Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Beclospin 400 micrograms/1 ml nebuliser suspension

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 ml single dose unit contains 400 micrograms beclometasone dipropionate anhydrous.

For a full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser suspension.
A white or almost white suspension.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

BECLOSPIN® is indicated for the:

- maintenance treatment of asthma, when the use of pressurised metered dose or dry powder inhalers is unsatisfactory or inappropriate, in adults and children up to 18 years of age;
- treatment of recurrent wheezing in children up to 5 years of age (see sections 4.2 and 4.4 paediatric population).

4.2 Posology and method of administration

The starting dose of nebulised beclometasone dipropionate should take into account the frequency and severity of symptoms.

The recommended initial doses are:

Adults and adolescents (from 12 years of age) :	800-1,600 micrograms twice daily (total daily dose: 1600 – 3200 micrograms)
Children (up 11 years of age):	400-800 micrograms twice daily (total daily dose: 800 – 1600 micrograms)

Normally, a daily dose of 3200 micrograms in adults and adolescents and 1600 micrograms in children up to 11 years of age should not be exceeded.

After improvement of control of asthma or wheezing, the total daily dose should be reduced to the lowest effective dose and a once daily dosing can be applied.

In patients with asthma, BECLOSPIN® must be used regularly on a daily basis; the duration of treatment should be defined on the basis of symptoms.

In children with recurrent wheezing, if no treatment benefit of is observed within 2-3 months, BECLOSPIN® should be discontinued. In addition, the duration of treatment of recurrent wheezing should not exceed 3 months, unless diagnosis of asthma is likely to avoid an unnecessary long-term exposure (see section 4.4).

Method of administration

For inhalation use only. BECLOSPIN® should not be injected or administered orally.

BECLOSPIN® should be administered preferably via jet nebuliser and the compressor equipped with the mouthpiece or suitable face mask.

Patients should be advised to carefully follow the manufacturer's instructions for the nebulizer device and should only use the settings recommended. Incorrect use of the nebuliser device could lead to incorrect dosing of the medicinal product.

Use of BECLOSPIN® with ultrasonic nebulisers is not recommended because it doesn't allow a correct administration of the medicinal product.

For instruction on preparation and dilution of the medicinal product, see section 6.6.

After inhaling the prescribed dose patients should rinse their mouth with water to minimise the risk of oropharyngeal thrush (see section 4.4).

4.3 Contraindications

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

4.4 Special warnings and precautions for use

The management of asthma should normally follow a stepwise programme and patient response should be monitored clinically and by lung function tests.

BECLOSPIN® is not indicated to relieve acute asthma symptoms for which an inhaled short-acting beta 2-agonists is required. Patients should be advised to have such relief medicinal product readily available.
Increasing use of bronchodilators, in particular short-acting inhaled beta 2-agonists to relieve symptoms indicates deterioration of asthma control. If patients find that short-acting relief bronchodilator treatment becomes less effective or they need more inhalations than usual, medical attention must be sought. In this situation patients should be reassessed and consideration given to the need for increased anti-inflammatory therapy (e.g. higher doses of inhaled corticosteroids or a course of oral corticosteroids).
Severe exacerbations of asthma must be treated in the normal way, e.g. by increasing the dose of inhaled beclometasone dipropionate and, if necessary, by giving a systemic steroid, and/or an antibiotic if appropriate, and by use of beta 2-agonist therapy.

Systemic effects may occur with any inhaled corticosteroid, particularly at high doses administered for long periods of time. These effects are much less likely to occur than with oral corticosteroids. Possible systemic effects include hypothalamic-pituitary-adrenal (HPA)-axis suppression, growth retardation in children and adolescents, decrease in bone mineral density, cataract and glaucoma and more rarely, a range of psychological or behavioural effects including psychomotor hyperactivity, sleep disorders, anxiety, depression or aggression (particularly in children). It is important, therefore, that the patient is reviewed regularly and the dose of inhaled corticosteroid is reduced to the lowest dose at which effective control of disease is maintained.
BECLOSPIN®
Some patients feel unwell for approximately 2 weeks during the withdrawal of treatment with systemic corticosteroids, even though their respiratory function remains the same or even improves. Such patients should be encouraged to continue treatment with beclometasone dipropionate by inhalation and withdrawal of the systemic corticosteroid, unless objective clinical signs of adrenal impairment are present.

The switch to BECLOSPIN® of patients who have been treated with systemic steroids for long periods of time, or at a high dose, needs special care, since recovery from any adrenocortical suppression sustained may take a considerable time. In any case, beclometasone dipropionate should be administered without discontinuing the systemic treatment; after approximately one week, the latter should be gradually reduced (the size of the reduction should correspond to the

maintenance dose of the systemic steroid), patient should be checked at regular intervals (in particular, adrenocortical function tests should be carried out) and dose of inhaled beclometsone dipropionate should be adjusted according to the results obtained.

Special care is necessary in patients with active or quiescent pulmonary tuberculosis and other infections. Patients suffering from tuberculosis should receive tuberculostatic therapy while being treated with beclometasone propionate.

Special care is needed in patients with viral, bacterial and fungal infections of the eye or of the mouth or respiratory tract. In case of bacterial infection of the respiratory tract an adequate antibiotic co-medication may be required.

The incidence of candidiasis seems to be related to the administered dose and treatment duration. This affection generally responds to a suitable topical antimycotic therapy, without discontinuing the treatment with beclometasone dipropionate.
It must be recommended that patients rinse their mouth with water immediately after inhalation to reduce the frequency of oral candidiasis.

Hoarseness is reversible and disappears after discontinuation of treatment and / or rest of the voice.

Paradoxical bronchospasm may occur with an immediate increase in wheezing, shortness of breath and cough after dosing. This should be treated immediately with a fast-acting inhaled bronchodilator. BECLOSPIN® should be discontinued immediately, the patient assessed and, if necessary, alternative therapy instituted.

Reduction or withdrawal of oral corticosteroid therapy may unmask clinical features of Churg-Strauss syndrome and hyper eosinophilic state.

Replacement of systemic steroid treatment with inhaled therapy sometimes also unmasks allergies such as allergic rhinitis or eczema previously controlled by the systemic medicinal product. These allergies should be symptomatically treated with antihistamines and/or topical medicinal product, including steroids for local use.

Visual disturbance
Visual disturbance may be reported with systemic and topical corticosteroid use. If a patient presents with symptoms such as blurred vision or other visual disturbances, the patient should be considered for referral to an ophthalmologist for evaluation of possible causes which may include cataract, glaucoma or rare diseases such as central serous chorioretinopathy (CSCR) which have been reported after use of systemic and topical corticosteroids.

Paediatric population
The decision to start nebulised beclometasone dipropionate for treatment of recurrent wheezing in children up to 5 years of age should be determined by the severity and frequency of wheezing episodes. Regular follow-up is essential to review the treatment response. If no treatment benefit is observed within 2-3 months or if a diagnosis of asthma is not likely, BECLOSPIN® should be discontinued to avoid unnecessary long-term exposure to inhaled corticosteroids and associated risks in children including growth retardation (see section 4.8).

It is recommended that the height of children receiving prolonged treatment with inhaled corticosteroids is regularly monitored. If growth impairment occurs, the treatment should be assessed with the aim of reducing the dose of inhaled corticosteroid. The benefits of the corticosteroid treatment and the possible risks on the growth suppression must be carefully weighed against one another. Consideration can be given to referring the patient to paediatric pulmonologist.
There is insufficient data available regarding the possible growth-inhibiting effect of inhaled corticosteroids in infants and toddlers less than 2 years.

4.5 Interaction with other medicinal products and other forms of interaction

Pharmacokinetic interactions
No formal pharmacokinetic drug-drug interaction studies have been conducted.
Beclometasone dipropionate undergoes a very rapid pre-systemic metabolism via esterase enzymes without involvement of cytochrome P450 system.

Beclomethasone is less dependent on CYP3A metabolism than some other corticosteroids, and in general interactions are unlikely; however the possibility of systemic effects with concomitant use of strong CYP3A inhibitors (e.g. ritonavir, cobicistat) cannot be excluded, and therefore caution and appropriate monitoring is advised with the use of such agents.

Pharmacodynamic interactions
If used concomitantly with systemic or intranasal steroids the suppressive effect on adrenal function will be additive.

4.6 Fertility, pregnancy and lactation

Pregnancy
No evidence of teratogenic effects in pregnant women using inhaled beclometasone was observed according to published data. However, possible effects on foetal development after high dose inhaled beclometasone dipropionate therapy could not be excluded.

Animal studies have shown reproductive toxicity (see section 5.3).

The possible benefits of inhaled beclometasone dipropionate for the mother must be weighed against the possible risk for the fetus or neonate. If treatment during pregnancy is necessary, the lowest effective dose of beclometasone dipropionate should be used.
Infants and neonates born to mothers receiving substantial doses of beclometasone dipropionate during pregnancy should be observed for adrenal suppression.

Breast-feeding
Since glucocorticoids are excreted in breast-milk, it is reasonable to assume that beclometasone dipropionate and its metabolites are also excreted into breast milk. However, at therapeutic doses of beclometasone dipropionate no effect on the breastfed newborns/infants are anticipated.
No harmful effects on the suckling infants have been reported for glucocorticoids. The benefits of breast-feeding are likely to outweigh any theoretical risk.
Beclometasone dipropionate can be used during breast-feeding. However, if high dose inhaled beclometasone dipropionate is used it is recommended to avoid breast-feeding for 4 h after administration.

Fertility
No specific studies have been performed with beclometasone dipropionate with regard to the safety in human fertility. Although results of animal studies have shown some impaired fertility, this occurs at high doses levels.

4.7 Effects on ability to drive and use machines

BECLOSPIN® has no or negligible influence on the ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile
The most common adverse reactions observed during clinical trials using inhaled beclometasone in the treatment of asthma and wheezing were laryngitis, pharyngitis and oral candidiasis.
A serious hypersensitivity reaction including oedema of the eye, face, lips and throat (angioedema) has been reported rarely.
Paradoxical bronchospasm may occur after dosing.

Tabulated list of adverse reactions
Adverse reactions observed in clinical trials with inhaled beclometasone in the treatment of asthma and wheezing are listed in the table below according the MedDRA system organ class and frequencies: 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).

System Organ Class	Adverse Reaction	Frequency
Infections and infestations	Laryngitis, pharyngitis	Very common
	Oral candidiasis	Common
	Herpes simplex	*Rare
Endocrine disorders	Adrenal suppression**	Very Rare
Immune system disorders	Hypersensitivity reactions with the following manifestations: angioedema, rash, urticaria, pruritus,	*Rare
Psychiatric disorders	Psychomotor hyperactivity, sleep disorders anxiety, depression, aggressiveness, behavioural changes (predominantly in children)	Not known
Nervous system disorders	Headache	Uncommon
	Tremor	*Rare
Eye disorders	Cataract**, glaucoma**	Very Rare
	Vision, blurred (see also section 4.4)	Uncommon
Respiratory, thoracic and mediastinal disorders	Cough	Common
	Throat irritation, hoarseness, dysphonia, paradoxical bronchospasm, wheezing	Uncommon
	Dyspnoea	*Rare
Gastrointestinal disorders	Nausea, dyspepsia	Common
Musculoskeletal and connective tissue disorders	Growth retardation* (in children and adolescents), bone density decreased*	Very rare
General disorders and administration site conditions	Asthenia	*Rare

* from spontaneous reporting

**systemic effects of inhaled corticosteroids

Description of selected adverse reactions
Systemic effect of inhaled corticosteroids (including beclometasone dipropionate) may occur particularly when administered at high doses for prolonged periods of time: these may include adrenal suppression, decrease in bone mineral density, growth retardation in children and adolescents, cataract and glaucoma (see section 4.4).

Measures to minimize the occurrence of candidiasis, hoarseness and paradoxical bronchospasm are described in section 4.4.

Paediatric population
Growth retardation and behavioural disorders may be more prevalent in children than in adults, particularly at high doses administered for prolonged periods of time.

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 HPRA Pharmacovigilance, Earlsfort Terrace, IRL - Dublin 2; Tel: +353 1 6764971; Fax: +353 1 6762517. Website: http://www.hpra.ie/; E-mail: medsafety@hpra.ie.

4.9 Overdose

The use of beclometasone dipropionate nebuliser suspension in doses exceeding those recommended over a long period of time could lead to the suppression of hypothalamic-pituitary-adrenal (HPA)-axis function. In this case monitoring of adrenal function is recommended. Patients with adrenal suppression are steroid dependent and have to be treated accordingly with supplementary systemic glucocorticosteroids. Treatment with BECLOSPIN® may continue at the lowest dose at which effective control of disease (asthma or wheezing) is maintained (see section 4.4).

With high doses for a very short period of time, suppression of HPA-axis may occur. In these cases no special emergency action needs to be taken. The HPA-axis function will recover within 1-2 days.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Other drugs for obstructive airway diseases, inhalants; Glucocorticoids
ATC code: R03 BA01.

Mechanism of action
The affinity of beclometasone dipropionate and its main active metabolite, beclometasone monopropionate (B17MP), for the human glucocorticoid receptor has been determined. The potency of B17MP is approximately 30-fold higher than the parent compound. Therefore the majority of the effect is related to B17MP systemic exposure.

Pharmacodynamic effects
Beclometasone dipropionate is a glucocorticoid with potent anti-inflammatory activity with limited mineralocorticoid activity; following administration to the respiratory system by inhalation a local effect in the lower respiratory tract is obtained. The systemic pharmacodynamic effects of beclometasone dipropionate and its active metabolite B17MP is assessed by measuring the effects on hypothalamo-pituitary adrenal (HPA)-axis function.
In healthy males a single dose of 1600 µg beclometasone dipropionate by nebulisation had no effect on 24-h urinary cortisol excretion, while a single dose of 3200 µg produced a urinary cortisol excretion reduction of about 10% without any significant differences between the two dosage treatments.
No significant effect on morning serum cortisol levels was reported in asthmatic patients after a 3-week treatment period of 1600 and 3200 µg per day b.i.d. via a nebulizer.

Clinical efficacy and safety
Besides evidence coming from long lasting use of inhaled beclometasone in the treatment of asthma and wheezing, the following data are a collection of the main supportive published data.

Asthma
A study in which the objective was to compare the efficacy and safety of nebulised beclometasone dipropionate versus fluticasone propionate suspension for nebulization was conducted in 205 adults patients aged 18-65 years with asthma randomized to a 12-week treatment period. Comparable efficacy in controlling asthma was demonstrated by the two treatments at study end in terms of pulmonary function tests, asthma exacerbations, symptoms and the use of rescue salbutamol (Terzano et al., 2003).

Paediatric population
Asthma
A double-blind, double-dummy, multicentre, randomized, parallel-group study compared the efficacy and safety of nebulised beclometasone dipropionate and beclometasone dipropionate administered with metered-dose inhalation in 151 patients, aged 6-16 years, with moderate to severe asthma for 4 weeks. Comparable improvements over baseline were reported at study end for the two treatment groups in morning pulmonary expiratory flow rate (primary endpoint), clinical symptoms scores and the use of rescue salbutamol. The two treatments were equally well tolerated (Bisca et al., 2003).

Efficacy and safety of nebulised beclometasone dipropionate in the treatment of severe persistent asthma in infants and young children aged 6 months to 6 years, in comparison to budesonide suspension for nebulization was assessed in a multicentre, randomized, controlled open-labelled study for 14 weeks. In the study 40.4% and 51.7% patients in the of nebulised beclometasone dipropionate and budesonide groups respectively did not experience any major exacerbation (primary endpoint). Both treatments were associated with a marked reduction in night-time wheezing and in the number of days of steroid use. Urinary cortisol and the time course of height and weight were unaffected by both treatments and of nebulised beclometasone dipropionate confirmed to have a neutral effect on bone metabolism (Delacourt et al., 2003).

Wheezing
Nebulised beclometasone dipropionate was evaluated in 276 children aged 1-4 years with frequent wheezing in a randomized, double-blind, 12-week controlled trial. Regular nebulised beclometasone dipropionate plus rescue salbutamol significantly increased the percentage of symptom-free days (primary endpoint, defined as a lack of wheezing, coughing, shortness of breath and patients/parents nocturnal awakenings in 24 h) (69.6 ± 20.89 [SD]; P = 0.034) vs placebo/rescue salbutamol (61.0 ± 24.83 [SD]) but not vs combination nebulised beclometasone dipropionate /rescue salbutamol (64.9 ± 24.74 [SD]) regardless of the presence of risk factors for developing asthma. In addition, the time to first exacerbation was longer in children treated with nebulised beclometasone dipropionate. In terms of safety, no change in the values of morning salivary cortisol was detected (Papi et al., 2009).

5.2 Pharmacokinetic properties

Beclometasone dipropionate (BDP) is a pro-drug that is hydrolysed via esterase enzymes to an active metabolite beclometasone monopropionate (B17MP) the most abundant metabolite in plasma.

Absorption
Following inhalation, systemic absorption of unchanged BDP occurs mainly through the lungs with negligible oral absorption of the swallowed dose. The systemic absorption of the main active metabolite B17MP arises from both lung deposition and oral absorption of the swallowed dose. The bioavailability of orally administered BDP is negligible but pre-systemic conversion to B17MP results in absorption of approximately 40% of the swallowed portion as B17MP. The absolute bioavailability following inhalation is approximately 2% and 62% of the nominal dose for BDP and B17MP respectively.

Distribution
Plasma protein binding is moderately high. Following intravenous dosing, the disposition of BDP and its active metabolite, B17MP, are characterised by high plasma clearance (150 and 120 L/h respectively), with a small volume of distribution at steady state for BDP (20 L) and larger tissue distribution for its active metabolite (424 L).

Biotransformation
The main product of metabolism is the active metabolite (B17MP). Minor inactive metabolites, beclometasone-21-monopropionate (B21MP) and beclometasone (BOH), are also formed but these contribute little to the systemic exposure.

Elimination
BDP is cleared very rapidly from the systemic circulation, by metabolism mediated via esterase enzymes that are found in most tissues. The renal excretion of BDP and its metabolites is negligible, faecal excretion is the major route of BDP elimination mainly as polar metabolites. The terminal elimination half-lives are 0.5 h and 2.7 h for BDP and B17MP respectively.

Linearity/non-linearity
There is an approximately linear increase in systemic exposure of the active metabolite B17MP with increasing inhaled dose.

Special populations
The pharmacokinetics of BDP in patients with renal or hepatic impairment has not been studied; however, as BDP undergoes a very rapid metabolism via esterase enzymes present in intestinal fluids, serum, lungs and liver to originate more polar products B21MP, B17MP and BOH, hepatic impairment is not expected to modify the pharmacokinetics and safety profile of BDP. As BDP or its metabolites were not traced in urine, an increase in systemic exposure is not envisaged in patients with renal impairment.

5.3 Preclinical safety data

Preclinical toxic effects of beclometasone dipropionate were confined to those associated with over-stimulation of the recognised pharmacological action.
In repeat-dose toxicity studies, administration of beclometasone dipropionate by nebulisation to rats (for 180 days) and dogs (for 90 days) had no effect on body weight and blood cells or on trophism of the airways mucosa. Hepatic and renal functions remained within normal values.

Beclometasone was teratogenic and embryolethal in animals after, subcutaneous and oral administration. Animal studies indicate that administration of glucocorticoids during pregnancy may increase the risk for intrauterine growth retardation, adult cardiovascular and/or metabolic disease and/or neurobehavioral development.

Beclometasone dipropionate demonstrated to be non-genotoxic.

No evidence of carcinogenicity was observed in a 95-week study in rats treated by inhalation.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Polysorbate 20
Sorbitan laurate
Sodium chloride
Purified water

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

2 years.

Use the ampoules within 3 months from the first opening of the pouch.

For 800 micrograms ampoule only: after the first opening of the ampoule, store it in a refrigerator (2°C – 8°C). The remaining quantity has to be used within 12 hours after first opening.

6.4 Special precautions for storage

Store the ampoules in the upright position in the original package (carton box) in order to protect from light.

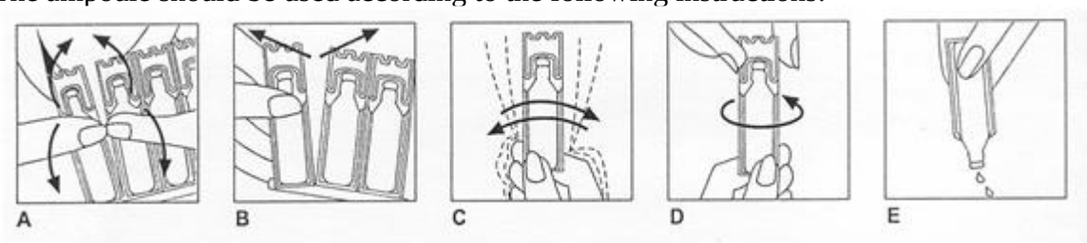
6.5 Nature and contents of container

Each polyethylene ampoule contains 400 micrograms beclometasone dipropionate suspension in 1 ml.

The 800 micrograms ampoule has a graduation mark to indicate half the content (corresponding to 400 micrograms).
Strips of 5 ampoules are packed in a heat sealed pouch of PET/Al/PE (Polyethylene Terephthalate/Aluminium/Polyethylene).
2, 4 or 8 pouches are packed into a carton, i.e. each carton contains 10, 20 or 40 ampoules.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

The ampoule should be used according to the following instructions:



1. Bend the ampoule backwards and forwards (Figure A).
2. Carefully separate a new ampoule from the strip, firstly from the top, then in the middle (Figure B), leaving the rest in the pouch.
3. Vigorously shake and turn the ampoule upside-down in order to make the suspension homogeneous. Repeat this operation, until the whole content is fully re-dispersed and mixed (Figure C).
4. Open the ampoule by rotating the flap as indicated by the arrow (Figure D).
5. Gently squeeze the ampoule content into the nebuliser chamber (Figure E).

The ampoule should be opened immediately before administration.

400 micrograms ampoule is for single use.

If only half dose of BECLOSPIN® 800 micrograms is needed hold the ampoule upside down, ensuring that the graduation mark is clearly visible and apply moderate pressure. Carefully squeeze out the content until the level of suspension in the ampoule reaches the graduation mark and no further. Once half the content is used, reinsert the cap upside down by pushing it onto the container. The ampoule closed in this way must be stored at 2-8◦C (in the refrigerator) and the remaining quantity has to be used within 12 hours after first opening.

BECLOSPIN® can be diluted. In this case, the content of the ampoule should be emptied into the nebuliser bowl. The quantity of sterile sodium chloride 9 mg/ml (0.9%) solution required should be added. Once the nebuliser bowl cap is inserted, the nebuliser should be shaken gently to mix the content.
ONLY sterile sodium chloride 9 mg/ml (0.9%) solution should be used.

The manufacturer’s instructions for use, maintenance and cleaning of the nebuliser must be followed.

Any unused product or waste material should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Chiesi Farmaceutici S.p.A.
26/A Via Palermo, 43122 Parma
Italy

8 MARKETING AUTHORISATION NUMBER

PA0584/004/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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10 DATE OF REVISION OF THE TEXT

May 2018