Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Salagen 5mg Film-coated Tablets.

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Pilocarpine Hydrochloride 5 mg.

For excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Film-coated tablet.
White, circular, biconvex film-coated tablets, marked “SAL” on one side and “5mg” on the other side.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

i. Alleviation of symptoms of salivary gland hypofunction due to post-radiation xerostomia.

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

4.2 Posology and method of administration

i. For patients with post-radiation xerostomia

The recommended oral dose for adults is 1 tablet of 5 mg three times daily. 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. The maximal therapeutic effect is obtained after 4-8 weeks of therapy. For patients who have not responded sufficiently 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 3 months of therapy.

ii. For Sjögren’s syndrome patients

The recommended dose for adults is one tablet of 5 mg four times daily. Tablets should be taken with a glass of water at mealtimes and bedtime. Efficacy was established by 6 weeks of use.

Use in the elderly

There is no evidence to suggest that dosage should be different in the elderly.

Use in children

Safety and effectiveness of this drug in children have not been established.

Use in patients with impaired hepatic function

Patients with impaired hepatic function should commence 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 t.d.s.

4.3 Contraindications

Salagen is contraindicated in patients with clinically significant, uncontrolled cardiorenal disease, uncontrolled asthma, and other chronic disease at risk for cholinergic agonists. In addition, Salagen is contraindicated in patients with known hypersensitivity to pilocarpine and when miosis is undesirable such as in acute iritis, or when a decrease in the depth of the anterior chamber is undesirable as in narrow-angle (angle closure) glaucoma.

4.4 Special warnings and precautions for use

Eye

Ocular formulations of pilocarpine have 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.

Careful examination of the fundus should be carried out prior to initiating therapy with Salagen.

Pulmonary disease

Pilocarpine has been reported to increase airway resistance in asthmatic patients. If the benefits are believed to outweigh the risks in patients with controlled asthma, Salagen should be administered with caution and under close medical supervision.

Patients with chronic bronchitis and/or chronic obstructive pulmonary disease have hyperactive airways and may experience adverse consequences of increased bronchial smooth muscle tone and increased bronchial secretions.

Cardiovascular disease

Patients with significant cardiovascular disease may be unable to compensate for transient changes in haemodynamics or heart rhythm induced by pilocarpine. If the benefits are believed to outweigh the risks in patients with significant controlled cardiovascular disease, Salagen should be administered with caution and under close medical supervision.

Biliary tract

Salagen should be administered with caution to patients with 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.

Gastrointestinal tract

In view of the risks of increased acid secretion, Salagen should be administered with caution in patients with peptic ulceration.

Central nervous system

Cholinergic agonists, like pilocarpine hydrochloride, may have dose-related central nervous system effects. This should be considered when treating patients with underlying cognitive or psychiatric disturbances.

Renal insufficiency

Insufficient information is available to determine the importance of renal excretion of pilocarpine and its metabolites in relation to metabolic inactivation so as to recommend dosage adjustments for 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 to patients with renal insufficiency.

General

Caution should be exercised in patients who are known or expected to sweat excessively and who cannot drink enough liquids, since dehydration could develop.

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 antagonize the anti-cholinergic effects of other drugs used concomitantly. These effects should be considered when anti-cholinergic properties may be contributing to the therapeutic effect of concomitant medication (i.e. 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 both efficacy studies.

4.6 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. However, pre and post natal studies in rats have shown some toxicity (see Section 5.3 for details).

Thus, Salagen should only be prescribed for a pregnant woman after careful evaluation by the physician of the risks and benefit of the treatment.

Nursing mothers

It is not known whether pilocarpine or its metabolites are secreted in human milk. Because many pharmaceutical substances do appear in human milk, the clinician should decide whether the patient is to discontinue breast-feeding or discontinue treatment.

Fertility

The effects of pilocarpine on male and female fertility are not known. Studies in rats have shown adverse effects on spermatogenesis and a possible impairment of female fertility (see Section 5.3 for details).

4.7 Effects on ability to drive and use machines

Caution should be advised while driving at night or performing 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.

i. For patients with post-radiation xerostomia

Based on the data of the 513 patients who were treated with Salagen in clinical trials, mild or moderate sweating was by far the most prevalent adverse experience, occurring in approximately half of the patients treated. Other adverse experiences observed were: rhinitis (12%), headache (12%), increased urinary frequency (11%), nausea (9%), dizziness (9%), vasodilatation (flushing) (9%), chills (8%), dyspepsia (8%), asthenia (7%), diarrhoea (6%), lacrimation (6%), and abdominal pain (5%). Adverse experiences occurring with a frequency of less than 5% were: vomiting, blurred vision, hypertension, constipation and abnormal vision.

In general, women more often reported adverse experiences than men, although this was not the case for sweating.

ii. For Sjögren's syndrome patients

Based on the data of the 255 patients (94% women) who were started with Salagen treatment in two placebo-controlled clinical trials at a dosage of 5 mg q.i.d., mild to moderate sweating was by far the most prevalent adverse experience (43%).

Other adverse experiences, rated by the investigator as having a possible or probable drug relationship, were: nausea (10%), increased urinary frequency (9%), headache (7%), vasodilatation (flushing) (8%), rhinitis (7%), dyspepsia (6%) and chills (6%). Adverse experiences occurring with a frequency of 1 to 5% were: increased salivation, diarrhoea, dizziness, palpitations, blurred vision, asthenia, abdominal pain, flu syndrome, vomiting, constipation, urinary urgency and flatulence.

These adverse experiences were not considered to be serious.

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

Based on the pharmacology of pilocarpine other possible adverse effects are:
respiratory distress, gastro-intestinal spasm, atrio-ventricular block, tachycardia, bradycardia, cardiac arrhythmia, hypotension, shock, mental confusion and tremors.

4.9 Overdose

Overdosage should be treated with atropine titration (0.5 mg to 1.0 mg given subcutaneously or intravenously) and supportive measures to maintain respiration and circulation. Adrenaline (0.3 mg to 1.0 mg, subcutaneously or intramuscularly) may also be of value in the presence of severe cardiovascular depression or bronchoconstrictor responses. It is not known if pilocarpine is dialysable. There is no safety information for doses greater than 10 mg t.d.s.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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.

i. For patients with post-radiation xerostomia

In two 12-week randomized, double-blind placebo-controlled clinical studies Salagen reduced dryness of the mouth, and increased salivary flow in patients with xerostomia resulting from radiation to the head and neck for cancer. In addition there was evidence of 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.

ii. For Sjögren's syndrome patients

Two separate 12-week randomized, 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. Specific dry mouth symptoms assessed by the patients such as severity of dry mouth, mouth discomfort, ability to sleep without drinking water; ability to swallow food without drinking; and a decreased use of saliva substitutes were significantly improved after 6 and 12 weeks of Salagen treatment. Specific dry eye symptoms improved significantly such as severity of visual blurring and ability to focus after 12 weeks of Salagen treatment.

5.2 Pharmacokinetic properties

In a multiple-dose pharmacokinetic study in volunteers given 5 or 10 mg of pilocarpine hydrochloride t.d.s. for two days, the T_{max} after the final dose was approximately 1 hour, the elimination $T_{½}$ was approximately 1 hour, and the mean $C_{max's}$ were 15 ng/ml and 41 ng/ml for the 5 and 10 mg doses, respectively.

Pharmacokinetics in elderly male volunteers were comparable to those in younger subjects. In a small number of healthy elderly female volunteers the mean C_{max} and AUC were approximately twice those of elderly and young male volunteers due to smaller volumes of distribution.

When taken with a high fat meal by healthy male volunteers, there was a decrease in the rate of absorption of pilocarpine from Salagen tablets. Mean $T_{max's}$ were 1.47 and 0.87 hours and mean $C_{max's}$ were 51.8 and 59.2 ng/ml for fed and fasted volunteers, respectively.

There is limited information available concerning the metabolism and elimination of pilocarpine in humans. Inactivation of pilocarpine is thought to occur at neuronal synapses and probably in plasma.

A single dose pharmacokinetic study in humans showed that an average of 30% of the orally administered dose of 10 mg pilocarpine could be detected in the urine after 12 hours, of which 14% was recovered as pilocarpic acid. No other metabolites were detected in the urine. It is expected that the remaining 70% is excreted via other routes and/or metabolized to unknown metabolites.

An *in-vitro* study showed that pilocarpine does not bind to plasma proteins.

5.3 Preclinical safety data

Carcinogenesis

Carcinogenicity studies were conducted in mice and rats with daily oral administration of pilocarpine hydrochloride at doses of 3, 10 and 30 mg/kg body weight/day, and 3, 9 and 18 mg/kg body weight/day, respectively for 104 weeks. The data reveal no carcinogenic hazard for humans.

Mutagenisis

There was no evidence of mutagenicity with pilocarpine hydrochloride in the Ames reverse mutation, Chinese Hamster Ovary chromosomal aberrations and *in-vivo* mouse bone marrow micronucleus tests. Pilocarpine hydrochloride was not genotoxic in an unscheduled DNA synthesis (UDS) test with rat hepatocytes.

Reproductive toxicity

Two studies were conducted in rats in which males and females were exposed to pilocarpine before and after mating, dosing in the females continuing to 21 days after parturition. There was evidence that doses of 18 mg/kg/day and above for 28 days to male rats would affect fertility adversely, decrease sperm motility and increase incidence of abnormal sperm. In females at these doses there was evidence of decreased fertility index and prolonged di-oestrus. Offspring survival was decreased.

For these changes to reproductive performance, 3 mg/kg/day was a No Effect dose.

The post-natal development of the surviving F1 generation was not affected by doses up to 72 mg/kg/day to the dams and the F2 generation was normal.

There was no evidence of a teratogenic effect at any dose in these studies.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Microcrystalline cellulose
Stearic acid

Film coating

Hypromellose
Titanium dioxide (E171)
Macrogol 400
Polysorbate 80
Carnauba wax

Printing ink

Shellac
Black iron oxide (E172)
Propylene glycol
Ammonium hydroxide

6.2 Incompatibilities

Not applicable.

6.3 Shelf Life

3 years.

6.4 Special precautions for storage

Do not store above 25ºC. Store in the original package.

6.5 Nature and contents of container

Al/PVC/PVDC blisters.
Each blister contains 14 tablets.
A cardboard box contains 1, 2 or 6 strips (14, 28 or 84 tablets) and a patient package insert.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal of a used medicinal product or waste materials derived from such medicinal product and other handling of the product

No special requirements.

7 MARKETING AUTHORISATION HOLDER

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8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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