Summary of Product Characteristics (SPC)

1. NAME OF THE MEDICINAL PRODUCT

Dalman AQ 50 mcg/100 mg Nasal Spray, suspension

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Active Ingredient:

In 100 mg spray:

Fluticasone propionate (INN)……50 micrograms

Excipient:

Benzalkonium chloride…….0.02 mg

For other excipients (see 6.1).

3. PHARMACEUTICAL FORM

Nasal spray, suspension

Off-white, opaque, homogeneous aqueous suspension in HDPE bottle.

4. CLINICAL PARTICULARS

4.1 Therapeutic Indications

DALMAN AQ nasal spray, suspension is indicated for the symptomatic treatment and prophylaxis of seasonal allergic rhinitis and perennial rhinitis including hay fever. Fluticasone propionate has a strong anti-inflammatory effect, but does not produce a noticeable systemic effect when applied topically to the nasal mucosa.

4.2 Posology and method of administration

Posology/administration frequency and duration:

Prophylaxis and symptomatic treatment of seasonal allergic rhinitis and perennial rhinitis

Adults and children over 12 years of age
Two sprays into each nostril once a day, preferably in the morning. In some cases two sprays into each nostril twice daily may be required. The maximum daily dose should not exceed four sprays into each nostril.

Route of Administration:

For full therapeutic benefit regular usage is essential. The absence of an immediate effect should be explained to the patient, as maximum relief may not be obtained until after 3 to 4 days of treatment.
DALMAN should only be administered intranasally.

Additional information for special population:

Renal/hepatic impairment

There is no sufficient information

Pediatric population:

Children 4-11 Years:
One in each nostril once a day, preferably in the morning one spraying is done. In some cases, you may need to do 2 times a day 1 spray in each nostril. The maximum daily dose should not exceed 2 sprays in each nostril.

Geriatric population:

The normal adult dosage is applicable.

4.3 Contraindications

DALMAN AQ Nasal Spray is contraindicated in patients with hypersensitivity to any of the suspension components.

4.4 Special warnings and special precautions for use

Local infection: Although the presence of infection in the nasal airways does not constitute a specific contraindication for intranasal fluticasone propionate therapy, this infection should be treated appropriately.

Caution should be exercised in patients who discontinue systemic steroid therapy and initiate intranasal fluticasone propionate therapy, especially if there is a reason to think that adrenal function is impaired.

Systemic effects of nasal corticosteroids, especially in high doses and long-term use, have been reported. These effects are much less likely to occur than with oral corticosteroids and may differ between patients and different corticosteroid preparations.

Growth retardation has been reported in children using certain nasal corticosteroids at approved doses. Regular monitoring of the height of children receiving long-term nasal corticosteroid therapy is recommended. In the event of growth retardation, treatment should be reviewed to reduce the nasal corticosteroid dose and, whenever possible, the lowest dose to control symptoms should be used. In addition, referral to a pediatrician should be considered.

During post-marketing use, clinically significant drug interactions have been reported in patients receiving fluticasone propionate and ritonavir; this has led to systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided unless the potential benefits to the patient outweigh the risk of systemic corticosteroid side effects (see *Interactions with Other Medicinal Products and Other Modes of Interaction*).

Full benefit may not be achieved unless treatment with DALMAN Nasal Spray, suspension is continued for several weeks.

Glaucoma and increased intraocular pressure have been reported rarely following intranasal administration of corticosteroids.

4.5 Interaction with other medicinal products and other forms of interaction

Under normal conditions, very low plasma concentrations of fluticasone propionate are achieved following intranasal dosing, due to extensive first-pass metabolism in the liver and intestine and high systemic clearance mediated by cytochrome P450 3A4. Therefore, clinically significant drug interactions mediated by fluticasone propionate are not expected.

In a drug interaction study in healthy volunteers, ritonavir (a highly potent cytochrome P450 3A4 inhibitor) was shown to greatly increase the plasma concentrations of fluticasone propionate, leading to a significant decrease in serum cortisol concentrations. Clinically

significant drug interactions have been reported in patients receiving intranasal or inhaled fluticasone propionate and ritonavir during post-marketing use; this has led to systemic corticosteroid effects, including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided unless the potential benefits to the patient outweigh the risk of systemic corticosteroid side effects.
Studies have shown negligible (erythromycin) and insignificant (ketoconazole) increases in systemic exposure of other cytochrome P450 3A4 inhibitors with no discernible decrease in serum cortisol concentrations of fluticasone propionate. However, caution should be exercised when co-administering potent cytochrome P450 3A4 inhibitors (eg, ketoconazole) because of the potential for increased systemic exposure to fluticasone propionate.

Additional information for special population

There is no sufficient information

Pediatric population

There is no sufficient information

4.6 Pregnancy and lactation

Pregnancy category is C.

Women with childbearing potential / Contraception

Studies on animals are insufficient in terms of the effects on pregnancy or embryonal / fetal development and / or postnatal and / or postnatal development. The potential risk for humans is unknown.

Pregnancy Period

There are insufficient data regarding its safety in human pregnancy. In animal reproduction studies, adverse effects typical of potent corticosteroids were seen only at high systemic exposure levels; direct intranasal administration provides minimal systemic exposure.
As with other drugs, the benefits of intranasal fluticasone propionate use during pregnancy and lactation should outweigh the possible risks that may arise from using the product or alternative treatment methods.

Lactation Period

It has not been studied whether fluticasone propionate is excreted in breast milk. In lactating laboratory rats, fluticasone propionate was seen in milk when measurable plasma levels were achieved following subcutaneous administration. However, plasma levels are low following intranasal administration of fluticasone propionate at recommended doses.

Reproduction Ability/Fertility

No sufficient information.

4.7 Effects on ability to drive and use machines

Fluticasone propionate is not expected to have any effect.

4.8 Undesirable effects

Data from large clinical studies have been used to determine the incidence of adverse events, from very common to rare. Frequencies of other adverse events (<1/10.000) were determined from post-marketing data and are based on the reporting rate rather than an actual frequency.
The frequency classification is as follows:
Very common 1/10
Common 1/100 and <1/10
Uncommon 1/1000 and <1/100
Rare 1/10,000 and <1/1000
Very rare <1/10,000
Unknown (it cannot be predicted on the basis of available data)

Immune system diseases

Very rare: Hypersensitivity reactions, anaphylaxis/anaphylactic reactions, bronchospasm, skin rash, edema of the face or tongue

Nervous System Disorders

Common: Headache, bad taste in mouth, bad odour.
As with other nasal sprays, bad taste in the mouth, bad odor and headache have been reported.

Eye diseases

Very rare: Glaucoma, increased intraocular pressure, cataract.

Few spontaneous reports have been described following long-term therapy. However, clinical studies lasting up to one year have shown that intranasal fluticasone propionate is not associated with an increased incidence of eye events such as cataracts, increased intraocular pressure, or glaucoma.

Diseases of the respiratory system:

Very common: Epistaxis.

Common: Nasal dryness, nasal irritation, dry throat, throat irritation

As with other intranasal medications, dryness, irritation and epistaxis of the nose and throat have been reported.

Very rare: Nasal septal perforation

Cases of nasal septal perforation have been reported following the use of intranasal corticosteroids.

4.9 Overdose

There are no data on the effect of acute or chronic overdose of intranasal fluticasone propionate. Intranasal administration of 2 mg fluticasone propionate twice daily for 7 days to healthy volunteers had no effect on hypothalamic-pituitary-adrenal (HPA) axis functions.

Long-term administration of higher than recommended doses may cause temporary suppression of adrenal function.

In these patients, fluticasone propionate treatment should be continued at a dose sufficient to control symptoms; adrenal function will return to normal within a few days and this can be monitored by measuring the plasma cortisol level.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Corticosteroids.

ATC Code: R01AD08

Fluticasone propionate has strong antiinflammatory activity but does not produce detectable systemic activity when administered topically to the nasal mucosa.

Fluticasone propionate causes little or no hypothalamic-pituitary-adrenal axis suppression following intranasal administration.

Following intranasal dosing of fluticasone propionate, (200mcg/day) no significant change in 24h serum cortisol AUC was found compared to placebo (ratio1.01, 90%CI 0.9-1.14).

5.2 Pharmacokinetic properties

Absorption:

Following intranasal dosing of fluticasone propionate, (200mcg/day) steady-state maximum plasma concentrations were not quantifiable in most subjects (<0.01ng/mL). The highest Cmax observed was 0.017ng/mL. Direct absorption in the nose is negligible due to the low aqueous solubility with the majority of the dose being eventually swallowed. When administered orally the systemic exposure is <1% due to poor absorption and pre-systemic metabolism. The total systemic absorption arising from both nasal and oral absorption of the swallowed dose is therefore negligible.

Distribution:

Fluticasone propionate has a large volume of distribution at steady-state (approximately 318L). Plasma protein binding is moderately high (91%).

Biotransformation:

Fluticasone propionate is rapidly cleared from the systemic circulation mainly by conversion to an inactive carboxylic acid metabolite by the cytochrome P450 enzyme CYP3A4 in the liver. Ingested fluticasone propionate also undergoes extensive first-pass metabolism. Caution should be exercised when co-administered with strong CYP3A4 inhibitors such as ketoconazole and ritonavir, as there is potential for increased systemic exposure to fluticasone propionate.

Elimination:

The elimination rate of intravenous administered fluticasone propionate is linear over the 250 1000mcg dose range and are characterized by a high plasma clearance (CL=1.1L/min). Peak plasma concentrations are reduced by approximately 98% within 3-4 hours and only low plasma concentrations were associated with the 7.8h terminal half-life. The renal clearance of fluticasone propionate is negligible (<0.2%) and less than 5% as the carboxylic acid metabolite. The major route of elimination is the excretion of fluticasone propionate and its metabolites in the bile.

5.3 Preclinical safety data

The toxicology appears only in the type of effects that potent corticosteroids have when administered at higher doses than recommended. No new effects were identified in repeated dose toxicity studies, reproductive toxicity studies, or teratology studies.

Fluticasone propionate did not show mutagenic activity *in vitro* and *in vivo* and did not show tumorigenic activity in rodents. Not irritating or sensitizing on animal models.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Dextrose, Microcrystalline cellulose and carboxymethyl cellulose sodium (Avicel RC591)

Benzalkonium chloride, Polysorbate 80, Disodium hydrogen phosphate, Citric acid, Purified water

6.2 Incompatibilities

There is no relevant data.

6.3 Shelf Life

24 months.

6.4 Special precautions for storage

Store below 25°C.

6.5 Nature and contents of container

DALMAN is available in HDPE bottles with a metered atomizer pump, nasal adapter and powder cover attached to the tip. When used as recommended, approximately 120 doses can be sprayed with each bottle.

6.6 Instructions for use and handling

Shake gently before use.
Before using DALMAN, you should wash your hands and remove the dust cover.

PREPARING YOUR SPRAY
If it is a new bottle or one that has not been used for several days, you must prime the spray for it to work well.
• While holding the bottle in an upright position, place your thumb on the base of the bottle and your fingers on both sides of the spray head.
• Keep the bottle upright by turning it away from you.
• Keeping your thumb steady, press down with your fingers. The spray will come out as a fine mist.

If it works: skip to "USING THE SPRAY".
If the spray did not work: or if you think it is clogged, go to the "CLEANING THE SPRAY" section. Do not use a needle or sharp object to open the clog or enlarge the spray hole. This will break the mechanism of the spray.

USING THE SPRAY (Follow the instructions below carefully.)
1. Gently shake the bottle.
2. Blow your nose lightly.
3. While holding the bottle in an upright position, place your thumb on the bottom of the bottle and your fingers on either side of the nozzle.
4. Cover one of your nostrils with your finger and place the spray nozzle into your open nostril.
5. Tilt your head slightly forward to keep the bottle in an upright position. Start breathing through your nose and press down with your fingers. Hold the nozzle inside your nostril while exhaling through your mouth.

6. Repeat step 5 above and spray the same nostril again.
7. Take out the spray nozzle and repeat the steps 3 - 6 for your other nostril.
8. After using the spray, wipe the spray head with a clean cloth and install the dust cover.

CLEANING THE SPRAY

• You should clean your nasal spray at least once a week.
• Remove the dust cover and then pull the spray nozzle upwards to remove it.
• Wash the sprayer head and dust cover with lukewarm tap water. Allow to dry at room temperature, then place the spray head and dust cover back on the bottle.
• If the spray head is clogged, you can remove it as above and soak in lukewarm water. Rinse with cold tap water, dry and replace.

Unused products or waste materials should be disposed of in accordance with the "Medical Waste Control Regulation" and "Packaging Waste Control Regulation".

7. MARKETING AUTHORISATION HOLDER

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8. MARKETING AUTHORISATION NUMBER

205/88 (in Turkey)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 08.06.2005 (in Turkey)
License renewal date:

10. DATE OF REVISION OF THE TEXT

02/12/2013