

SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Pilocarpine Hydrochloride 5 mg Film-coated Tablets

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each tablet contains 5 mg of pilocarpine hydrochloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.

White to off white circular, biconvex film coated tablets with embossing “P 5”.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Alleviation of symptoms of salivary gland hypofunction in patients with severe xerostomia following irradiation for head and neck cancer.

Treatment of symptoms of dry mouth and dry eyes in patients with Sjögren's syndrome.

4.2 Posology and method of administration

Posology

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 Populations

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 (see Section 4.4 and Section 5.2).

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 listed in section 6.1.

Pilocarpine Hydrochloride is contraindicated in patients with clinically significant, uncontrolled cardiorenal disease, uncontrolled asthma and other chronic disease at risk for cholinergic agonists.

Pilocarpine Hydrochloride is contraindicated in cases where miosis is undesirable, such as in acute iritis.

4.4 Special warnings and precautions for use

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 Hydrochloride 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 Hydrochloride 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 Hydrochloride 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 Hydrochloride should be administered with caution in patients with narrow-angle glaucoma.

4.5 Interaction with other medicinal products and other forms of interaction

Pilocarpine Hydrochloride should be administered with caution to patients taking beta adrenergic antagonists because of the possibility of conduction disturbances.

Concurrent administration of Pilocarpine Hydrochloride 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, medroxyprogesterone 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 (see section 5.2).

4.6 Fertility, Pregnancy and lactation

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 (see section 5.3).

Pilocarpine Hydrochloride 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 breastfeeding or to discontinue from Pilocarpine Hydrochloride 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 (see section 5.3). The safety margin for the effects on fertility is unknown.

Based on the results of available studies in animals (see section 5.3) as a precautionary measure, Pilocarpine Hydrochloride 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 Effects on ability to drive and use machines

Patients who experience dizziness during Pilocarpine Hydrochloride 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 Hydrochloride 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.

Very common ($\geq 1/10$); common ($\geq 1/100$, $< 1/10$); uncommon ($\geq 1/1,000$, $< 1/100$); rare ($\geq 1/10,000$, $< 1/1,000$); very rare ($< 1/10,000$), not known (cannot be estimated from the available data).

Nervous system disorders

- Very common: headache
- Common: dizziness

Eye disorders

- Common: lacrimation; blurred vision; abnormal vision; conjunctivitis; eye pain

Cardiac disorders

- Common: flushing (vasodilatation); hypertension; palpitations

Respiratory, thoracic and mediastinal disorders

- Common: rhinitis

Gastrointestinal disorders

- Common: dyspepsia; diarrhoea; abdominal pain; nausea, vomiting; constipation, increased salivation
- Uncommon: flatulence

Skin and subcutaneous tissue disorders

- Very common: sweating
- Common: allergic reactions, including rash, pruritus

Renal and urinary disorders

- Very common: increased urinary frequency
- Uncommon: urinary urgency

General disorders and administration site conditions

- Very common: flu syndrome
- Common: asthenia, chills

There is no indication of a difference between older and younger patients receiving Pilocarpine Hydrochloride as regards to 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, atrioventricular block, tachycardia, bradycardia, cardiac arrhythmia, hypotension, shock, tremors, and mental status changes including memory loss, hallucinations, lability of affect, confusion, agitation.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 Pharmacodynamic properties

Pharmacotherapeutic group: Parasympathomimetic

ATC Code: N07A X01

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.

Pharmacodynamic effects

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 is vasodepression, but administration of pilocarpine may produce hypertension after a brief episode of hypotension. Bradycardia and tachycardia have both been reported with use of pilocarpine.

Clinical efficacy and safety

In a study in healthy male volunteers an increase in salivary flow following single 5 and 10 mg doses of Pilocarpine Hydrochloride was noted 20 minutes after administration, and lasted for 3 to 5 hours with a peak at 1 hour.

For head and neck cancer patients:

In two 12-week randomised, double-blind placebo-controlled clinical studies in patients with xerostomia resulting from irradiation to the head and neck for cancer, Pilocarpine Hydrochloride treatment reduced dryness of the mouth; in one of these studies this did not occur until after 12 weeks of treatment. Also, Pilocarpine Hydrochloride treatment increased salivary flow. The greatest improvement in dryness was noted in patients with no measurable salivary flow at baseline.

In both studies, some patients noted improvement in the overall condition of xerostomia, speaking without drinking liquids, and mouth comfort, and there was reduced use of concomitant therapy (i.e. artificial saliva) for dry mouth.

For Sjögren's syndrome patients:

Two separate 12-week randomised, double-blind placebo-controlled clinical studies were conducted in patients diagnosed with primary or secondary Sjögren's syndrome. In both studies, the majority of patients best fit the European criteria for having primary Sjögren's syndrome. The ability of Pilocarpine Hydrochloride to stimulate saliva production was assessed. Relative to placebo, an increase in the amount of saliva being produced was observed following the first dose and was maintained throughout the duration of the trials in an approximate dose response fashion.

Compared to placebo a statistically significant global improvement for both dry mouth and dry eyes was observed.

Efficacy of Pilocarpine Hydrochloride has not been established in patients with the Sjögren's syndrome during long term treatment (>12 weeks).

5.2 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 T_{max} after the final dose was approximately 1 hour, the elimination $T_{1/2}$ was approximately 1

hour, and the mean C_{\max} 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 Hydrochloride tablets. Mean T_{\max} were 1.47 and 0.87 hours and mean C_{\max} 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 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.

5.3 Preclinical safety data

Genotoxicity and carcinogenicity:

Pilocarpine did not indicate a genotoxic potential in a series of *in vitro* and *in vivo* genotoxicity studies. In lifetime oral carcinogenicity studies in rodents Pilocarpine did not cause an increase in tumour incidence in mice, but was associated with an increased incidence in benign pheochromocytomas in rats at >15 times the exposure at the maximum recommended human dose and therefore not considered relevant to clinical use. Preclinical data revealed no special hazard for humans based on conventional studies of genotoxicity and carcinogenic potential.

Fertility

Animal studies have shown adverse effects on the male reproductive tract following chronic exposures to pilocarpine. Impaired spermatogenesis was observed in rats and dogs following 28-day and 6-month oral exposures respectively. Histopathological changes were also observed in the testes and bulbourethral glands of mice given pilocarpine for 2 years.

The safety margin for the effects in humans is unknown. However, body surface area [mg/m^2] comparisons suggest that the lowest dose associated with impaired fertility, (3 $\text{mg}/\text{kg}/\text{day}$ in the dog), is approximately 3 times the maximum recommended human dose, therefore a risk to humans cannot be ruled out. A study in rats has also indicated a possible impairment of female fertility (see section 4.6).

Reproductive toxicity:

Studies in pregnant rats showed treatment-related reductions in the mean fetal body weight and increases in the incidence of skeletal variations [at approximately 26 times the maximum recommended dose for a 50 kg human, based on comparisons of body surface area (mg/m^2)]. These effects occurred at doses that were maternally toxic. There was no evidence of a teratogenic effect in the animal studies. Treatment related increases in the incidence of stillbirths with decreased neonatal survival and reduced mean body weight of pups were observed in pre- and postnatal studies. A safety margin for these effects cannot be calculated. However, body surface area [mg/m^2] comparisons suggest that the effect occurred at approximately 5 times the maximum recommended dose for a 50 kg human. The clinical relevance of these findings is unknown (see section 4.6).

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose

Pregelatinised starch

Colloidal anhydrous silica

Stearic acid

Opadry white OY-7300 (containing hypromellose, titanium dioxide [E171] and macrogol 400)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

2 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

PVC/PE/PVdC foiled aluminium blister.

A carton contains 14, 21, 28 or 84 tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

No special requirements.

7 MARKETING AUTHORISATION HOLDER

Strandhaven Limited t/a Somex Pharma
Ilford
Essex
IG3 8BS.UK

8 MARKETING AUTHORISATION NUMBER(S)

PL 15764/0162

**9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION**

28/09/2021

10 DATE OF REVISION OF THE TEXT

22/10/2021