PACKAGE INSERT
Ubretid® 5 mg tablets

Composition
Each tablet UBRETID® 5 mg contains 5 mg distigmine bromide

Properties and efficacy
UBRETID® increases the activity of the musculature of the gastrointestinal tract and the tonicity of the urinary bladder, the sphincteric tonicity, the tonicity of the ureter and of the skeletal muscles.

Clinical application
The use of the drug in therapy is based on both its parasympathomimetic as well as its muscle tone increasing effect on the skeletal muscle.

Indications
Functional insufficiency of the vesical sphincteral apparatus
Hypotonia of the urinary bladder
Chronic hypotonic constipation and megacolon
In various neurological indications (peripheral paralyses of the striated muscles, myasthenia gravis pseudoparalytica) a functional improvement can be obtained.

General instruction for dosage
Method of administration
For oral administration with some fluid in the morning on empty stomach about half an hour before breakfast.

Duration of use
Duration of treatment will depend on the course of the disease and will be determined by the physician. Ubretid 5mg tablets are principally suitable for long-term treatment.

When using UBRETID®, its slow onset of action and its long duration of action as well as the individual response of the patient should be considered. The dosage level has to be individualized for each patient, dependent upon the patient´s weight, clinical status, response to therapy, and the drug´s long duration of action.

Posology

As a rule, the initial oral dose is usually one UBRETID® 5 mg tablet taken daily in the morning, half an hour before breakfast on an empty stomach. If however, due to preceding or simultaneous food intake a dose of UBRETID® does not take effect, this should by no means be compensated by repeating the medication within a few hours as this might lead to an uncontrolled accumulation. The long duration of effects of UBRETID® might allow dosage interval of 2 to 3 days.

The strong and prolong effects of UBRETID® have to be taken into account with special caution in the treatment of vagotonic patient in particular his/her autonomic nervous system.

Indication-related instructions:

Functional Insufficiency of the vesicosphincteral system
Oral therapy will be sufficient; it is recommended that UBRETID® 5 mg (one tablet), be given daily at the commencement of treatment until an improvement is observed. Usually the effect can be maintained by administering one to two tablets every other or third day. The tablets should always be taken in the morning on an empty stomach, half an hour before breakfast.

Chronic hypotonic constipation, megacolon
UBRETID® is particularly suitable for the treatment of megacolon and of the hypokinetic form of habitual constipation especially for breaking the habit of taking laxatives.
The individual optimal dosage is usually arrived at by gradually increasing the dosage, Oral therapy is continued until normal intestinal function has been restored (10 to 14 days).
Intial dose: half a tablet daily half an hour before breakfast and increasing this dosage by half a tablet (maximum two tablets daily) every third day. Close observation is required owing to the danger of overdosage leading to cumulation.

Peripheral paralysis, particularly after poliomyelitis and diphtheria, posttraumatic paralysis; bulbar paralysis, amyotrophic lateral sclerosis
After testing the individual response to short acting anticholinesteterases, UBRETID®, three tablets, should be given every day. The relief from fatigue will set in after some hours and then will last for one day and a half to two days.

Myasthenia gravis pseudoparalytica
In mild and moderately severe cases the oral treatment will be sufficient. During the first week one tablet (5 mg) should be taken daily on empty stomach taken in the morning about half an hour before breakfast is recommended. During the second week the daily doses should be increased to one and a half tablets (7.5 mg) and to two tablets (10 mg) during the third week. Dosage is individualized depending on the severity of the condition, the degree and duration of response and the side effects encountered.

Dosing instructions for special patient populations:
For patients with impaired hepatic function no dosage adjustment is required.
No dosing recommendations can be given for patients with impaired renal function as no studies are available.
For elderly patients (>65 years) dosage should be reduced.
The safety of UBRETID® has not been established in children.

Contraindications
UBRETID® must not be used in:
Hypersensitivity to the active substance or to any of the excipients as well as bromine allergy, severe vagotonia (dominance of the parasympathetic part of the autonomic- vegetavitive-nervous system) accompanied by low blood pressure, slow heart rate, hyperacidity, hyperperistalsis of intestine and stomach, increased salivation, perpheral circulatory disturbances, mechanical obstruction to urinary outflow, obstructive ileus, stenosis or spasms in the intestinal tract, in the biliary ducts and urinary passages, gastric ulcers, enteritis; very low blood pressure, increased muscular tone, muscular spasm (tetany), falling sickness (epilepsy), shaking palsy (Parkinson‘s disease), postoperative shock and circulatory crises; non-treated cardiac insufficiency, cardiac infarction, congestive heart failure, recent

myocardial infarction, cardiac arrhythmias, in particular bradycardia and AV block, bronchial asthma, Iritis, myotonia, and thyrotoxicosis.

Special warnings and precautions for use

- Peptic ulcers
- Duodenal ulcers
- Epilepsy
- Cardiac dysfunction (arrhythmias, bradycardia, myocardial ischemia)
- Hypotension
- Hyperthyroidism
- Parkinsonism
- Recent intestinal and bladder surgery
- Enteritis
- Tetany

This medicine contains lactose. Patients with rare hereditary galactose intolerance, Lapp-Lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Caution is advised in situations in which potentiation of the effects of acetylcholine is undesirable, e.g. with cardiac dysfunction

Before starting treatment of disorders of neurogenic bladder emptying intravesical obstruction must have been excluded.

In the course of treatment excessive increase of intravesical pressure must be avoided and protection of the upper urinary tract must be ensured.

For any concomitant use of UBRETID® together with atropine sulfate (suppression of the muscarine-type adverse effects) it should be considered that atropine may mask the initial signs of overdose.

Patients with rare hereditary problems of galactose intolerance, lactase deficiency or glucose-galactose malabsorption should not take UBRETID® Tablets.

Interactions

UBRETID® and a few other drugs may interact with each other. Anticholinergics like atropine substances and agents with atropine-type effects influencing psychic states (psychopharmaceuticals), drugs such as tricyclic and tetracyclic antidepressants, as well as neuroleptics, lithium and antihistamines, for the treatment of hypersensitivity reactions (allergies) and certain (curare-like) muscle relaxants (discontinuation before surgery) substances causing muscular atony cancel the effect of UBRETID®.

The effects of depolarizing muscle relaxants (e.g. succinylcholine, suxamethonium or decamethonium), particularly in their initial phase of action may be prolonged by UBRETID® and should therefore not be used concomitantly, while the nicotine-type effects are mostly unaffected.

A few aminoglycoside antibiotics (neomycin, streptomycin, kanamycin) increase the disturbance of neuromuscular conduction in patients with myasthenia have a minor blocking effect on muscles and nerves and thus decrease the effect of UBRETID®. Therefore, increase of dosage may be required.

Patients pre-treated with beta-blockers may develop persistent bradycardia and increased hypotension.

Use with caution in patients receiving concomitantly drugs acting on the cardiovascular system, e.g. beta blockers, drugs with local anaesthetic properties and muscle relaxants. Antiarrhythmics like quinidine, procainamide, propafenone, or beta-blockers reduce the effect of UBRETID® due to their parasympatholytic potency.

In myasthenia gravis, where short acting cholinergic drugs are taken concurrently, their dosage should be reduced to the minimum required to control symptoms.

Glucocorticoids may reduce the effect of UBRETID®. This may require an increased dose of UBRETID® especially for myasthenia gravis, but it may also be associated with an increased risk of a cholinergic crisis.

As esterase inhibitors, also contained in many insecticides, and cholinergics will mutually potentiate their effects, the possibility of this interaction should be considered in exposed patients.

Concomitant use of UBRETID® with other direct or indirect parasympathomimetics may lead to a cholinergic crisis in patients with myasthenia gravis.

The muscarine-like side-effects to overdosage can be promptly overcome by atropine (1 mg atropine sulfate orally, subcutaneously, possibly also intravenously). Owing to the prolonged UBRETID® effect the administration of atropine must be repeated several times, if necessary. Concomitant use of UBRETID® and dipyrimadole reduces the therapeutic effect of UBRETID®.

In case of extreme overdosage and the resulting cholinergic crisis it is mandatory that the patient be admitted to the intensive care unit for stationary anaesthic treatment.

Fertility, pregnancy and lactation

No adequate experience is available on the use of UBRETID® during pregnancy. UBRETID® should be avoided during pregnancy, especially during the first trimester, unless the benefit outweighs risk of treatment. For any critical and compelling indication careful risk/benefit evaluation must be undertaken for short term use.

Newborns from females having been treated with distigmine bromide for myasthenia gravis may show a transient muscle weakness. This neonatal myasthenia appears to derive from the transplacental passage from anti-acetycholine-receptors of the immunoglobulin G antibodies.

No information is available on lactation. It has not been established whether the active substance of UBRETID® is excreted in breast milk. Therefore use of this product in lactating women is not recommended. If treatment with UBRETID® is judged to be essential, breastfeeding must be discontinued during the treatment.

Effects on ability to drive and use machines

UBRETID® may impair the mental alertness required for driving a car and operating machinery.

The patient should be supervised in the early stages of dosage titration to guard against the possibility of myasthenic crisis or cholinergic crisis.

In some cases UBRETID® may impair visual function as a result of miosis and accommodation disturbances and may thus affect the ability to drive and operate machines.

Undesirable effects
Evaluation of undesirable effects has been based on the following frequency categories:
Very common (≥1/10), common (≥1/100, <1/10), Uncommon (≥1/1,000, <1/100), Rare (≥1/10,000, <1/1,000), Very rare (<1/10,000), Not known (cannot be estimated from the available data)

The adverse effects of UBRETID® are dose-dependent and are predominantly manifested in muscarine-type, more rarely nicotine-type adverse effects and are frequently the first signs of overdosage.

Muscarine-type adverse effects (may be avoided by concomitant use of atropine or atropine-like substances):

Eye disorders
Common: Miosis, lacrimation increased
Uncommon: Cycloplegia, vision blurred

Cardiac disorders
Very common: Bradycardia
Rare: Ventricular tachycardia
Very rare: Atrial fibrillation, angina pectoris, cardiac arrest

Vascular disorders
Uncommon: Hypotension

Cardiovascular adverse effects during the postoperative phase are of special importance. Frequently bradycardia may occur, in isolated cases also cardiac arrest.
Paradoxical reactions are possible (tachycardia, hypertension).

Respiratory, thoracic and mediastinal disorders
Uncommon: Increased bronchial secretion
Rare: Bronchospasm
Very rare: Respiratory difficulties in patients with progressive muscle dystrophy

Gastrointestinal disorders
Very common: Diarrhea, nausea, vomiting
Common: Salivary hyper-secretion
Uncommon: Gastro-intestinal hypermotility, abdominal pain,
Rare: Dysphagia

Skin and subcutaneous tissue disorders
Very common: Hyperhydrosis

Renal and urinary disorders
Uncommon: Urinary incontinence

Nicotinic-type adverse effects (may not be antagonized by atropine or atropine-like substances):

Musculoskeletal and connective tissue disorders
Rare: Muscle fasciculations, spasms, swallowing problems, muscle weakness, in extreme cases paralysis by neuromuscular block which must be diagnostically differentiated from the symptoms of myasthenia gravis.

Other adverse effects:

Immune system disorders:
Very rare: Anaphylactic reactions

Psychiatric disorders
Very rare: Anxiety, depression, anger, hallucinations, restlessness

Nervous system disorder
Rare: Dizziness, somnolence, headache, dysarthria
Very rare Generalised tonic-clonic seizure and paralysis

Skin and subcutaneous tissue disorders
Rare: Rash

Reproductive system and breast disorders
Rare: Menstrual disorder

Overdose

As with any cholinergic substances, a substantial overdosage of UBRETID® may lead to a "cholinergic crisis" characterised by both muscarinic and nicotinic effects, with increasing muscle weakness and possibly with life-threatening paralysis of respiratory musculature. These effects may include excessive sweating, lachrimation, miosis, ciliary spasm, nystagmus, increased peristalsis, involuntary defaecation and urination or desire to urinate, bradycardia and other arrhytmias, hypotension, muscle cramps, fasciculations, weakness and paralysis, tight chest, wheezing, and increased bronchial secretion combined with bronchoconstriction. Other potential effects include blood pressure drop, bronchospasm, bradycardia and – paradoxically – tachycardia; in such a case the patient will need to be hospitalized. If needed, artificial ventilation must be initiated.

CNS effects include ataxia, convulsions, coma, slurred speech, restlessness, agitation, and fear.

In patients with myasthenia gravis, in whom other symptoms of overdosage may be mild or absent, the major symptom of cholinergic crisis is increased muscular weakness, which must be differentiated from the muscular weakness caused by an exacerbation of the disease itself (myasthenic crisis).

A cholinergic crisis must be diagnostically differentiated from a myasthenic crisis with very similar symptoms. The latter will require immediate administration or dose increase of UBRETID®.

Treatment of cholinergic crisis:
In mild overdosage, observation may be all that is required. In more severe poisoning, the stomach should be emptied aspiration. Administration of UBRETID® should be discontinued immediately. Muscarinic effects as a result of substantial overdosing may be suppressed with the antidote atropine (1 – 2 mg; if needed up to 4 mg atropine sulfate given preferably intravenously, or else intramuscularly). Because of the prolonged distigmine bromide activity atropine administration may need to be repeated several times to control the muscarinic effects until signs of mild atropism (dry mouth, mydriasis) appear.

Cholinesterase reactivators such as pralidoxime will antagonize inhibitors like UBRETID® to a lesser extent than the administration of serum cholinesterases.

Further supportive treatment, including assisted respiration and oxygen, should be given as required.

Pharmacological Properties

Pharmacodynamic Properties

Distigmine bromide binds to acetylcholinesterase, the enzyme responsible for destruction of acetylcholine, thereby prolonging cholinergic activity. Acetylcholine serves as a carrier substance for the transmission to the target organ for almost all parasympathetic nerves, several of the anatomically sympathetic nerves (e.g. the autonomic nerves of the perspiratory glands) as well as the sensomotor nerves of the skeletal muscle.

Distigmine produces miosis and accommodation is also blocked temporarily. Distigmine acts on the gastrointestinal tract by increasing gastric and intestinal contractions. The drug increases the tonus in the urinary bladder, the sphincters, the ureters, and the striated muscles. However, in prolonged use or higher doses, depolarisation of the motor end-plate may occur leading to decreased muscle activity and paralysis. Distigmine causes increased secretion by secretory glands innervated by postganglionic cholinergic fibers. This results in increased salivation, increased intestinal secretion leading to diarrhea and increased bronchial secretions. The predominant effect of distigmine on the heart is bradycardia.

Pharmacokinetic Properties

Absorption:
Distigmine is poorly absorbed after oral administration. The bioavailability is 5%.

Distribution and metabolism:
Distigmine is a quaternary ammonium compound. It is difficult for these substances to pass the cell membrane, they do not pass the blood-brain barrier and thus do not affect the efficacy of acetylcholine as carrier substance of stimuli in the central nervous system.

Maximum inhibition of plasma cholinesterase occurs about 9 h after a single intramuscular dose of 0.5 mg distigmine bromide and persists for 24 h before returning to normal after 48h.

Distigmine is hydrolysed by plasma esterases.

Elimination:
Following oral administration distigmine is eliminated by faecal excretion (88%) and by renal excretion (6.5%). Following intravenous administration distigmine is eliminated by faecal excretion (4%) and by renal excretion (85%).

After oral and intravenous administration of radioactively-labeled distigmine, the plasma half-life was 70 and 60 hours, respectively.

Preclinical Safety Data
There is no nonclinical safety information on Distigmine Bromide.

Tolerance effects
There is no information on induced tolerance.

Package sizes
20, 50 tablets
Not all pack sizes are available locally.

Storage
Protection from light, store drug in outer packing!
Store below 25° C

List of excipients

Magnesium stearate
Talc
Maize starch
Pregelatinised starch
Lactose monohydrate

Date of revision: May 2021

Local Registration Holder
Celltrion Healthcare Singapore Private Limited
65 Chulia Street #41-02 OCBC Centre
Singapore 049513