Annex III

Product information

Note:

This product information is the outcome of the referral procedure to which this Commission decision relates.

The product information may be subsequently updated by the Member State competent authorities, in liaison with the reference Member State, as appropriate, in accordance with the procedures laid down in Chapter 4 of Title III of Directive 2001/83/EC.

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

CLENIL and associated names (see Annex I) 400 micrograms nebuliser suspension
CLENIL and associated names (see Annex I) 800 micrograms nebuliser suspension
[See Annex I - To be completed nationally]

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule contains 400 micrograms beclometasone dipropionate anhydrous in 1 ml.
Each ampoule contains 800 micrograms beclometasone dipropionate anhydrous in 2 ml.

For the 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

{INVENTED NAME} 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, {INVENTED NAME} 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, {INVENTED NAME} 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. {INVENTED NAME} should not be injected or administered orally.

{INVENTED NAME} 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 {INVENTED NAME} 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.

{INVENTED NAME} 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.
{INVENTED NAME}
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 {INVENTED NAME} 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. {INVENTED NAME} 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.

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, {INVENTED NAME} 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.

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

{INVENTED NAME} 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
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 the national reporting system listed in Appendix V.

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 {INVENTED NAME} 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
Water for injections

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

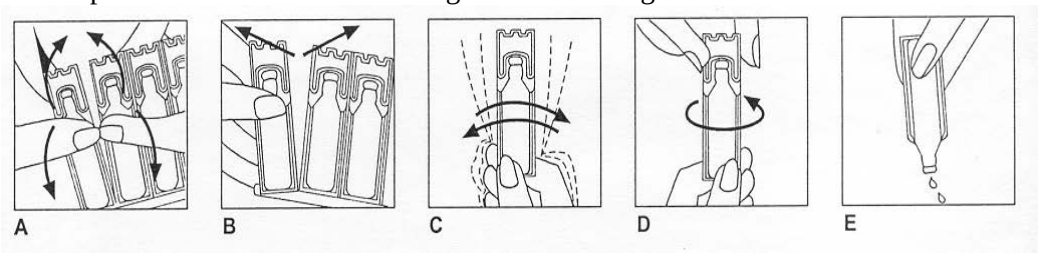
Store the ampoules in the upright position in the original package (carton box) in order to protect from light.

6.5 Nature and contents of container

Each polyethylene ampoule contains 400 micrograms beclometasone dipropionate suspension in 1 ml.
Each polyethylene ampoule contains 800 micrograms beclometasone dipropionate suspension in 2 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 {INVENTED NAME} 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.

{INVENTED NAME} 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 NUMBER(S)

[to be completed nationally]

8. MARKETING AUTHORISATION NUMBER(S)

[to be completed nationally]

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

[to be completed nationally]

10. DATE OF REVISION OF THE TEXT

[to be completed nationally]

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

CLENIL and associated names (see Annex I) 400 micrograms nebuliser suspension
[See Annex I - To be completed nationally]
beclometasone dipropionate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml ampoule contains 400 micrograms beclometasone dipropionate.

3. LIST OF EXCIPIENTS

Excipients: polysorbate 20, sorbitan laurate, sodium chloride, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Nebuliser suspension
10 ampoules
20 ampoules
40 ampoules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For inhalation use. {INVENTED NAME} should not be injected or administered orally.
Read the package leaflet before use.
For single use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp:

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

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[to be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[to be completed nationally]

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

{INVENTED NAME} 400 micrograms

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

PARTICULARS TO APPEAR ON THE OUTER PACKAGING
CARTON BOX

1. NAME OF THE MEDICINAL PRODUCT

CLENIL and associated names (see Annex I) 800 micrograms nebuliser suspension
[See Annex I - To be completed nationally]
beclometasone dipropionate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 2 ml ampoule contains 800 micrograms beclometasone dipropionate.

3. LIST OF EXCIPIENTS

Excipients: polysorbate 20, sorbitan laurate, sodium chloride, water for injections

4. PHARMACEUTICAL FORM AND CONTENTS

Nebuliser suspension
10 ampoules
20 ampoules
40 ampoules

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For inhalation use. {INVENTED NAME} should not be injected or administered orally.
Read the package leaflet before use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp:
Use the ampoules within 3 months from the first opening the pouch.
After the first opening of the ampoule, store in a refrigerator (2°C – 8°C). The remaining quantity has to be used within 12 hours after first opening.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[to be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[to be completed nationally]

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

{INVENTED NAME} 800 micrograms

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC: {number}
SN: {number}
NN: {number}

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING POUCH

1. NAME OF THE MEDICINAL PRODUCT

CLENIL and associated names (see Annex I) 400 micrograms nebuliser suspension
[See Annex I - To be completed nationally]
beclometasone dipropionate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 1 ml ampoule contains 400 micrograms beclometasone dipropionate.

3. LIST OF EXCIPIENTS

Excipients: polysorbate 20, sorbitan laurate, sodium chloride, water for injections

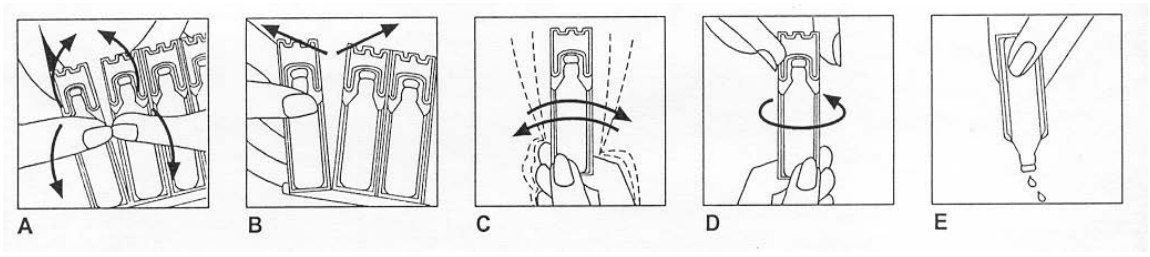
4. PHARMACEUTICAL FORM AND CONTENTS

Nebuliser suspension
5 ampoules containing 1 ml suspension each

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For inhalation use. {INVENTED NAME} should not be injected or administered orally.
Read the package leaflet before use.
For single use.

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.
Do not use with ultrasonic nebulisers.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp:

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

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[to be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[to be completed nationally]

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

PARTICULARS TO APPEAR ON THE INTERMEDIATE PACKAGING POUCH

1. NAME OF THE MEDICINAL PRODUCT

CLENIL and associated names (see Annex I) 800 micrograms nebuliser suspension
[See Annex I - To be completed nationally]
beclometasone dipropionate

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each 2 ml ampoule contains 800 micrograms beclometasone dipropionate.

3. LIST OF EXCIPIENTS

Excipients: polysorbate 20, sorbitan laurate, sodium chloride, water for injections

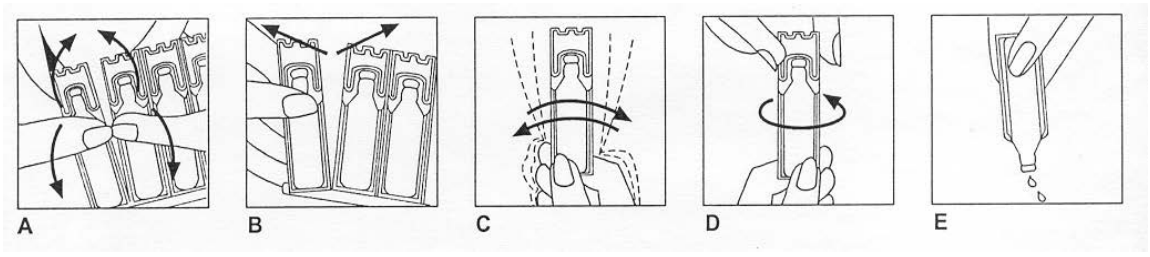
4. PHARMACEUTICAL FORM AND CONTENTS

Nebuliser suspension
5 ampoules containing 1 ml suspension each

5. METHOD AND ROUTE(S) OF ADMINISTRATION

For inhalation use. {INVENTED NAME} should not be injected or administered orally.
Read the package leaflet before use.

The unit dose 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). In order to obtain a half vial, pour the content into the nebuliser up to the half dose mark indicated on the sides of the vial.

The ampoule should be opened immediately before administration.
If only half dose of {INVENTED NAME} 800 micrograms is needed, reinsert the cap upside down by pushing it onto the vial. The vial closed in this way must be stored at 2-8°C (in the refrigerator) and pour

the content into the nebuliser up to the graduation mark indicated on the sides of the ampoule. The remaining quantity has to be used within 12 hours after first opening.

Do not use with ultrasonic nebulisers.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE REACH AND SIGHT OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

Exp:
Use the ampoules within 3 months from the first opening the pouch.
After the first opening of the ampoule, store it in a refrigerator (2–8°C). The remaining quantity has to be used within 12 hours after first opening.

9. SPECIAL STORAGE CONDITIONS

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

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

[to be completed nationally]

12. MARKETING AUTHORISATION NUMBER(S)

[to be completed nationally]

13. BATCH NUMBER

Batch:

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription.

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Ampoule

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

{INVENTED NAME} 400 mcg

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

Ampoule

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

{INVENTED NAME} 800 mcg

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

Exp

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

6. OTHER

B. PACKAGE LEAFLET

PACKAGE LEAFLET: INFORMATION FOR THE USER

CLENIL and associated names (see Annex I) 400 micrograms nebuliser suspension
CLENIL and associated names (see Annex I) 800 micrograms nebuliser suspension
[See Annex I - To be completed nationally]

Beclometasone dipropionate

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

In this leaflet:

1. WHAT {INVENTED NAME} IS AND WHAT IT IS USED FOR

{INVENTED NAME} contains the active substance beclometasone dipropionate. It belongs to a group of medicines called corticosteroids which have an anti-inflammatory action reducing the swelling and irritation in the walls of the airways (e.g. nose, lungs), and so ease breathing problems.

{INVENTED NAME} is indicated to treat asthma in adults and children up to 18 years of age when the use of pressurised or dry powder inhalers is unsatisfactory or inappropriate.
{INVENTED NAME} is also indicated to treat recurrent wheezing in children up to 5 years of age.

2. WHAT YOU NEED TO KNOW BEFORE YOU USE {INVENTED NAME}

Do not use {INVENTED NAME}:
- If you are allergic to the active substance or any of the other ingredients of this medicine listed in section 6.

Warnings and precautions
Talk to you doctor or pharmacist before using {INVENTED NAME} if any of the following applies to you:
- You are being, or have ever been, treated for tuberculosis (TB).
- Your condition seems to be getting worse. Perhaps you are more wheezy and short of breath than usual, or your nebuliser seems to be less effective.
- Your doctor may need to increase the dose of {INVENTED NAME} or give you a course of corticosteroid tablets, or change your treatment altogether.
- You have an infection in your chest. Your doctor may prescribe a course of antibiotics.
- If you have an infection of nasal and paranasal cavities you have to be treated with suitable therapies,

although this does not represent specific contraindication to the use of {INVENTED NAME}.

If you develop an immediate increase in wheezing, shortness of breath and cough after using {INVENTED NAME}, you should discontinued immediately {INVENTED NAME} and you should contact your doctor.

Immediately after inhalation the mouth should be rinsed with water to reduce the frequency of fungal infections in the mouth.

Switching from corticosteroid tablets to {INVENTED NAME}
Switching from corticosteroid tablets to an inhaled corticosteroid treatment might make you feel generally unwell or you might develop a rash, eczema or a runny nose and sneezing (rhinitis).
You should see your doctor as soon as possible if you experience these symptoms. Do not stop treatment with {INVENTED NAME} unless your doctor tells you to.

If you have been taking corticosteroid tablets at high doses or for a long time, your dose may be gradually reduced, approximately one week after you started treatment with {INVENTED NAME}. During this time your doctor will monitor the level of corticosteroids in your body regularly.

If you have been treated for a long time with high doses of inhaled corticosteroid, you may require an **extra corticosteroid treatment in times of stress**. For example:

- during admission to hospital after a serious accident,
- before an operation,
- or if you have a chest infection or other serious illness.

Your doctor will decide if you need a course of corticosteroid tablets or possibly a corticosteroid injection and will also advise you as to how long you need to take the course of corticosteroid tablets and how you should reduce these as you get better.

Children and adolescents
If your child is below 5 years of age and is receiving prolonged treatment of recurrent wheezing with {INVENTED NAME}, your doctor will regularly monitor his/her height to evaluate if growth impairment occurs and whether to stop the treatment.

Other medicines and {INVENTED NAME}
Tell your doctor or pharmacist if you are taking or have recently taken or might take any other medicines.

Tell your doctor if you are taking other corticosteroid medications as they may interact with {INVENTED NAME} and could make any side effects worsening.

Pregnancy, breast-feeding and fertility
If you are pregnant or breast-feeding, think you may be pregnant or you are planning to have a baby, ask your doctor or pharmacist for advice before using this medicine.

Because growth retardation and damage to the unborn child cannot be excluded upon prolonged treatment with corticosteroids (such as beclometasone dipropionate contained in {INVENTED NAME}) during pregnancy, your doctor will decide whether your disease requires treatment with {INVENTED NAME}.

Corticosteroids pass into breast milk at low amounts. Damage to the infant is not reported to date. Nevertheless, as precautionary measure when high doses of beclometasone dipropionate are inhaled you should avoid breast-feeding for 4 h after administration.

Driving and using machines
{INVENTED NAME} is unlikely to affect your ability to drive and use machines. However if you experience side effects such as dizziness and/or trembling, your ability to drive or operate machines may be affected.

3. HOW TO TAKE {INVENTED NAME}

Always use this medicine exactly as your doctor has told you. Check with your doctor or pharmacist if you are not sure.

The starting dose should be prescribed by your doctor according to the frequency and severity of your disease. The dose may then be adjusted by your doctor until effective control of symptoms is reached.

The recommended initial doses are:

Adults and adolescents (from 12 years of age):

- 800-1600 micrograms twice daily which correspond to a total daily amount of 1600-3200 micrograms.

Children (up to 11 years of age):

- 400-800 micrograms twice daily which correspond to a total daily dose of 800-1600 micrograms.

{INVENTED NAME}
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.
In case of asthma disease, {INVENTED NAME} must be used regularly on a daily basis. Your doctor will decide the duration of your treatment.

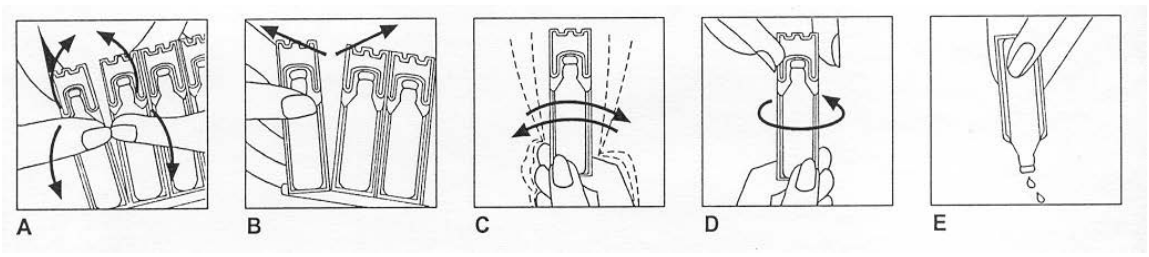
If your child suffers from recurrent wheezing, the duration of treatment should not exceed 3 months, unless otherwise prescribed by the paediatrician.

You can used {INVENTED NAME} 800 micrograms ampoule to get 400 micrograms (half the content) using the graduation mark as described below.

Method of administration
{INVENTED NAME} is for inhalation use only. Do not inject into a vein or use orally.

{INVENTED NAME} must be administered by inhalation from a suitable device (jet nebuliser) according to your doctor instructions.
Use of {INVENTED NAME} with ultrasonic nebulisers is not recommended.

Instructions for use:
Use the ampoule according to the following instructions:



1. Bend the ampoule backwards and forwards to loosen it from the strip (Figure A).
2. Carefully separate a new ampoule from the strip. Starting from the top, then in the middle (Figure B). Leave the rest in the pouch.
3. Vigorously shake and turn the ampoule upside-down in order to mix the suspension. Repeat this operation, until the whole content is fully dispersed and mixed (Figure C).

4. Open the ampoule by rotating the entrance 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 {INVENTED NAME} 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 container 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.

Dilution:
Your doctor may decide that your dose should be diluted.
In this case, empty the contents of the ampoule into the nebuliser bowl then add the quantity of sterile sodium chloride 9 mg/ml (0.9%) solution that your doctor has told you to use. Then put the top on the nebuliser bowl and shake gently to mix the contents.
The dose of nebuliser suspension may need to be diluted in order to obtain a final volume suitable for the particular nebuliser being used, to aid administration of small volumes or if a prolonged delivery time is desirable.

During nebulisation
Place the mask or mouth piece
Turn on the nebuliser.
Breathe normally. Nebulisation should not last more than 10 to 15 minutes.

After nebulisation
Do not forget to rinse the mouth, lips and the region of the face covered by the mask with water.
After inhalation, any unused suspension remaining in the nebuliser chamber must be discarded.

Cleaning:
Follow the manufacturer's instructions for cleaning your nebuliser. It is important that your nebuliser is kept clean.

If you use more {INVENTED NAME} than you should:
It is important that you use your dose as advised by your doctor. You should not increase or decrease your dose without seeking medical advice.

If you have used more {INVENTED NAME} than you should, tell your doctor as soon as possible. Your doctor may want to check the corticosteroid levels in your blood and therefore, may need to take a blood sample.

If you forget to use {INVENTED NAME}:
If you forget to use a dose, use it as soon as you remember. If it is almost time for your next dose, do **not** use the missed dose, just use the next dose when it is due. **Do not use a double dose** to make up for a forgotten dose.

{INVENTED NAME}{INVENTED NAME}If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. POSSIBLE SIDE EFFECTS

Like all medicines, this medicine can cause side effects, although not everybody gets them.

The following side effects have been reported. Tell your doctor as soon as possible if you suffer from any of these side effects but do not stop treatment unless told to do so. Your doctor will try to prevent these effects by prescribing {INVENTED NAME} in the lowest effective dose.

V**ery common side effects** (may affect more than 1 in 10 people):

- sore throat (pharyngitis, laryngitis). Gargling with water immediately after inhalation may help to prevent this effect.

Common side effects (may affect up to 1 in 10 people):

- cough
- nausea (feeling sick) and stomach pains.
- thrush in the mouth, tongue and throat. Rinsing your mouth or gargling with water immediately after inhalation may help to prevent these effects.

Uncommon side effects (may affect up to 1 in 100 people):

- headache
- throat irritation, hoarse voice
- worsening shortness of breath, cough and wheezing (which is known as paradoxical bronchospasm). If this occurs do not take another dose of {INVENTED NAME}. Then contact your doctor straightaway. Your doctor is likely to assess your asthma or wheezing and if necessary may start you on another course of treatment. You may be told that you should not use {INVENTED NAME} again.

Rare side effects (may affect up to 1 in 1000people):

- cold sores (herpes simplex) painful blisterlike vesicles on your lips and in your mouth
- tremor (involuntary trembling)
- feeling tired.
- an allergic reaction (swelling of the eyes, face, lips and throat leading to severe difficulty in breathing, skin rashes, hives, itching or redness)

The following effects may also occur more likely in children

- Sleeping problems, depression or feeling worried, restless, nervous, over-excited or irritable

At high doses over a long period of time, {INVENTED NAME} may affect the normal production of corticosteroids in the body. Affected children and adolescents may grow more slowly than others, so it is important that they will have their height checked regularly by their doctor. Bone thinning and eye problems, which include clouding of the lens of the eye (cataract), increase in pressure in the eye (glaucoma) have been reported.

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine

5. HOW TO STORE {INVENTED NAME}

Keep this medicine out of the sight and reach of children.

Do not use {INVENTED NAME} after the expiry date which is stated on the carton, pouch and ampoule.

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

After first opening the pouch, write the date in the box provided on the pouch. Do not use the ampoule after 3 months from the date of first opening the pouch.
For 800 micrograms ampoule: after the first opening of the ampoule, store it in a refrigerator (2–8°C). The remaining quantity has to be used within 12 hours after first opening.

Do not use {INVENTED NAME} if the packaging is damaged.

Do not throw away any medicines via wastewater <or household waste>. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What {INVENTED NAME} contains
The active substance is beclometasone dipropionate.
Each ampoule contains 400 micrograms beclometasone dipropionate suspension in 1 ml.
Each ampoule contains 800 micrograms beclometasone dipropionate suspension in 2 ml.
The 800 micrograms ampoule has a graduation mark to indicate half the content (corresponding to 400 micrograms).

The other ingredients are polysorbate 20, sorbitan laurate, sodium chloride, water for injections.

What {INVENTED NAME} looks like and contents of the pack
{INVENTED NAME} is a white or almost white nebuliser suspension.

{INVENTED NAME} nebuliser suspension comes in polyethylene ampoules containing 1 ml ({INVENTED NAME} 400 micrograms) or 2 ml ({INVENTED NAME} 800 micrograms). There are strips 5 ampoules in each sealed pouch, in pack sizes of 10 ampoules (2 pouches), 20 ampoules (4 pouches) or 40 ampoules (8 pouches).

Not all pack sizes may be marketed.

Marketing Authorisation Holder and Manufacturer

Marketing Authorisation Holder: {See **ANNEX I** of referal}
Manufacturer: Chiesi Farmaceutici S.p.A., 26/A via Palermo, 43122 Parma, Italy.

This medicinal product is authorised in the Member States of the EEA under the following names:

{See **ANNEX I** of referal}

This leaflet was last revised in [MM/YYYY]