Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Brodilaten 2.5 mg/2.5 ml nebuliser solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

2.5 mL of nebuliser solution contain 2.50 mg salbutamol (as salbutamol sulfate).

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser solution.
Clear and colourless solution.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Brodilaten is indicated in adults, adolescents and children aged 4 to 11 years. Brodilaten 2.5 mg / 2.5 mL Nebuliser solution is not indicated for babies and children under 4 years of age, see section 4.2.
Brodilaten is indicated for treatment of severe acute exacerbations of chronic obstructive pulmonary disease (COPD), and in the treatment of acute severe asthma.

4.2 Posology and method of administration

Posology

Adults (including the elderly): 2.5 mg to 5 mg salbutamol up to four times a day. Up to 40 mg per day can be given under strict medical supervision in hospital.

Paediatric Population
Children aged 12 years and over: Dose as per adult population.
Children aged 4-11 years: 2.5 mg to 5 mg up to four times a day.

The clinical efficacy of nebulised salbutamol in infants under 18 months is uncertain. As transient hypoxaemia may occur, supplemental oxygen therapy should be considered.

Brodilaten is intended to be used undiluted. However, if prolonged delivery time (more than 10 minutes) is required, the solution may be diluted with sterile normal saline to a 1:1 dilution.

Method of administration

Brodilaten is for inhalation use only, to be breathed in through the mouth, under the direction of a physician, using a suitable nebuliser.

The solution should not be injected or swallowed.

For single use only. Use immediately after first opening the single-dose container. Any solution remaining in the nebuliser after nebulisation should be discarded.

Brodilaten may be administered from a suitable nebuliser, e.g. PARI LC SPRINT nebuliser, after the single dose ampoule has been opened and its contents transferred to the nebuliser chamber. For full instructions on the use of the nebuliser the patient should be instructed to read the leaflet of the respective device carefully before starting the inhalation.

Active substance delivery characteristics were studied *in vitro* using the PARI TurboBoy SX compressor with LC SPRINT junior familie nebuliser device with the following settings:

Salbutamol	Droplet size distribution (micrometer)			Active substances delivery rate (micrograms/min)		Total active substances delivered (micrograms/2.5 mL)		Settings	
	D10	D50	D90	Adults	Paediatric	Adults	Paediatric	Min / Max Flow:	3.0 L / min / 6.0 L / min
2.5mg/2.5mL	0.25	2.99	7.80	159.5	170.8	807.3	650.2	Min / Max Operating Pressure:	0.5 bar / 2.0 bar

The delivered dose of Brodilaten may vary depending on the nebuliser system used. The use of an alternative nebuliser system(s) may alter the pulmonary deposition of the active substance, this in
turn may alter the efficacy and safety of the product and dose adjustment may then become necessary.

The nebulised solution may be inhaled through a face mask, T-piece or via an endotracheal tube. Intermittent positive pressure ventilation (IPPV) may be used but is rarely necessary. When there is a risk of anoxia through hypoventilation, oxygen should be added to the inspired air.

As many nebulisers operate on a continuous flow basis, it is likely that some nebulised drug will be released into the local environment. Brodilaten should therefore be administered in a well-ventilated room, particularly in hospitals when several patients may be using nebulisers at the same time.

Dilution: Brodilaten may be diluted with sterile normal saline. Solutions in nebulisers should be replaced daily.

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

Brodilaten must only be used by inhalation, to be breathed in through the mouth, and must not be injected or swallowed.

Bronchodilators should not be the only or main treatment in patients with severe or unstable asthma. Severe asthma requires regular medical assessment, including lung-function testing, as patients are at risk of severe attacks and even death. Physicians should consider using the maximum recommended dose of inhaled corticosteroid and/or oral corticosteroid therapy in these patients.

Patients receiving treatment at home should seek medical advice if treatment with Brodilaten becomes less effective. The dosage or frequency of administration should only be increased on medical advice.

Patients being treated with Brodilaten may also be receiving other dosage forms of short-acting inhaled bronchodilators to relieve symptoms. Patients who are prescribed regular anti-inflammatory therapy (e.g., inhaled corticosteroids) should be advised to continue taking their anti-inflammatory medication even when symptoms decrease, and they do not require Brodilaten. Increasing use of bronchodilators, in particular short-acting inhaled β_2*agonists* to relieve symptoms, indicates deterioration of asthma control, and patients should be warned to seek medical advice as soon as possible. The patient should be instructed to seek medical advice if short-acting relief bronchodilator treatment becomes less effective or more inhalations than usual are required. In this situation patients should be assessed and consideration given to the need for increased anti-inflammatory therapy (e.g. higher doses of inhaled corticosteroid or a course of oral corticosteroid).

Overuse of short-acting beta-agonists may mask the progression of the underlying disease and contribute to deteriorating asthma control, leading to an increased risk of severe asthma exacerbations and mortality.
Patients who take more than twice a week "as needed" salbutamol, not counting prophylactic use prior to exercise, should be re-evaluated (i.e., daytime symptoms, night-time awakening, and activity limitation due to asthma) for proper treatment adjustment as these patients are at risk for overuse of salbutamol.

Salbutamol should be administered cautiously to patients suffering from thyrotoxicosis.

Cardiovascular effects may be seen with sympathomimetic drugs, including salbutamol. There is some evidence from post-marketing data and published literature of rare occurrences of myocardial ischaemia associated with salbutamol. Patients with underlying severe heart disease (e.g. ischaemic heart disease, arrhythmia or severe heart failure) who are receiving salbutamol should be warned to seek medical advice if they experience chest pain or other symptoms of worsening heart disease. Attention should be paid to assessment of symptoms such as dyspnoea and chest pain, as they may be of either respiratory or cardiac origin.

Sportsmen should be warned that this drug contains an active substance, which may induce a positive result in anti-doping controls.

Brodilaten should be used with care in patients known to have received large doses of other sympathomimetic drugs.

Potentially serious hypokalaemia may result from *$\beta_2$agonist* therapy, mainly from parenteral and nebulised administration. Particular caution is advised in acute severe asthma as this effect may be potentiated by hypoxia and by concomitant treatment with xanthine derivatives, steroids and diuretics. Serum potassium levels should be monitored in such situations.

In common with other *βadrenoceptor* agonists, salbutamol can induce reversible metabolic changes such as increased blood glucose levels. Diabetic patients may be unable to compensate for the increase in blood glucose and the development of ketoacidosis has been reported. Concurrent administration of corticosteroids can exaggerate this effect.

Lactic acidosis has been reported in association with high therapeutic doses of intravenous and nebulised short-acting *βagonist* therapy, mainly in patients being treated for an acute exacerbation of bronchospasm in severe asthma or chronic obstructive pulmonary disease (see Section 4.8 and 4.9). Increase in lactate levels may lead to dyspnoea and compensatory hyperventilation, which could be misinterpreted as a sign of asthma treatment failure and lead to inappropriate intensification of short-acting*βagonist* treatment. It is therefore recommended that patients are monitored for the development of elevated serum lactate and consequent metabolic acidosis in this setting.

A small number of cases of acute angle-closure glaucoma have been reported in patients treated with a combination of nebulised salbutamol and ipratropium bromide. A combination of nebulised salbutamol with nebulised anticholinergics should therefore be used cautiously. Patients should receive adequate instruction in correct administration and be warned not to let the solution or mist enter the eye.

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting bronchodilator and therefore should be treated with an alternative presentation or a different rapid acting inhaled bronchodilator and should be treated straightaway. Brodilaten should be discontinued immediately, the patient assessed and alternative therapy instituted, if necessary. For on-going use a different rapid-acting may be required.

4.5 Interaction with other medicinal products and other forms of interaction

Salbutamol and non-selective *βblocking* drugs such as propranolol, should not usually be prescribed together.

4.6 Fertility, pregnancy and lactation

Pregnancy
Administration of drugs during pregnancy should only be considered if the expected benefit to the mother is greater than any possible risk to the fetus. As with the majority of drugs, there is little published evidence of the safety of salbutamol in the early stages of human pregnancy, but in animal studies there was evidence of some harmful effects on the fetus at very high dose levels.

Breast-feeding

As salbutamol is probably secreted in breast milk, its use in nursing mothers requires careful consideration. It is not known whether salbutamol has a harmful effect on the neonate, and so its use should be restricted to situations where it is felt that the expected benefit to the mother is likely to outweigh any potential risk to the neonate.

Fertility

There is no information on the effects of salbutamol on human fertility. There were no adverse effects on fertility in animals (see section 5.3).

4.7 Effects on ability to drive and use machines

Brodilaten has no or negligible influence on the ability to drive and use machines.

4.8 Undesirable effects

Adverse events are listed below by system organ class and frequency. Frequencies are defined as: very common (≥1/10), common (≥1/100 to <1/10), uncommon (≥1/1000 to <1/100), rare (≥1/10,000 to <1/1000) and very rare (<1/10,000). Very common and common events were generally determined from clinical trial data. Rare, very rare and unknown events were generally determined from spontaneous data.

System Organ Class	Frequency	Adverse Drug Reaction
Immune system disorders	Very rare	Hypersensitivity reactions including angioedema, urticaria, bronchospasm, hypotension and collapse
Metabolism and nutrition disorders	Rare	Hypokalaemia. Potentially serious hypokalaemia may result from *β_2 agonist* therapy
	Unknown	Lactic acidosis (see section 4.4)
Nervous system disorders	Common	Tremor, headache
	Very rare	Hyperactivity
Cardiac disorders	Common	Tachycardia
	Uncommon	Palpitations
	Very rare	Cardiac arrhythmias including atrial fibrillation, supraventricular tachycardia and extrasystoles
	Unknown	Myocardial ischaemia* (see section 4.4)
Vascular disorders	Rare	Peripheral vasodilatation
Respiratory, thoracic and mediastinal disorders	Very rare	Paradoxical bronchospasm
Gastrointestinal disorders	Uncommon	Mouth and throat irritation
Musculoskeletal and connective tissue disorders	Uncommon	Muscle spasm

* reported spontaneously in post-marketing data therefore frequency regarded as unknown.

As with other inhalation therapy, paradoxical bronchospasm may occur with an immediate increase in wheezing and shortness of breath after dosing. Paradoxical bronchospasm responds to a rapid-acting bronchodilator and therefore should be treated with an alternative presentation or a different rapid-acting inhaled bronchodilator and should be treated straightaway. Brodilaten should be discontinued immediately, the patient assessed and alternative therapy instituted, if necessary. For on-going use a different rapid-acting may be required.

Paediatric population

In addition, very rare adverse events of psychiatric / behavioral disorders regarding nervousness and agitation, as well as pruritus have been reported in paediatric population.

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: www. hpra.ie, E-mail: medsafety@hpra.ie.

4.9 Overdose

The most common signs and symptoms of overdose with salbutamol are transient *βagonist* pharmacologically mediated events, including tachycardia, tremor, hyperactivity and metabolic effects including hypokalaemia and lactic acidosis (see sections 4.4 and 4.8). Any effects of overdosage are therefore likely to be related to the salbutamol component. Manifestations of overdosage with salbutamol may include nausea, vomiting and hyperglycemia, particularly in children and when overdose is due to oral salbutamol.
Hypokalaemia may occur following overdose with salbutamol. Serum potassium levels should be monitored. Metabolic acidosis has also been observed with overdosage of salbutamol, including lactic acidosis which has been reported in association with high therapeutic doses as well as overdoses of short-acting *βagonist* therapy, therefore monitoring for elevated serum lactate and consequent metabolic acidosis (particularly if there is persistence or worsening of tachypnea despite resolution of other signs of bronchospasm such as wheezing) may be indicated in the setting of overdose.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Andrenergics, inhalants. Selective *$\beta_2$andrenoreceptoragonists*

ATC code: R03AC02

Salbutamol is a selective *$\beta_2$agonist* providing short-acting (4-6 hour) bronchodilation with a fast onset (within 5 minutes) in reversible airways obstruction. At therapeutic doses it acts on the *$\beta_2$adrenoceptors* of bronchial muscle. With its fast onset of action, it is particularly suitable for the management and prevention of asthma attacks.

5.2 Pharmacokinetic properties

Salbutamol administered intravenously has a half-life of 4 to 6 hours and is cleared partly renally, and partly by metabolism to the inactive 4'-O-sulfate (phenolic sulfate) which is also excreted primarily in the urine. The faeces are a minor route of excretion. Most of a dose of salbutamol given intravenously, orally or by inhalation is excreted within 72 hours. Salbutamol is bound to plasma proteins to the extent of 10%.

After administration by the inhaled route between 10 and 20% of the dose reaches the lower airways. The remainder is retained in the delivery system or is deposited in the oropharynx from where it is swallowed. The fraction deposited in the airways is absorbed into the pulmonary tissues and circulation, but is not metabolised by the lung. On reaching the systemic circulation it becomes accessible to hepatic metabolism and is excreted, primarily in the urine, as unchanged drug and as the phenolic sulfate.

The swallowed portion of an inhaled dose is absorbed from the gastrointestinal tract and undergoes considerable first-pass metabolism to the phenolic sulfate. Both unchanged drug and conjugate are excreted primarily in the urine.

5.3 Preclinical safety data

Non-clinical data reveal no special safety concerns for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenicity. Effects seen in repeat dose toxicity studies were related to the *βadrenergic* activity of salbutamol.

In mice dosed subcutaneously in the range 0.025-2.5 mg/kg, cleft palate formation occurred in 4.5% and 9.3% of foetuses at 0.25 and 2.5 mg/kg, respectively (approximately 1/10 and 1.0 times the maximum recommended daily inhalation dose clinically on a mg/m^2 basis). A reproduction study in rabbits revealed cranioschisis in 37% of foetuses administered salbutamol orally at 50 mg/kg (approximately 80 times the clinical dose on the basis given above).

In an oral fertility and general reproductive performance study in rats at doses of 2 and 50 mg/kg/day, with the exception of a reduction in number of weanlings surviving to day 21 post partum at 50 mg/kg/day, there were no adverse effects on fertility, embryofetal development, litter size, birth weight or growth rate.

High doses of *βadrenoceptor* agonists have been shown to induce mesovarian leiomyomas in rats. No such findings have been found in humans.

Findings concerning teratogenicity in rabbits at high systemic dosage exposure and the induction of benign mesovarian leiomyomas in rats are not considered of clinical concern.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Sodium chloride
Water for injections
Sulfuric acid (for pH adjustment)

6.2 Incompatibilities

None known.

6.3 Shelf life

3 years if unopened.

3 months after opening the overwrap protective pouch, (see below).

6.4 Special precautions for storage

Store below 25°C.

Store the ampoules in the outer carton and pouch, in order to protect from light. The ampoules should be protected from light after opening the overwrap protective pouch.

6.5 Nature and contents of container

Brodilaten are supplied as packs of 30 or 60 low density polyethylene ampoules overwrapped in non-transparent protective aluminium pouches and packed in carton boxes. Each ampoule contains 2.5 mL of solution.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Partly used, opened or damaged single-dose containers should be disposed of in accordance with local requirements.

7 MARKETING AUTHORISATION HOLDER

Noridem Enterprises Limited
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Mitsi Building 3, Office 115
1065 Nicosia
Cyprus

8 MARKETING AUTHORISATION NUMBER

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9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

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