1. Name of the medicinal product

Salagen

2. Qualitative and quantitative composition

Each film-coated tablet contains 5 mg of pilocarpine hydrochloride.

For a full list of excipients, see section 6.1.

3. Pharmaceutical form

Film-coated tablet

4. Clinical particulars

4.1 Therapeutic indications

- The treatment of symptoms of dry mouth from xerostomia and salivary gland hypofunction caused by radiotherapy for cancer of the head and neck.
- The treatment of symptoms of dry mouth in patients with Sjogren's Syndrome detected by biopsy.

4.2 Posology and method of administration

Regardless of the indication, the starting dose in patients with moderate hepatic impairment should be 5 mg twice daily, followed by adjustment based on therapeutic response and tolerability. Patients with mild hepatic insufficiency do not require dosage reductions. The use of pilocarpine in patients with severe hepatic insufficiency is not recommended. If needed, refer to the Hepatic Insufficiency subsection of the Precautions section of this label for definitions of mild, moderate and severe hepatic impairment.

Head & Neck Cancer Patients: The recommended initial dose of Salagen Tablets is 5 mg taken three times a day. Dosage should be titrated according to therapeutic response and tolerance. The usual dosage range is up to 15-30 mg per day. (Not to exceed 10 mg per dose.) Although early improvement may be realized, at least 12 weeks of uninterrupted therapy with Salagen Tablets may be necessary to assess whether a beneficial response will be achieved. The incidence of the most common adverse events increases with dose. The lowest dose that is tolerated and effective should be used for maintenance.

Sjogren's Syndrome Patients: The recommended dose of Salagen Tablets is 5 mg taken four times a day. Efficacy was established by 6 weeks of use.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

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

Salagen 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, Salagen 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.

Salagen 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 Salagen 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.

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

4.5 Interaction with other medicinal products and other forms of interaction

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

Concurrent administration of Salagen 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).

Salagen 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 Salagen 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 meaure, Salagen 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 Salagen 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 Salagen 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, <1/1000); 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; diarrhea; 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 Salagen 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, 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

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: Parasympathominetic, 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 Salagen 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, Salagen treatment reduced dryness of the mouth; in one of these studies this did not occur until after 12 weeks of treatment. Also, Salagen 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 Salagen 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 Salagen 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 $T_{2}^{1/2}$ 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 Salagen 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.

<u>Elderly</u>

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/m²] comparisons suggest that the lowest dose associated with impaired fertility, (3 mg/kg/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/m²]. 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/m2] 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

Binder/diluent:

Microcrystalline cellulose

Acidifier/lubricant:

Stearic acid

Film coating:

Opadry White, OY-7300

Polish:

Carnauba wax

6.2 Incompatibilities Not applicable

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials **6.4 Special precautions** for storage

Do not store above 25°C.

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

6.5 Nature and contents of container

100 tablets, HDPE bottle with child resistant (push down and turn) screw with silica gel desiccant. Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements.

7. Manufacturer

Pantheon inc, Canada

2100 Syntex Court, Mississauga, Ontario, Canada L5N 7K9 8.Marketing authorisation holder

Megapharm Ltd, P.O.B 519 Hod Hasharon 4510501 Israel

9. Marketing authorisation number(s)

101-65-28557

10. Reviewed on

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