Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Bileni 137 micrograms / 50 micrograms per actuation, Nasal Spray Suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each g of suspension contains 1000 micrograms azelastine hydrochloride and 365 micrograms fluticasone propionate. One actuation (0.14 g) delivers 137 micrograms azelastine hydrochloride (= 125 micrograms azelastine) and 50 micrograms fluticasone propionate.

Excipient with known effect:
One actuation (0.14 g) delivers 0.014 mg benzalkonium chloride.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nasal spray, suspension.

White, homogeneous suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Relief of symptoms of moderate to severe seasonal and perennial allergic rhinitis if monotherapy with either intranasal antihistamine or glucocortocoid is not considered sufficient.

4.2 Posology and method of administration

Posology
For full therapeutic benefit regular usage is essential.

Contact with the eyes should be avoided.

Adults and adolescents (12 years and older)
One actuation in each nostril twice daily (morning and evening).

Children below 12 years
Bileni Nasal Spray is not recommended for use in children below 12 years of age as safety and efficacy has not been established in this age group.

Elderly
No dose adjustment is required in this population.

Renal and hepatic impairment
There are no data in patients with renal and hepatic impairment.

Duration of treatment
Bileni Nasal Spray is suitable for long-term use.
The duration of treatment should correspond to the period of allergenic exposure.

Method of administration
Bileni Nasal Spray is for nasal use only.

Instruction for use
Preparing the spray:

The bottle should be shaken gently before use for about 5 seconds by tilting it upwards and downwards and the protective cap be removed afterwards. Prior to first use Bileni Nasal Spray must be primed by pressing down and releasing the pump 6 times. If Bileni Nasal Spray has not been used for more than 7 days it must be reprimed once by pressing down and releasing the pump.

Using the spray:
The bottle should be shaken gently before use for about 5 seconds by tilting it upwards and downwards and the protective cap be removed afterwards.
After blowing the nose the suspension is to be sprayed once into each nostril keeping the head tilted downward (see figure). After use the spray tip is to be wiped and the protective cap to be replaced.



4.3 Contraindications

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

4.4 Special warnings and precautions for use

During post-marketing use, there have been reports of clinically significant drug interactions in patients receiving fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side-effects (see section 4.5).

Systemic effects of nasal corticosteroids may occur, particularly when prescribed at high doses for prolonged periods. These effects are much less likely to occur than with oral corticosteroids and may vary in individual patients and between different corticosteroid preparations. Potential systemic effects may include Cushing's syndrome, Cushingoid features, adrenal suppression, growth retardation in children and adolescents, cataract, glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children).

Bileni Nasal Spray undergoes extensive first-pass metabolism, therefore the systemic exposure of intranasal fluticasone propionate in patients with severe liver disease is likely to be increased. This may result in a higher frequency of systemic adverse events.
Caution is advised when treating these patients.

Treatment with higher than recommended doses of nasal corticosteroids may result in clinically significant adrenal suppression. If there is evidence for higher than recommended doses being used, then additional systemic corticosteroid cover should be considered during periods of stress or elective surgery.

In general the dose of intranasal fluticasone formulations should be reduced to the lowest dose at which effective control of the symptoms of rhinitis is maintained. Higher doses than the recommended one (see section 4.2) have not been tested for Bileni. As with all intranasal corticosteroids, the total systemic burden of corticosteroids should be considered whenever other forms of corticosteroid treatment are prescribed concurrently.

Growth retardation has been reported in children receiving nasal corticosteroids at licensed doses. Since growing up is also given in adolescents it is recommended that the growth of adolescents receiving prolonged treatment with nasal corticosteroids is regularly monitored, too. If growth is slowed, therapy should be reviewed with the aim of reducing the dose of nasal corticosteroid if possible, to the lowest dose at which effective control of symptoms is maintained.

Close monitoring is warranted in patients with a change in vision or with a history of increased ocular pressure, glaucoma and/or cataracts.

If there is any reason to believe that adrenal function is impaired, care must be taken when transferring patients from systemic steroid treatment to Bileni Nasal Spray.

In patients who have tuberculosis, any type of untreated infection, or have had a recent surgical operation or injury to the nose or mouth, the possible benefits of the treatment with Bileni Nasal Spray should be weighed against possible risk.

Infections of the nasal airways should be treated with antibacterial or antimycotical therapy, but do not constitute a specific contraindication to treatment with Bileni Nasal Spray.

Bileni contains benzalkonium chloride. It may cause irritation of the nasal mucosa and bronchospasm.

4.5 Interaction with other medicinal products and other forms of interaction

Fluticasone propionate

Under normal circumstances, low plasma concentrations of fluticasone propionate are achieved after intranasal dosing, due to extensive first pass metabolism and high systemic clearance mediated by cytochrome P450 3A4 in the gut and liver. Hence, clinically significant drug interactions mediated by fluticasone propionate are unlikely.

A drug interaction study in healthy subjects has shown that ritonavir (a highly potent cytochrome P450 3A4 inhibitor) can greatly increase fluticasone propionate plasma concentrations, resulting in markedly reduced serum cortisol concentrations. During postmarketing use, there have been reports of clinically significant drug interactions in patients receiving intranasal or inhaled fluticasone propionate and ritonavir, resulting in systemic corticosteroid effects including Cushing's syndrome and adrenal suppression. Therefore, concomitant use of fluticasone propionate and ritonavir should be avoided, unless the potential benefit to the patient outweighs the risk of systemic corticosteroid side effects.

Studies have shown that other inhibitors of cytochrome P450 3A4 produce negligible (erythromycin) and minor (ketoconazole) increases in systemic exposure to fluticasone propionate without notable reductions in serum cortisol concentrations. Nevertheless, care is advised when co-administering potent cytochrome P450 3A4 inhibitors (e.g. ketoconazole), as there is potential for increased systemic exposure to fluticasone propionate.

Azelastine hydrochloride

No specific interaction studies with azelastine hydrochloride nasal spray have been performed. Interaction studies at high oral doses have been performed. However, they bear no relevance to azelastine nasal spray as given recommended nasal doses result in much lower systemic exposure. Nevertheless, care should be taken when administering azelastine hydrochloride in patients taking concurrent sedative or central nervous medications because sedative effect may be enhanced. Alcohol may also enhance this effect (see section 4.7).

4.6 Fertility, pregnancy and lactation

Fertility
There are only limited data with regard to fertility (see section 5.3).

Pregnancy
There are no or limited amount of data from the use of azelastine hydrochloride and fluticasone propionate in pregnant women. Therefore, Bileni Nasal Spray should be used during pregnancy only if the potential benefit justifies the potential risk to the foetus (see section 5.3)

Lactation
It is unknown whether nasally administered azelastine hydrochloride/metabolites or fluticasone propionate/metabolites are excreted in human breast milk. Bileni Nasal Spray should be used during lactation only if the potential benefit justifies the potential risk to the newborns/infant (see section 5.3).

4.7 Effects on ability to drive and use machines

Bileni Nasal Spray has minor influence on the ability to drive and use machines.

In isolated cases fatigue, weariness, exhaustion, dizziness or weakness that may also be caused by the disease itself, may occur when using Bileni Nasal Spray. In these cases, the ability to drive and use machines may be impaired. Alcohol may enhance this effect.

4.8 Undesirable effects

Commonly, dysgeusia, a substance-specific unpleasant taste, may be experienced after administration (often due to incorrect method of application, namely tilting the head too far backwards during administration).

Adverse reactions are listed below by system organ class and frequency. Frequencies are defined as:

Very common	(≥1/10)
Common	(≥1/100 to <1/10)
Uncommon	(≥1/1,000 to <1/100)
Rare	(≥1/10,000 to <1/1,000)
Very rare	(<1/10,000)
Not known	(cannot be estimated from the available data)

Frequency **System Organ Class**	***Very common***	***Common***	***Uncommon***	***Rare***	***Very rare***
Immune system disorders					Hypersensitivity including anaphylactic reactions, angioedema (oedema of the face or tongue and skin rash), bronchospasm
Nervous system disorder		Headache, Dysgeusia (unpleasant taste), unpleasant smell			Dizziness, somnolence (drowsiness, sleepiness)

Eye disorders*					Glaucoma, increased intraocular pressure, cataract
Respiratory, thoracic and mediastinal disorders	Epistaxis		Nasal discomfort (including nasal irritation, stinging, itching), sneezing, nasal dryness, cough, dry throat, throat irritation		Nasal septal perforation**, mucosal erosion
Gastrointestinal disorders				Dry mouth	Nausea
Skin and subcutaneous tissue disorders					Rash, pruritus, urticaria
General disorders and administration site conditions					Fatigue (weariness, exhaustion), weakness (see section 4.7)

***** A very small number of spontaneous reports have been identified following prolonged treatment with intranasal fluticasone propionate.

** Nasal septal perforation has been reported following the use of intranasal corticosteroids.

Systemic effects of some nasal corticosteroids may occur, particularly when administered at high doses for prolonged periods (see section 4.4).

Growth retardation has been reported in children receiving nasal corticosteroids. Growth retardation may be possible in adolescents, too (see section 4.4).

In rare cases osteoporosis was observed, if nasal glucocorticoids were administered long-term.

4.9 Overdose

With the nasal route of administration overdose reactions are not anticipated.

There are no data from patients available on the effects of acute or chronic overdosage with intranasal fluticasone propionate.

Intranasal administration of 2 milligrams fluticasone propionate (10 times the recommended daily dose) twice daily for seven days to healthy human volunteers has no effect on hypothalamo-pituitary-adrenal (HPA) axis function.

Administration of doses higher than those recommended over a long period of time may lead to temporary suppression of adrenal function.
In these patients, treatment with Bileni Nasal Spray should be continued at a dose sufficient to control symptoms; the adrenal function will recover in a few days and can be verified by measuring plasma cortisol.

In the event of overdose after incidental oral uptake, disturbances of the central nervous system (including drowsiness, confusion, coma, tachycardia and hypotension) caused by azelastine hydrochloride are to be expected based on the results of animal experiments.

Treatment of these disorders must be symptomatic. Depending on the amount swallowed, gastric lavage is

recommended. There is no known antidote.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Decongestants and other nasal preparations for topical use, corticosteroids/ fluticasone, combinations, ATC code: R01AD58.

Mechanism of action and pharmacodynamic effects
Bileni Nasal Spray contains azelastine hydrochloride and fluticasone propionate, which have different modes of action and show synergistic effects in terms of improvement of allergic rhinitis and rhino-conjunctivitis symptoms.

Fluticasone propionate
Fluticasone propionate is a synthetic trifluorinated corticosteroid that possesses a very high affinity for the glucocorticoid receptor and has a potent anti-inflammatory action, e.g. 3-5 fold more potent than dexamethasone in cloned human glucocorticoid receptor binding and gene expression assays.

Azelastine hydrochloride
Azelastine, a phthalazinone derivative is classified as a potent long-acting anti-allergic compound with selective H_1-antagonist, mast cell stabilizing and anti-inflammatory properties. Data from *in vivo* (preclinical) and *in vitro* studies show that azelastine inhibits the synthesis or release of the chemical mediators known to be involved in early and late stage allergic reactions, e.g. leukotrienes, histamine, platelet-activating factor (PAF) and serotonin.
A relief of nasal allergic symptoms is observed within 15 minutes after administration.

Bileni Nasal Spray
In 4 clinical studies in adults and adolescents with allergic rhinitis Bileni Nasal Spray one spray in each nostril twice daily significantly improved nasal symptoms (comprising rhinorrhoea, nasal congestion, sneezing and nasal itching) compared with placebo, azelastine hydrochloride alone and fluticasone propionate alone. It significantly improved ocular symptoms (comprising itching, tearing/watering and redness of the eyes) and the patients' disease-related quality of life (Rhinoconjunctivitis Quality of Life Questionnaire – RQLQ) in all 4 studies.

In comparison to a marketed fluticasone propionate nasal spray substantial symptom improvement (50% reduction in nasal symptoms severity) was achieved significantly earlier (3 days and more) with Bileni Nasal Spray. The superior effect of Bileni Nasal Spray to fluticasone propionate nasal spray was maintained throughout one-year study in patients with chronic persistent allergic rhinitis and nonallergic/vasomotor rhinitis.

5.2 Pharmacokinetic properties

Absorption
After intranasal administration of two sprays per nostril (548 mcg of azelastine hydrochloride and 200 mcg of fluticasone) of Bileni Nasal Spray, the mean (± standard deviation) peak plasma exposure (C_{max}) was 194.5 ± 74.4 pg/mL for azelastine and 10.3 ± 3.9 pg/mL for fluticasone propionate and the mean total exposure (AUC) was 4217 ± 2618 pg/mL*hr for azelastine and 97.7 ± 43.1 pg/mL*hr for fluticasone. The median time to peak exposure (t_{max}) from a single dose was 0.5 hours for azelastine and 1.0 hours for fluticasone.

Fluticasone systemic exposure was ~50% increased comparing Bileni Nasal Spray with a marketed fluticasone nasal spray. Bileni Nasal Spray was equivalent to a marketed azelastine nasal spray with respect to azelastine systemic exposure. There was no evidence of pharmacokinetic interactions between azelastine hydrochloride and fluticasone propionate.

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

The volume of distribution of azelastine is high indicating distribution predominantly into the peripheral tissue. The level of protein binding is 80-90%. Additionally, both drugs have broad therapeutic windows. Therefore, drug displacement reactions are unlikely.

Biotransformation
Fluticasone propionate is cleared rapidly from the systemic circulation, principally by hepatic metabolism to an inactive carboxylic acid metabolite, by the cytochrome P450 enzyme CYP3A4. Swallowed fluticasone propionate is also subject to extensive first pass metabolism. Azelastine is metabolized to *N*-desmethylazelastine via various CYP isoenzymes, mainly CYP3A4, CYP2D6 and CYP2C19.

Elimination
The elimination rate of intravenous administered fluticasone propionate is linear over the 250—1000 microgram dose range and are characterised by a high plasma clearance (CL=1.1 l/min). Peak plasma concentrations are reduced by approximately 98% within 3-4 hours and only low plasma concentrations were associated with the 7.8 h 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. Plasma elimination half-lives after a single dose of azelastine are approximately 20-25 hours for azelastine and about 45 hours for the therapeutically active metabolite *N*-desmethylazelastine. Excretion occurs mainly via the faeces. The sustained excretion of small amounts of the dose in the faeces suggests that some enterohepatic circulation may take place.

5.3 Preclinical safety data

Fluticasone propionate
Findings in general toxicology studies were similar to those observed with other glucocorticoids and are associated with exaggerated pharmacological activity. These findings are not likely to be relevant for humans given recommended nasal doses which results in minimal systemic exposure. No genotoxic effects of fluticasone propionate have been observed in conventional genotoxicity tests. Further, there were no treatment-related increases in the incidence of tumours in two year inhalation studies in rats and mice.
In animal studies glucocorticoids have been shown to induce malformations including cleft palate and intra-uterine growth retardation. Again this is not likely to be relevant for humans given recommended nasal doses which results in minimal systemic exposure (see section 5.2).

Azelastine hydrochloride
Azelastine hydrochloride displayed no sensitising potential in the guinea pig. Azelastine demonstrated no genotoxic potential in a battery of in vitro and in vivo tests, nor any carcinogenic potential in rats or mice. In male and female rats, azelastine at oral doses greater than 3 mg/kg/day caused a dose-related decrease in the fertility index; no substance-related alterations were found in the reproductive organs of males or females during chronic toxicity studies, however, embryotoxic and teratogenic effects in rats, mice and rabbits occurred only at maternal toxic doses (for example, skeletal malformations were observed in rats and mice at doses of 68.6 mg/kg/day).

Bileni Nasal Spray
Repeated dose intranasal toxicity studies in rats for a period up to 90 days and in dogs for 14 days with Bileni Nasal Spray revealed no new adverse effects in comparison to the individual components.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Disodium edetate
Glycerol
Microcrystalline cellulose
Carmellose sodium
Polysorbate 80
Benzalkonium chloride
Phenylethyl alcohol

Purified water

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

In-use shelf life (after first use): 6 months

6.4 Special precautions for storage

Do not refrigerate or freeze.

6.5 Nature and contents of container

Type I amber glass bottle fitted with a spray pump, a nasal polypropylene applicator (actuator) and a dust cap, containing 6.4 g (at least 28 actuations) and 23 g (at least 120 actuations) suspension.

Pack sizes:
1 bottle with 6.4 g suspension in 10 ml bottles (at least 28 actuations), 1 bottle with 23 g suspension in 25 ml bottles (at least 120 actuations)
Multipacks containing 64 g (10 bottles with 6.4 g) nasal spray, suspension Multipacks containing 69 g (3 bottles with 23 g) nasal spray, suspension

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

No special requirements for disposal.

7 MARKETING AUTHORISATION HOLDER

Meda Health Sales Ireland Limited
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8 MARKETING AUTHORISATION NUMBER

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10 DATE OF REVISION OF THE TEXT