10 μM. To the best of our knowledge there have been no human studies associating therapeutic phenylephrine use with the development of cardiac myocyte hypertrophy.

7. Description

Deletus BL is supplied for oral administration.
Each 5 ml of Deletus BL contains Dextromethorphan Hydrobromide 10 mg, Bilastine 3.3 mg & Phenylephrine Hydrochloride 5 mg.

8. Pharmaceutical particulars

8.1 Incompatibilities

Not applicable

8.2 Shelf Life

Refer pack

8.3 Packaging Information

Refer pack

8.4 Storage condition & handling instructions

Refer pack

9. Patient Counseling Information

Read this entire leaflet carefully before you start taking this medicine because it contains important information for you.

• 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 only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.

• If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet.

10. Details of manufacturer
Refer pack for manufacturer details.

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12. Date of revision
Version 2.0, dated 31/01/2025

For Product Complaints/Adverse events or Queries please write to
webmasterindia@abbott.com