"To be sold by retail on the prescription of a Specialist only"

Pilocarpine Tablets

Jögren

1. **Generic Name**
Pilocarpine tablets 5 mg

2. **Qualitative and Quantitative composition**
Each film-coated tablet contains 5 mg of pilocarpine hydrochloride.

3. **Dosage form and strength**
5 mg Film-coated tablets for oral use

4. **Clinical particulars**

4.1. **Therapeutic indications**

- Alleviation of symptoms of salivary gland hypofunction in patients with severe xerostomia following irradiation for headand neck cancer.
- Treatment of symptoms of dry mouth and dry eyes in patients with Sjögren's syndrome.

4.2. **Dosage and Administration**

Dosage

- For head and neck cancer patients:
The recommended initial dose for adults is 1 tablet of 5 mg three times daily.
The maximal therapeutic effect is normally obtained after 4 to 8 weeks of therapy.
For patients who have not responded sufficiently after 4 weeks and who tolerate the dose of 5 mg three times daily, doses of up to a maximum of 30 mg daily may be considered.
However, higher daily doses are probably accompanied by an increase in drug-related adverse effects. Therapy should be discontinued if no improvement in xerostomia is noted after 2 to 3 months of therapy.

- For Sjögren's syndrome patients:
The recommended dose for adults is one tablet of 5 mg four times daily.
For patients who have not responded sufficiently to a dosage of 5 mg four times daily and who tolerate this dosage, increasing the dose up to a maximum of 30 mg daily, divided over the day, may be considered. Therapy should be discontinued if no improvement in the symptoms of dry mouth and dry eyes is noted after 2 to 3 months.

Special population

Use in the elderly: There is no evidence to suggest that dosage should be different in the elderly.
Paediatric population: The safety and efficacy of this medicinal product in the paediatric population have not been established.
Use in patients with impaired hepatic function: Patients with moderate and severe cirrhosis should start treatment on a reduced daily dosage schedule. Depending on the safety and tolerability, the dosage may gradually be increased to the normal daily dosage schedule of 5 mg three times a day.
Use in patients with impaired renal function: Insufficient information is available to determine the importance of renal excretion of pilocarpine and its metabolites so as to recommend dosage adjustments for patients with renal insufficiency.

Method of Administration

- For head and neck cancer patients:
Tablets should be taken with a glass of water during or directly after meals. The last tablet should always be taken in conjunction with the evening meal.
- For Sjögren's syndrome patients:
Tablets should be taken with a glass of water at mealtimes and bedtime.

4.3. **Contraindications**

Hypersensitivity to the active substance or to any of the excipients of the product.
Pilocarpine is contraindicated in patients with clinically significant, uncontrolled cardio-renal disease, uncontrolled asthma and other chronic disease at risk for cholinergic agonists.
Pilocarpine is contraindicated in cases where miosis is undesirable, such as in acute iritis.

4.4. **Special warning and Precautions**

Caution should be exercised in patients who are known or expected to sweat excessively and who cannot drink enough liquids, since dehydration could develop.
Pilocarpine has been reported to increase airway resistance in asthmatic patients. Also, patients with significant cardiovascular disease may be unable to compensate for transient changes in haemodynamics or heart rhythm induced by pilocarpine. Therefore, pilocarpine should be administered to patients with controlled asthma or significant cardiovascular disease only if the benefits are believed to outweigh the risks, and under close medical supervision.
Pilocarpine should be used with caution in patients with the following illnesses/pathologies:

- Chronic bronchitis and/or chronic obstructive pulmonary disease. These patients have hyperactive airways and may experience adverse effects due to increased bronchial smooth muscle tone and increased bronchial secretions.
- Known or suspected cholelithiasis or biliary tract disease. Contractions of the gallbladder or biliary smooth muscle could precipitate complications including cholecystitis, cholangitis and biliary obstruction.
- Peptic ulceration, due to the risk of increased acid secretion.
- Underlying cognitive or psychiatric disturbances. Cholinergic agonists, like pilocarpine hydrochloride, may have dose-related central nervous system effects.
- Caution should be exercised when administering pilocarpine in patients with renal insufficiency.
- Pilocarpine may increase ureteral smooth muscle tone and could theoretically precipitate renal colic (or "ureteral reflux"), particularly in patients with nephrolithiasis.
- Pilocarpine should be administered with caution in patients with narrow-angle glaucoma.

4.5. **Drug interactions**

Pilocarpine should be administered with caution to patients taking beta adrenergic antagonists because of the possibility of conduction disturbances.
Concurrent administration of pilocarpine and drugs with parasympathomimetic effects is expected to result in additive pharmacologic effects.
Pilocarpine might antagonise the anticholinergic effects of other drugs used concomitantly (e.g. atropine, inhaled ipratropium).
While no formal drug interaction studies have been performed, the following concomitant drugs were used in at least 10% of patients in either or both Sjögren's efficacy studies: acetylsalicylic acid, artificial tears, calcium, conjugated estrogens, hydroxychloroquine sulfate, ibuprofen, levothyroxine sodium, medroxy progesterone acetate, methotrexate, multivitamins, naproxen, omeprazole, paracetamol, and prednisone. There were no reports of drug toxicities during either efficacy study.
In in vitro studies pilocarpine has been found to be an inhibitor of CYP2A6.
In vivo inhibition and therefore an interaction with CYP2A6 substrates (e.g. irbesartan, coumarin) cannot be ruled out.

4.6. **Use in special population**

Pregnancy: The safety of this medicinal product for use in human pregnancy has not been established. There are no known human data for the effects of pilocarpine on foetal survival and development. Studies in animals have shown reproductive toxicity. Pilocarpine is not recommended during pregnancy and in women of child bearing potential not using contraception.

Breastfeeding: Animal studies have shown excretion of pilocarpine in milk at concentrations similar to those seen in plasma. It is not known whether pilocarpine is secreted in human milk. A decision must be made whether to discontinue breast-feeding or to discontinue from pilocarpine therapy.

Fertility: The effects of pilocarpine on male and female fertility are not known. Studies in mice, rats and dogs have shown adverse effects on spermatogenesis. A study in rats has also indicated a possible impairment of female fertility. The safety margin for the effects on fertility is unknown.
Based on the results of available studies in animals as a precautionary measure, Pilocarpine tablets should be administered to individual human males who are attempting to father a child, only, if the expected benefit justifies potential impairment of fertility.

4.7. **Effect on ability to drive and use machines**

Patients who experience dizziness during pilocarpine treatment should be advised not to drive or operate machinery.

Pilocarpine has been reported to cause impairment of depth perception and visual blurring. The latter may result in decreased visual acuity, especially at night and in patients with central lens changes. If this occurs, patients should be advised not to drive at night or perform hazardous activities in reduced lighting.

4.8. **Undesirable effects**

Most of the adverse experiences observed during pilocarpine treatment were a consequence of exaggerated parasympathetic stimulation. These adverse experiences were dose-dependent and usually mild and self-limited. However, severe adverse experiences might occasionally occur and therefore careful monitoring of the patient is recommended.

In controlled clinical trials the following adverse reactions were observed:

Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Nervous system disorders: headache, dizziness

Eye disorders: lacrimation; blurred vision; abnormal vision; conjunctivitis; eye pain

Cardiac disorders: flushing (vasodilatation); hypertension; palpitations

Respiratory, thoracic and mediastinal disorders: rhinitis

Gastrointestinal disorders: dyspepsia; diarrhoea; abdominal pain; nausea, vomiting; constipation, increased salivation, flatulence

Skin and subcutaneous tissue disorders: sweating, allergic reactions, including rash, pruritus

Renal and urinary disorders: increased urinary frequency, urinary urgency

General disorders and administration site conditions: flu syndrome, asthenia, chills

There is no indication of a difference between older and younger patients receiving pilocarpine as regards reporting adverse experiences, except for dizziness, which was reported significantly more often by patients aged over 65 years.

The following adverse effects, which are due to the intrinsic pharmacological properties of pilocarpine, have been published in the medical literature: respiratory distress, gastro-intestinal spasm, atrio-ventricular block, tachycardia, bradycardia, cardiac arrhythmia, hypotension, shock, tremors, and mental status changes including memory loss, hallucinations, lability of affect, confusion and agitation.

Reporting of suspected adverse reactions

Health care professionals, patients/consumers are advised to closely monitor the possibility of the above Adverse drug reactions associated with the use of the above drugs. If such reactions are encountered, please report to Hetero Healthcare by writing the case or complaints to"drugsafety@heterohealthcare.com"

4.9. **Overdose**

Overdose may lead to a 'cholinergic crisis' characterised by both muscarinic and nicotinic effects.

Signs of overdose due to muscarinic effects may include abdominal cramps, diarrhoea, nausea and vomiting, involuntary defecation and urination, sweating, salivation, increased bronchial secretions, miosis, bradycardia and hypotension.

Nicotinic effects may include involuntary twitching, fasciculations and generalised weakness.

Parenteral atropine may be used as an antidote to the muscarinic effects. Supportive treatment should be given as required; artificial respiration should be instituted if respiratory depression is severe.

5. **Pharmacological properties**

5.1. **Mechanism of action**

Pilocarpine is a cholinergic parasympathomimetic agent exerting a broad spectrum of pharmacologic effects with predominant muscarinic action. Pilocarpine, in appropriate dosage, can increase secretion by exocrine glands such as the sweat, salivary, lacrimal, gastric, pancreatic and intestinal glands and the mucous cells of the respiratory tract.

5.2. **Pharmacodynamic properties**

Dose-related smooth muscle stimulation of the intestinal tract may cause increased tone, increased motility, spasm and tenesmus. Bronchial smooth muscle tone may increase. The tone and motility of urinary tract, gallbladder and biliary duct smooth muscle may be enhanced.

Pilocarpine may have paradoxical effects on the cardiovascular system. The expected effect of a muscarinic agonist isvaso depression, but administration of pilocarpine may produce hypertension after a brief episode of hypotension. Bradycardia and tachycardia have both been reported with use of pilocarpine.

5.3. **Pharmacokinetic properties**

Absorption: In a multiple-dose pharmacokinetic study in volunteers given 5 or 10 mg of pilocarpine hydrochloride three times daily for two days, the Tmax after the final dose was approximately 1 hour, the elimination $t_{½}$ was approximately 1 hour, and the mean Cmax were 15 ng/ml and 41 ng/ml for the 5 and 10 mg doses, respectively.

When taken with a high-fat meal, there was a decrease in the rate of absorption of pilocarpine from pilocarpine tablets. Mean T max were 1.47 and 0.87 hours and mean Cmax were 51.8 and 59.2 ng/ml for fed and fasted male volunteers, respectively.

Distribution: Pilocarpine is extensively distributed with an apparent volume of distribution of 2.1 L/kg. Data from animal studies indicates that pilocarpine is distributed into breast milk at concentrations similar to plasma. Preclinical data also suggests that pilocarpine can cross the blood brain barrier at high dose. Pilocarpine does not bind to plasma proteins.

Metabolism: Pilocarpine is primarily metabolized by CYP2A6 and has demonstrated a capacity to inhibit CYP2A6 in vitro. Serum esterases are also involved in the biotransformation of pilocarpine to pilocarpic acid.

Elimination: Approximately 35% of dose is eliminated as 3-hydroxypilocarpine in urine and 20% of dose is excreted unchanged in the urine. Mean elimination half-lives for pilocarpine is 0.76 and 1.35 hours after repeated oral doses of 5 and 10 mg of pilocarpine hydrochloride, respectively.

Elderly: Pilocarpine area under the curve (AUC) values in elderly male volunteers were comparable to those in younger males. In a small number of healthy elderly female volunteers the mean AUC was approximately twice that of elderly and young male volunteers due to reduced volumes of distribution. However, the observed difference in pharmacokinetics was not reflected in the incidence of adverse events between young and elderly female patients. No dosage adjustment is required in elderly subjects.

Renal impairment: A pharmacokinetic study of pilocarpine in patients with mild and moderately impaired renal function showed that there was no significant difference in clearance and exposure compared with subjects with normal renal function.

6. **Pharmaceutical particulars**

6.1. **Incompatibilities**

Not applicable

6.2. **Shelf life**

6.3. **Packing information**

Bottle of 60 tablets

6.4. **Storage and handling instructions**

Do not store above 25°C.

Store in the original package in order to protect from light and moisture.

6.5. **Details of manufacturer**

HETERO HEALTHCARE LIMITED

AIIDC Industrial Growth Centre, Changsari,
Niz Sindurighopa (Village),
Sila Sindurighopa (Mouza),
Kamrup (Dist), Assam - 781101

6.6. **Details of permission or license number with date**

HETERO HEALTHCARE LIMITED

7-2-A 2, Hetero Corporate, Industrial Estate,
Sanath Nagar, Hyderabad - 500018,
Telangana, India.

6.7. **Date of revision**

23/11/2021