SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

VEBULIS 10 mcg/ml Inhalation Solution for Nebulisation

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

1 ml of inhalation solution for nebulisation contains
Active substance:
Iloprost……...0.01 mg

Excipient(s) with known effect:
Ethanol……..0.81 mg
Sodium chloride…….....9 mg

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Inhalation solution for nebulisation
Colourless, clear, visible particle free solution

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

To improve exercise capacity and symptoms, classified as NYHA functional class III and IV;
- Primary (idiopathic and familial) pulmonary hypertension,
- Pulmonary hypertension due to scleroderma without interstitial pulmonary disease

4.2 Posology and method of administration

Drug product	Suitable inhalation device (nebuliser) to be used		
VEBULIS 10 mcg/ml	Breelib	I-Neb AAD	Venta-Neb

Posology/frequency and duration of administration
Recommended dose:
Adults:
At initiation of VEBULIS treatment, the first inhaled dose should be 2.5 microgram. If this dose is well tolerated, dosing can be increased to 5 microgram and maintained at that dose. In case of poor tolerability of the 5 microgram dose, the dose can be reduced to 2.5 microgram.

The dose per inhalation session should be administered 6 to 9 times per day according to the individual need and tolerability.

Depending on the desired dose at the mouthpiece and on the nebuliser, the duration of an inhalation session is approximately 4 to 10 minutes.

Duration of treatment:
The duration of treatment depends on clinical status and is left to the physician's discretion.

Method of administration:
VEBULIS should only be initiated and monitored by a physician experienced in the treatment of pulmonary hypertension.

VEBULIS is intended for inhalation use by nebulisation.

The ready-to-use VEBULIS inhalation solution is administered with a suitable inhalation device (nebuliser) recommended in section 6.6 Special precautions for disposal and other handling. Previous treatments should be continued and adjusted to individual needs (see section 4.5).

Breelib
Breelib is a small handheld, battery-powered, breath activated, vibrating mesh technology system.

VEBULIS 10 mcg/ml inhalation solution for nebulisation (1 ampoule) delivers 2.5 microgram at the mouthpiece of the Breelib nebuliser.

At initiation of VEBULIS treatment or if the patient is switched from an alternative device, the first inhalation should be made with 1 ml ampoule of VEBULIS 10 microgram/ml (see section 4.4). If inhalation with VEBULIS 10 microgram/ml is well tolerated, the dose should be increased. This dose should be maintained. In case of poor tolerability of the increased dose, the dose should be reduced by using 1 ml ampoule of VEBULIS 10 microgram/ml (see section 4.4).

The duration of an inhalation session with Breelib nebuliser is approximately 3 minutes, which reflects the higher delivery rate of the Breelib compared to other nebulisers.

Patients initiating VEBULIS treatment or switching from an alternative device to Breelib should be closely supervised by the treating physician to ensure that dose and speed of inhalation are well tolerated.

When using the Breelib nebuliser please follow the instructions for use provided with the device.
Fill the medication chamber with VEBULIS immediately before use.

HaloLite and Prodose
Two compressed air nebuliser systems, HaloLite and Prodose, have been shown to be suitable nebulisers for the administration of iloprost. With both systems, the mass median aerodynamic diameter of the aerosol droplet (MMAD) with iloprost was between 2.6 and 2.7 micrometres. For each inhalation session the content of one 2 ml ampoule of VEBULIS inhalation solution for nebulisation, will be transferred into the nebuliser medication chamber immediately before use. HaloLite and Prodose are dosimetric systems. They stop automatically after the pre-set dose has been delivered. The inhalation time depends on the patient's breathing pattern.

Device	Dose of iloprost at mouthpiece	Estimated inhalation time (frequency of 15 breaths per minute)
HaloLite and Prodose	2.5 microgram 5 microgram	4-5 minutes 8-10 minutes

For a dose of 5 mcg iloprost at mouthpiece it is recommended to complete two inhalation cycles with 2.5 mcg pre-set dose program with a filling of one ampoule containing 2 ml VEBULIS inhalation solution for nebulisation, which shows 2 coloured rings (white – pink).

Venta-Neb
Venta-Neb, a portable ultrasonic battery-powered nebuliser, has also been shown to be suitable for the administration of inhaled iloprost. The measured MMAD of the aerosol droplets was 2.6 micrometres. For each inhalation session, the content of one ampoule containing 2 ml VEBULIS inhalation solution for nebulisation and showing two coloured rings (white – pink) will be transferred into the nebuliser medication chamber immediately before use.

Two programs can be operated:
P1 Program 1: 5 microgram active substance on the mouthpiece 25 inhalation cycles.
P2 Program 2: 2.5 microgram active substance on the mouthpiece 10 inhalation cycles.
The selection of the pre-set program is made by the physician.

Venta-Neb prompts the patient to inhale by an optical and an acoustic signal. It stops after the pre-set dose has been administered.

To obtain the optimal droplet size for the administration of VEBULIS inhalation solution for nebulisation, the green baffle plate should be used. For details, refer to the instruction manual of the Venta-Neb nebuliser.

Device	Dose of iloprost at mouthpiece	Estimated inhalation time
Venta-Neb	2.5 microgram 5 microgram	4 minutes 8 minutes

I-Neb AAD
The I-Neb AAD system is a portable, hand-held, vibrating mesh technology nebuliser system. This system generates droplets by ultrasound, which forces the solution through a mesh. The I-Neb AAD nebuliser has been shown to be suitable for the administration of inhaled iloprost. The Mass Median Aerodynamic Diameter (MMAD) of the aerosol is measured 2.1 micrometres.

This nebuliser monitors the breathing pattern to determine the aerosol pulse time required to deliver the pre-set dose of 2.5 or 5 microgram iloprost.

The pre-set dose provided by the I-Neb AAD system is controlled by the medication chamber in combination with a control disc. There are two different colour coded medication chambers. For each medication chamber there is a corresponding colour coded control disc:

For the 2.5 microgram dose, the medication chamber with the red coloured latch is used together with the red control disc.

For the 5 microgram dose, the medication chamber with the purple coloured latch is used together with the purple control disc.

For each inhalation session with the I-Neb AAD, the content of one 1 ml ampoule of VEBULIS, with two coloured rings is transferred into the medication chamber immediately before use.

Device	Dose of iloprost at mouthpiece	Estimated inhalation time
I-Neb AAD	2.5 microgram 5 microgram	3.2 minutes 6.5 minutes

Patients stabilized on one nebuliser should not switch to another nebuliser without close supervision by the treating doctor.

The efficacy and tolerability of inhaled iloprost when administered with other nebulising systems, which provide different nebulisation characteristics of iloprost solution, have not been established.

Additional information on special populations
Renal impairment
There is no need for dose adaptation in patients with a creatinine clearance >30 ml/min (as determined from serum creatinine using the Cockroft and Gault formula). Patients with a creatinine clearance of ≤30 ml/min were not investigated in the clinical trials. Data with intravenously administered iloprost indicated that the elimination is reduced in patients with renal failure requiring dialysis. Therefore, the same dosing recommendations as in patients with hepatic impairment are to be applied (see section 4.2 Additional information on special populations – Hepatic impairment).

Hepatic impairment:
Iloprost elimination is reduced in patients with hepatic dysfunction (see section 5.2).
To avoid undesired accumulation over the day, special caution has to be exercised with these patients during initial dose titration. Initially, doses of 2.5 microgram iloprost should be administered, with dosing intervals of 3-4 hours (corresponds to administration of maximum 6 times per day). Thereafter, dosing intervals may be shortened cautiously based on individual tolerability. If a dose up to 5 microgram iloprost is indicated, again dosing intervals of 3-4 hours should be chosen initially and shortened according to individual tolerability. A further undesired accumulation of the medicinal product following treatment over several days is not likely due to the overnight break in administration of the medicinal product.

Paediatric population:
The safety and efficacy of inhaled iloprost in children aged up to 18 years have not been established.
No data from controlled clinical trials are available. VEBULIS should not be used in patients under 18 years of age.

Geriatric population:
Age and gender are not of clinical relevance to the pharmacokinetics of iloprost.

4.3 Contraindications

- Hypersensitivity to the active substance (iloprost) or to any of the excipients (For the full list of excipients, see section 6.1)
- Conditions where the effects of VEBULIS on platelets might increase the risk of haemorrhage (e.g. active peptic ulcers, trauma, intracranial haemorrhage)
- Severe coronary heart disease or unstable angina
- Myocardial infarction within the last six months
- Decompensated cardiac failure if not under close medical supervision
- Severe arrhythmias
- Suspected pulmonary congestion
- Cerebrovascular events (e.g. transient ischemic attack, stroke) within the last 3 months.
- Pulmonary hypertension due to venous occlusive disease.
- Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to pulmonary hypertension.

4.4 Special warnings and precautions for use

The use of VEBULIS is not recommended in patients with unstable pulmonary hypertension, with advanced right heart failure. In case of deterioration or worsening of right heart failure transfer to other medicinal products should be considered.

Hypotension:
Blood pressure should be checked while initiating VEBULIS. In patients with low systemic blood pressure and in patients with postural hypotension or receiving medicinal products known to reduce blood pressure levels, care should be taken to avoid further hypotension. VEBULIS should not be initiated in patients with systolic blood pressure less than 85 mmHg.
Physicians should be alerted to the presence of concomitant conditions or medicinal products that might increase the risk of hypotension and syncope (see section 4.5).

Syncope:
Physicians should be alert for the presence of concomitant conditions or drugs that may increase the risk of syncope (see section 4.5).
The pulmonary vasodilatory effect of inhaled iloprost is of short duration (1-2 hours). Syncope is a common symptom of the disease itself and can also occur under therapy. Patients who experience syncope in association with pulmonary hypertension should avoid any exceptional straining, for example during physical exertion. Before physical exertion, it might be useful to inhale. The increased occurrence of syncope can reflect therapeutic gaps, insufficient effectiveness and/or deterioration of the disease. The need to adapt and/or change the therapy should be considered (see section 4.8).

Patients with diseases of the respiratory tract:
VEBULIS inhalation might entail the risk of inducing bronchospasm; especially in patients with bronchial hyperactivity (see section 4.8). Moreover, the benefit of inhaled iloprost has not been established in patients with concomitant chronic obstructive pulmonary disease (COPD) and severe asthma. Patients with concomitant acute pulmonary infections, COPD and severe asthma should be carefully monitored.

Pulmonary veno-occlusive disease:
Pulmonary vasodilators may significantly worsen the cardiovascular status of patients with pulmonary veno-occlusive disease. Should signs of pulmonary oedema occur, the possibility of associated pulmonary veno-occlusive disease should be considered and treatment with VEBULIS should be discontinued.

Interruption of therapy:
In case of interruption of VEBULIS therapy, the risk of rebound effect is not formally excluded. Careful monitoring of the patient should be performed when inhaled iloprost therapy is stopped and an alternative treatment should be considered in critically ill patients.

Renal or hepatic impairment:
Data with intravenously administered iloprost indicated that the elimination is reduced in patients with hepatic dysfunction and in patients with renal failure requiring dialysis (see section 5.2). A cautious initial dose titration using dosing intervals of 3-4 hours is recommended (see section 4.2).

Serum glucose levels:
Prolonged oral treatment with iloprost clathrate in dogs up to one year was associated with slightly increased fasted serum glucose levels. It cannot be excluded that this is also relevant to humans on

prolonged inhaled iloprost therapy.
Undesirable exposure:
To minimize accidental exposure, it is recommended to use VEBULIS with nebulisers with inhalation-triggered systems (Breelib, HaloLite/Prodose or I-Neb), and to keep the room well ventilated.
Newborns, infants and pregnant women should not be subjected to VEBULIS in the room air.

Skin and eye contact, oral ingestion:
VEBULIS inhalation solution for nebulisation should not come into contact with skin and eyes; oral ingestion of VEBULIS should be avoided. During nebulisation sessions, a facial mask must be avoided and only a mouthpiece should be used.

Switching to the Breelib nebuliser
Limited data are available on the use of the Breelib nebuliser. For patients being switched from an alternative device to the Breelib nebuliser the first inhalation should be made with VEBULIS 10 microgram/ml (1 ml ampoule) delivering 2.5 microgram iloprost at the mouthpiece and under close medical supervision to ensure that the faster inhalation provided by Breelib is well tolerated. First dosing with 2.5 microgram should be done even if patients had already been stable on 5 microgram inhaled with an alternative device (see section 4.2).

This medicinal product contains less than 1 mmol sodium (23 mg) per dose; i.e. essentially sodium-free". No side effects due to sodium are expected at this dose.

This medicinal product contains small amounts of ethanol (alcohol), less than 100 mg per dose.

4.5 Interaction with other medicinal products and other forms of interaction
Iloprost may increase the effects of vasodilatators and antihypertensive agents and then favour the risk of hypotension (see section 4.4). Caution is recommended in case of co-administration of VEBULIS with other antihypertensive or vasodilatating agents as dose adjustment might be required.

Since iloprost inhibits platelet function, its use with the following substances may enhance iloprost-mediated platelet inhibition, thereby increasing the risk of bleeding:
- Anticoagulants such as
  - heparin
  - oral anticoagulants (either coumarin-type or direct)
- or other inhibitors of platelet aggregation, such as
  - acetylsalicylic acid
  - non-steroidal anti-inflammatory medicinal products
  - non-selective phosphodiesterase inhibitors like pentoxifylline
  - selective phosphodiesterase 3 (PDE3) inhibitors like cilostazol or anagrelide
  - ticlopidine
  - clopidogrel
  - glycoprotein IIb/IIIa antagonists, like
    - abciximab
    - eptifibatide
    - tirofiban
  - defibrotide.

A careful monitoring of the patients taking anticoagulants or other inhibitors of platelet aggregation

according to common medical practice is recommended.

Intravenous infusion of iloprost has no effect either on the pharmacokinetics of multiple oral doses of digoxin or on the pharmacokinetics of co-administered tissue plasminogen activator (t-PA) in patients.

Although, clinical studies have not been conducted, *in vitro* studies investigating the inhibitory potential of iloprost on the activity of cytochrome P450 enzymes revealed that no relevant inhibition of drug metabolism via these enzymes by iloprost is to be expected.

Additional information on special populations
Paediatric population
The safety and efficacy of inhaled iloprost in children aged up to 18 years have not been established.
No data from controlled clinical trials are available. Therefore, VEBULIS should not be used in patients under 18 years of age.

4.6 Fertility, pregnancy and lactation
General recommendation
Pregnancy category is C.

Women of childbearing potential/Contraception
Women of childbearing potential should use effective contraceptive measures during treatment with VEBULIS.

Pregnancy
There is a limited amount of data from the use of iloprost in pregnant women. Animal studies have shown reproductive effects (see section 5.3). The potential risk for humans is unknown.

If pregnancy occurs during treatment, VEBULIS should only be used after careful risk-benefit assessment (see section 4.4).

Women with pulmonary hypertension (PH) should avoid pregnancy as it may lead to life-threatening exacerbation of the disease.

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

There is a limited amount of data from the use of iloprost in pregnant women. If a pregnancy occurs, taking into account the potential maternal benefit, the use of VEBULIS during pregnancy may be considered, only following careful benefit-risk evaluation, in those women who choose to continue their pregnancy, despite the known risks of pulmonary hypertension during pregnancy.

Newborns, babies and pregnant women should not be in the same room while using VEBULIS.

Breast-feeding
It is not known whether iloprost/metabolites are excreted in human breast milk. Evidence from non-clinical data indicates a low rate of excretion of iloprost and/or its metabolites in milk. Therefore, breastfeeding should be avoided during treatment with VEBULIS.

Reproductive ability / Fertility

Animal studies have shown that iloprost has no harmful effects on fertility.

4.7 Effects on ability to drive and use machines

Care should be taken during the initiation of treatment until the effect on individuals is determined. In those with hypotensive symptoms such as dizziness, the ability to drive or use machinery may be severely affected.

4.8 Undesirable effects

In addition to local effects resulting from administration of iloprost by inhalation such as cough, adverse reactions with iloprost are related to the pharmacological properties of prostacyclins. The most frequently observed adverse reactions in clinical trials include vasodilatation, headache and cough. The most serious adverse reactions are hypotension, bleeding events and bronchospasm.

The adverse drug reactions observed with iloprost are represented in the table below. They are classified according to System Organ Class (MedDRA version 14). The most appropriate MedDRA term is used to describe a certain reaction and its synonyms and related conditions.

The adverse drug reactions (ADR) reported below are based on pooled clinical trial data from phase II and III clinical trials involving 131 patients taking the medicinal product and on data from post-marketing surveillance.

Adverse drug reactions are listed in order of frequency. The following terms and frequencies are used: 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). Within each frequency grouping, undesirable effects are presented in order of decreasing severity.

Blood and lymphatic system disorders
Very common : Bleeding events*§
Not known : Thrombocytopenia

Immune system disorders
Not known : Hypersensitivity

Nervous system disorders
Very common : Headache
Common : Dizziness

Cardiac disorders
Common : Tachycardia, palpitations

Vascular disorders
Very common : Vasodilatation, flushing
Common : Hypotension*, syncope§

Respiratory, thoracic and mediastinal disorders
Very common : Cough, chest discomfort/chest pain
Common : Dyspnoea, pharyngolaryngeal pain, throat irritation
Not known : Bronchospasm*, wheezing, nasal congestion

Gastrointestinal disorders
Very common : Nausea
Common : Diarrhoea, vomiting, mouth and tongue irritation including pain
Not known : Dysgeusia

Skin and subcutaneous tissue disorders
Common : Rash

Musculoskeletal and connective tissue disorders
Very common : Pain in jaw/trismus
Common : Back pain

General disorders and administration site conditions
Very common : Peripheral oedema[§]

* Life-threatening and/or fatal cases have been reported.
[§] See section "Description of selected adverse reactions"

Description of selected adverse reactions:
As expected from patients with pulmonary hypertension, syncope is common and its frequency did not differ significantly between treatment groups. The presence of increased syncope may be related to deterioration of the disease or insufficient effectiveness of the product (see Section 4.4).

Bleeding events (mostly epistaxis and haemoptysis) were very common as expected in this patient population with a high proportion of patients taking anticoagulant co-medication. The risk of bleeding may be increased in patients when potential inhibitors of platelet aggregation or anticoagulants are given concomitantly (see section 4.5). Fatal cases included cerebral and intracranial haemorrhage.

In clinical trials peripheral oedema was reported in 12.2% of patients on iloprost and 16.2% of patients on placebo. Peripheral oedema is a very common symptom of the disease itself, but can also occur under therapy.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorization 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 national reporting system.

4.9 Overdose
Symptoms
Cases of overdose were reported. Symptoms of overdoses are mainly related to the vasodilatory effect of iloprost. Frequently observed symptoms following overdose are dizziness, headache, flushing, nausea, jaw pain or back pain. Hypotension, an increase of blood pressure, bradycardia or tachycardia, vomiting, diarrhoea and limb pain might also be possible.

Management
A specific antidote is not known. Interruption of the inhalation session, monitoring and symptomatic measures are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents, platelet aggregation inhibitors excluding heparin
ATC Code: B01AC11
Iloprost, the active substance of VEBULIS, is a synthetic prostacyclin analogue. The following pharmacological effects have been observed *in vitro*:

- Inhibition of platelet aggregation, platelet adhesion and release reaction (release of specific granules in the platelets which start primary homeostasis)
- Dilatation of arterioles and venules
- Increase of capillary density and reduction of increased vascular permeability caused by mediators such as serotonin or histamine in the microcirculation
- Stimulation of endogenous fibrinolytic potential
- Anti-inflammatory effects like reduced leukocyte adhesion to damaged endothelium *in vivo*, and leukocyte accumulation in tissue following injury and release of tumour necrosis factor.

The pharmacological effects after inhalation of VEBULIS are:
Direct vasodilatation of the pulmonary arterial bed occur with consecutive significant improvement of pulmonary artery pressure, pulmonary vascular resistance and cardiac output as well as mixed venous oxygen saturation.

In a small, randomised, 12-week double-blinded, placebo-controlled study (the STEP trial), 34 patients treated with bosentan 125 mg twice per day for at least 16 weeks who were in stable haemodynamic conditions before enrolment, tolerated the addition of inhaled iloprost at the concentration of 10 microgram/ml (up to 5 microgram 6 to 9 times per day during waking hours). The mean daily inhaled dose was 27 microgram and the mean number of inhalations per day was 5.6. The acute adverse effects in patients receiving concomitant bosentan and iloprost were consistent with those observed in the larger experience of the phase 3 study in patients receiving only iloprost. No reliable conclusion could be drawn on efficacy of the association as the sample size was limited and the study was of short duration.

No clinical trial data are available comparing directly in intra-patient observations the acute haemodynamic response after intravenous to that after inhaled iloprost. The haemodynamics observed suggest an acute response with preferential effect of inhaled treatment on the pulmonary vessels. The pulmonary vasodilatory effect of each single inhalation levels off within one to two hours.

However, the predictive value of these acute haemodynamic data are considered to be of limited value as acute response does not in all cases correlate with long-term benefit of treatment with inhaled iloprost.

Efficacy in adults patients with pulmonary hypertension
A randomized, double-blind, multi-centre, placebo-controlled phase III trial (study RRA02997) has been conducted in 203 adult patients (inhaled iloprost at the concentration of 10 mcg/ml n=101; placebo n=102) with stable pulmonary hypertension. Inhaled iloprost (or placebo) was added to patients' current therapy, which could include a combination of anticoagulants, vasodilators (e.g. calcium channel blockers), diuretics, oxygen, and digitalis, but not PGI2 (prostacyclin or its analogues).

108 of the patients included were diagnosed with primary pulmonary hypertension, 95 were

diagnosed with secondary pulmonary hypertension of which 56 were associated with chronic thromboembolic disease, 34 with connective tissue disease (including CREST and scleroderma) and 4 were considered appetite suppressant medicinal product related. The baseline 6-minute walk test values reflected a moderate exercise limitation: in the iloprost group the mean was 332 metres (median value: 340 metres) and in the placebo group the mean was 315 metres (median value: 321 metres). In the iloprost group, the median daily inhaled dose was 30 microgram (range 12.5 to 45 microgram/day). The primary efficacy endpoint defined for this study, was a combined response criterion consisting of improvement in exercise capacity (6-minute walk test) at 12 weeks by at least 10% versus baseline, and improvement by at least one NYHA class at 12 weeks versus baseline, and no deterioration of pulmonary hypertension or death at any time before 12 weeks. The rate of responders to iloprost was 16.8% (17/101) and the rate of responders in the placebo group was 4.9% (5/102) (p=0.007).

In the iloprost group, the mean change from baseline after 12 weeks of treatment in the 6-minute walking distance was an increase of 22 metres (-3.3 metres in the placebo group, no data imputation for death or missing values).

In the iloprost group the NYHA class was improved in 26% of patients (placebo: 15%) (p = 0.032), unchanged in 67.7% of patients (placebo: 76%) and deteriorated in 6.3% of patients (placebo: 9%).

Invasive hemodynamic parameters were assessed at baseline and after 12 weeks treatment. A subgroup analysis showed that no treatment effect was observed as compared to placebo on the 6-minute walk test in the subgroup of patients with secondary pulmonary hypertension.

A mean increase in the 6-minute walk test of 44.7 metres from a baseline mean value of 329 metres vs. a change of -7.4 metres from a baseline mean value of 324 metres in the placebo group (no data imputation for death or missing values) was observed in the subgroup of 49 patients with primary pulmonary hypertension receiving treatment of inhaled iloprost for 12 weeks (46 patients in the placebo group).

Paediatric population
No study has been performed with iloprost in children with pulmonary hypertension.

5.2 Pharmacokinetic properties

General properties

Absorption:
When iloprost at the concentration of 10 microgram/ml is administered via inhalation in patients with pulmonary hypertension or healthy volunteers (iloprost dose at the mouthpiece: 5 microgram: inhalation time in between 4.6 – 10.6 min), mean peak serum concentrations of about 100 to 200 picogram/ml were observed at the end of inhalation session. These concentrations decline with half-lives between approximately 5 and 25 minutes. Within 30 minutes to 2 hours after the end of inhalation, iloprost is not detectable in the central compartment (limit of quantification 25 picogram/ml).

Distribution
No studies performed following inhalation.
Following intravenous infusion, the apparent steady-state volume of distribution was 0.6 to 0.8 l/kg in healthy subjects. Total plasma protein binding of iloprost is concentration-independent in the range of 30 to 3,000 picogram/ml and amounts to approximately 60%, of which 75% is due to albumin binding.

Biotransformation:
No studies to investigate the metabolism of iloprost were performed following inhalation of iloprost.

After intravenous administration, iloprost is extensively metabolised via ß-oxidation of the carboxyl side chain. No unchanged substance is eliminated. The main metabolite is tetranor-iloprost, which is found in the urine in free and conjugated form. Tetranor-iloprost is pharmacologically inactive as shown in animal experiments. Results of in vitro studies reveal that CYP 450-dependent metabolism plays only a minor role in the biotransformation of iloprost. Further in vitro studies suggest that metabolism of iloprost in the lungs is similar after intravenous administration or inhalation.

Elimination:
No studies performed following inhalation.

In subjects with normal renal and hepatic function, the disposition of iloprost following intravenous infusion is characterized in most cases by a two-phase profile with mean half-lives of 3 to 5 minutes and 15 to 30 minutes. The total clearance of iloprost is about 20 ml/kg/min, which indicates extrahepatic contribution to the metabolism of iloprost.

A mass-balance study was done using ^{3}H-iloprost in healthy subjects. Following intravenous infusion, the recovery of total radioactivity is 81%, and the respective recoveries in urine and faeces are 68% and 12%. The metabolites are eliminated from plasma and urine in 2 phases, for which half-lives of about 2 and 5 hours (plasma) and 2 and 18 hours (urine) have been calculated.

Pharmacokinetics after use with different nebulisers:
Breelib nebuliser:
Pharmacokinetics of iloprost were investigated in a randomized, crossover study with 27 patients, stable on iloprost 10 microgram/ml inhaled with I-Neb, following inhalation of single doses of 2.5 or 5 microgram iloprost using the Breelib or the I-Neb AAD nebuliser. Following inhalation of these doses with the Breelib, the maximum plasma concentrations (C_{max}) and systemic exposures (AUC ($0–t_{last}$)) increased dose-proportionally.

C_{max} and AUC ($0–t_{last}$) after inhalation of 5 microgram iloprost administered as iloprost 20 microgram/ml using the Breelib were 77% and 42%, respectively higher compared to inhalation of the same dose using iloprost 10 microgram/ml and the I-Neb AAD system. C_{max} and AUC ($0–t_{last}$) of iloprost after inhalation with Breelib were, however, still in the range of values observed with iloprost 10 microgram/ml using other inhalers across different studies.

I-Neb AAD nebuliser:
Pharmacokinetics under the specific study conditions of extended inhalation time, were investigated in a randomised, crossover study with 19 healthy adult men following inhalation of single doses of iloprost 10 microgram/ml and iloprost 20 microgram/ml (dose of 5 microgram iloprost at the mouthpiece) using the I-Neb. Comparable systemic exposures (AUC ($0–t_{last}$)) and approximately 30% higher maximum serum concentrations (C_{max}) were found following inhalation of iloprost 20 microgram/ml compared to iloprost 10 microgram/ml which was in line with the observed shorter inhalation time using iloprost 20 microgram/ml.

Special patient populations:
Renal impairment

In a study with intravenous infusion of iloprost, patients with end-stage renal failure undergoing intermittent dialysis treatment are shown to have a significantly lower clearance (mean CL = 5±2 ml/min/kg) than that observed in patients with renal failure not undergoing intermittent dialysis treatment (mean CL = 18±2 ml/min/kg).

Hepatic impairment
Because iloprost is extensively metabolized by the liver, the plasma levels of the active substance are influenced by changes in hepatic function. In an intravenous study, results were obtained involving 8 patients suffering from liver cirrhosis. The mean clearance of iloprost is estimated to be 10 ml/min/kg.

Gender:
Gender is not of clinical relevance to the pharmacokinetics of iloprost.

Elderly
Pharmacokinetics in elderly patients have not been investigated

5.3 Preclinical safety data

Systemic toxicity:
In acute toxicity studies, single intravenous and oral doses of iloprost caused severe symptoms of intoxication or death (intravenous) at doses about two orders of magnitude above the intravenous therapeutic dose. Considering the high pharmacological potency of iloprost and the absolute doses required for therapeutic purposes the results obtained in acute toxicity studies do not indicate a risk of acute adverse effects in humans. As expected for a prostacyclin, iloprost produced hemodynamic effects (vasodilatation, reddening of skin, hypotension, inhibition of platelet function, respiratory distress) and general signs of intoxication such as apathy, gait disturbances, and postural changes.

In systemic toxicity studies with repeated (continuous) IV infusion, a slight reduction of the blood pressure occurred at doses above 14 ng/kg/min. and severe undesired effects (hypotension, disturbance of respiratory function) appeared only after extremely high dosages.

Based on C_{max} values in rats the systemic exposure in these parenteral studies was approximately 3.5 times higher than the maximum achievable exposure after inhalation. This highest achievable dose of 48.7 mcg/kg/day was also the “no observed adverse effect level” (NOAEL) as evaluated in inhalation toxicity studies in rats up to 26 weeks. Following inhalation the systemic exposure based on AUC values in rats exceeded the corresponding therapeutic exposure in human patients by approximately 13 times.

In a chronic inhalation study in rats over 26 weeks, the highest achievable dose of 48.7 microgram/kg/day was identified as 'no observed adverse effect level' (NOAEL). Systemic exposures exceeded human therapeutic exposures after inhalation by factors of more than 10 (C_{max}, cumulative AUC).

Genotoxic potential, tumorigenicity
In vitro (bacterial, mammalian cells, human lymphocytes) and *in vivo* studies (micronucleus test) for genotoxic effects have not produced any evidence for a mutagenic potential.
No tumourigenic potential of iloprost was observed in tumourigenicity studies in rats and mice.

Reproductive toxicology:
In embryo- and fetotoxicity studies in rats continuous intravenous administration of iloprost led to

anomalies of single phalanges of the forepaws in a few foetuses/pups without dose dependence.

These alterations are not considered as teratogenic effects, but are most likely related to iloprost induced growth retardation in late organogenesis due to hemodynamic alterations in the fetoplacental unit. No disturbance of postnatal development and reproductive performance was seen in the offspring that were raised, indicating that the observed retardation in rats was compensated during the postnatal development. In comparable embryotoxicity studies in rabbits and monkeys, no such digit anomalies or other gross-structural anomalies were observed even after considerably higher dose levels, which exceeded the human dose multiple times. In rats, passage of low levels of iloprost and/or metabolites into the milk was observed (less than 1% of iloprost dose given intravenously). No disturbance of post-natal development and reproductive performance was seen in animals exposed during lactation.

Local tolerance, contact sensitizing and antigenicity potential
In inhalation studies in rats, the administration of an iloprost formulation with a concentration of 20 microgram/ml up to 26 weeks did not cause any local irritation of the upper and lower respiratory tract. A dermal sensitization (maximization test) and an antigenicity study in guinea pigs showed no sensitizing potential.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol
Trometamol
Sodium chloride
Hydrochloric acid
Water for injection

6.2 Incompatibilities

In the absence of compatibility studies, this medicinal product must not be mixed with other medicinal products.

6.3 Shelf life

36 months

6.4 Special precautions for storage

Keep at room temperature below 25°C.

6.5 Nature and contents of packaging

Primary packaging material: 3 ml, colourless, Type I glass ampoules containing 2 ml of inhalation solution for nebulisation, ring coded with two coloured rings (white and pink).
Each cardboard box contains 30 ampoules of VEBULIS 10 mcg/ml inhalation solution for nebulisation and a package leaflet.

6.6 Special precautions for disposal and other handling

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

A new ampoule of VEBULIS should be used with each inhalation session. Just before use, the entire content of one ampoule of VEBULIS should be placed in the chamber of the nebulizer.

After each inhalation session, any solution remaining in the nebuliser should be discarded. In addition, instructions for hygiene and cleaning of the nebulisers provided by the device manufacturers should be followed carefully.

Use with nebulisers:
In general, suitable nebulisers to be used for the inhalation therapy with VEBULIS 10 mcg/ml inhalation solution for nebulisation are registered according to the regional medical device regulations and work with compressed air, ultrasound or vibrating mesh technology.

Nebulisers suitable for inhalation of iloprost fulfil the following requirements:
The nebulisers deliver 2.5 microgram or 5 microgram iloprost at the mouthpiece in a time period of approximately 4 to 10 minutes. The Mass Median Aerodynamic Diameter (MMAD) of the aerosol is between 1 and 5 micrometres.

Following nebulisers have been tested and found appropriate for the administration of iloprost 10 microgram/ml:
- HaloLite AAD (Philips Respironics)
- Prodose AAD (Philips Respironics)
- Venta-Neb (Nebu-Tec)
- I-Neb AAD (Philips Respironics)

To minimize accidental exposure, it is recommended to use VEBULIS with nebulisers with inhalation-triggered systems and to keep the room well ventilated.

Switching to a different nebulizer should be done under the supervision of the treating physician.

Using the I-Neb AAD system:
While using the I-Neb AAD system, the following instructions should be followed.

The dose delivered by the I-Neb AAD system is controlled by the medication chamber with a control disc. Each medication chamber has a corresponding colour-coded control disc.

For 2.5 microgram dose, red latch drug reservoir is used with the red control disc. For 5 microgram dose, purple latch medication cup is used with the purple control disc.

With the I-Neb AAD, in each inhalation session, the contents of the solution ampoule for a VEBULIS 10 mcg/ml nebuliser with a two-coloured ring is transferred to the appropriate nebuliser drug reservoir just before use.

Using the Breelib system
When using the Breelib nebuliser, the instructions for use provided with the device should be followed.
The medication tank must be filled with VEBULIS just before use.

It is recommended to ventilate the room in order to minimize the risk of unintentional inhalation of VEBULIS.

7. MARKETING AUTHORISATION HOLDER

DEVA Holding A.Ş.

Halkalı Merkez Mah. Basın Ekspres Cad. No:1
34303 Küçükçekmece – İSTANBUL / TÜRKİYE

8. MARKETING AUTHORISATION NUMBER

2015/955

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10. DATE OF REVISION OF THE TEXT

25.04.2021