SUMMARY OF PRODUCT CHARACTERISTICS

1 NAME OF THE MEDICINAL PRODUCT

Iloprost 20 microgram/ml nebuliser solution

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each ampoule with 1 ml solution contains 20 microgram iloprost (as iloprost trometamol).

Excipient with known effect

Each ml contains 1.62 mg ethanol 96%.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Nebuliser solution.

Clear and colourless solution free of visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

Treatment of adult patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms.

4.2 Posology and method of administration

Drug product	**Suitable inhalation device (nebuliser) to be used**		
Iloprost 10 microgram/ml	Breelib*	I-Neb AAD**	Venta-Neb***
Iloprost 20 microgram/ml	Breelib*	I-Neb AAD**	

* Breelib is a trademark of Bayer Intellectual Property GmbH.
** I-NEB is a trademark of RIC Investments, LLC.
*** Venta-Neb is a trademark of NEBU-TEC med. Produkte Eike Kern GmbH.

Iloprost should only be initiated and monitored by a physician experienced in the treatment of pulmonary hypertension.

Posology

Dose per inhalation session

At initiation of Iloprost treatment the first inhaled dose should be 2.5 microgram iloprost as delivered at the mouthpiece of the nebuliser. If this dose is well tolerated, dosing should be increased to 5 microgram iloprost and maintained at that dose. In case of poor tolerability of the 5 microgram dose, the dose should be reduced to 2.5 microgram iloprost.

Daily dose

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

Duration of treatment

The duration of treatment depends on clinical status and is left to the physician's discretion. Should patients deteriorate on this treatment intravenous prostacyclin treatment should be considered.

Special populations

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 using Iloprost 10 microgram/ml with dosing intervals of 3 – 4 hours (corresponds to administration of max. 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. An accumulation of iloprost following treatment over several days is not likely due to the overnight break in administration of the medicinal product.

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 (see above) are to be applied.

Paediatric population

The safety and efficacy of Iloprost in children aged up to 18 years have not been established.

No data from controlled clinical trials are available.

Method of administration

Iloprost is intended for inhalation use by nebulisation.

To minimise accidental exposure it is recommended to keep the room well ventilated.

The ready-to-use Iloprost nebuliser solution is administered with a suitable inhalation device (nebuliser) (see below and section 6.6).

Patients stabilised on one nebuliser should not switch to another nebuliser without supervision by the treating physician as different nebulisers have been shown to produce aerosols with slightly different physical characteristics and delivery of the solution that may be faster (see section 5.2).

- **Breelib**

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

Iloprost 10 microgram/ml and Iloprost 20 microgram/ml nebuliser solution

Iloprost 10 microgram/ml nebuliser solution (1 ml ampoule) delivers 2.5 microgram and Iloprost 20 microgram/ml nebuliser solution delivers 5 microgram at the mouthpiece of the Breelib nebuliser.

At initiation of Iloprost treatment or if the patient is switched from an alternative device, the first inhalation should be made with 1 ml ampoule of Iloprost 10 microgram/ml (see section 4.4). If inhalation with Iloprost 10 microgram/ml is well tolerated, the dose should be increased by using Iloprost 20 microgram/ml. This dose should be maintaned. In case of poor tolerability of Iloprost 20 microgram/ml, the dose should be reduced by using 1 ml ampoule of Iloprost 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 nebulizers.

Patients initiating Iloprost 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 Iloprost immediately before use.

- **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 Iloprost 10 microgram/ml and 20 microgram/ml nebuliser solution. The Mass Median Aerodynamic Diameter (MMAD) of the aerosol measured using I-Neb nebulising systems equipped with power level 10 disc was similar between iloprost 20 microgram/ml (golden programme) and iloprost 10 microgram/ml (purple programme) nebuliser solutions (around 2 micrometres) but with faster delivery when using iloprost 20 microgram/ml.

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

Iloprost 10 microgram/ml nebuliser solution

At initiation of Iloprost treatment with I-Neb system the first inhaled dose should be 2.5 microgram iloprost as delivered at the mouthpiece of the nebuliser using 1 ml ampoule of Iloprost 10 microgram/ml. If this dose is well tolerated, dosing should be increased to 5 microgram iloprost using 1 ml ampoule of Iloprost 10 microgram/ml and maintained at that dose. In case of poor tolerability of the 5 microgram dose, the dose should be reduced to 2.5 microgram iloprost.

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.

For the 2.5 microgram dose of Iloprost 10 microgram/ml the medication chamber with the red coloured latch is used together with the red control disc.

For the 5 microgram dose of Iloprost 10 microgram/ml 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 Iloprost 10 microgram/ml, is transferred into the medication chamber immediately before use.

Drug product	**Dosage**	**I-Neb AAD**		**Estimated inhalation time**
		Medication chamber latch	**Control disc**	
Iloprost 10 microgram/ml	2.5 mcg	red	red	3.2 min
	5 mcg	purple	purple	6.5 min

Iloprost 20 microgram/ml nebuliser solution

Only patients who are maintained at the 5 microgram dose and who have repeatedly experienced extended inhalation times with Iloprost 10 microgram/ml, which could result in incomplete inhalation, may be considered suitable for switching to Iloprost 20 microgram/ml.

Close supervision by the treating physician is necessary if switching from Iloprost 10 microgram/ml to Iloprost 20 microgram/ml to control the acute tolerance relating to faster delivery rate of iloprost with the double concentration.

This nebuliser monitors the breathing pattern to determine the aerosol pulse time required to deliver the pre-set dose of 5 microgram iloprost. For the 5 microgram dose of Iloprost 20 microgram/ml the medication chamber with the gold coloured latch is used together with the gold control disc.

For each inhalation session with the I-Neb AAD, the content of one 1 ml ampoule of Iloprost 20 microgram/ml is transferred into the medication chamber immediately before use.

Drug product	**Dosage**	**I-Neb AAD**	
		Medication chamber latch	**Control disc**
Iloprost 20 microgram/ml	5 mcg	golden	golden

<u>Other nebulising systems</u>

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.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Conditions where the effects of Iloprost 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 6 months.
- Decompensated cardiac failure if not under close medical supervision.
- Severe arrhythmias.
- Cerebrovascular events (e.g. transient ischaemic 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 Iloprost 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 Iloprost. 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. Iloprost 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

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

Iloprost inhalation might entail the risk of inducing bronchospasm, especially in patients with bronchial hyperactivity (see section 4.8). Moreover, the benefit of 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 Iloprost should be discontinued.

Interruption of therapy

In case of interruption of Iloprost 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 1 year was associated with slightly increased fasted serum glucose levels. It cannot be excluded that this is also relevant to humans on prolonged Iloprost therapy.

Undesirable exposure to Iloprost

To minimise accidental exposure, it is recommended to use Iloprost with nebulisers with inhalation-triggered systems (such as Breelib or I-Neb), and to keep the room well ventilated.

Newborns, infants, and pregnant women should not be subjected to Iloprost in the room air.

Skin and eye contact, oral ingestion

Iloprost nebuliser solution should not come into contact with skin and eyes; oral ingestion of Iloprost solution should be avoided. During nebulisation sessions a facial mask must be avoided and only a mouthpiece should be used.

Iloprost contains ethanol

This medicine contains 1.5 mg of ethanol in 1 ml of the nebuliser solution which is equivalent to 1.62 mg 96% ethanol (v/v). The small amount of alcohol in this medicine will not have any noticeable effects.

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 Iloprost 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).

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 Iloprost 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).
- 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.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should use effective contraceptive measures during treatment with Iloprost.

Pregnancy

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 Iloprost 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.

Breast-feeding

It is not known whether iloprost/metabolites are excreted in human breast milk. Very low levels of iloprost into milk were observed in rats (see section 5.3). A potential risk to the breast-feeding child cannot be excluded and it is preferable to avoid breast-feeding during Iloprost therapy.

Fertility

Animal studies have not shown harmful effect of iloprost on fertility.

4.7 Effects on ability to drive and use machines

Iloprost has major influence on the ability to drive and use machines for patients experiencing hypotensive symptoms such as dizziness.

Care should be exercised during initiation of therapy until any effects on the individual have been determined.

4.8 Undesirable effects

Summary of the safety profile

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 (≥ 20%) in clinical trials include vasodilatation (including hypotension), headache and cough. The most serious adverse reactions were hypotension, bleeding events, and bronchospasm.

Tabulated list of adverse reactions

The adverse reactions reported below are based on pooled clinical trial data from phase II and III clinical trials involving 131 patients taking iloprost and on data from post-marketing surveillance. The frequencies of adverse reactions are defined as very common (≥ 1/10) and common (≥ 1/100 to < 1/10). The adverse reactions identified only during post-marketing surveillance, and for which a frequency could not be estimated from clinical trial data, are listed under “Frequency not known”.

Within each frequency grouping, adverse reactions are presented in order of decreasing seriousness.

System organ class (MedDRA)	**Very common**	**Common**	**Not known**
Blood and lymphatic	Bleeding events*[§]		Thrombocytopenia

system disorders			
Immune system disorders			Hypersensitivity
Nervous system disorders	Headache	Dizziness	
Cardiac disorders		Tachycardia Palpitations	
Vascular disorders	Vasodilatation Flushing	Syncope§ (see section 4.4) Hypotension*	
Respiratory, thoracic and mediastinal disorders	Chest discomfort / chest pain Cough	Dyspnoea Pharyngolaryngeal pain Throat irritation	Bronchospasm* (see section 4.4) / wheezing
Gastrointestinal disorders	Nausea	Diarrhoea Vomiting Mouth and tongue irritation including pain	Dysgeusia
Skin and subcutaneous tissue disorders		Rash	
Musculoskeletal and connective tissue disorders	Pain in jaw / trismus		
General disorders and administration site condition	Peripheral oedema§		

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

Description of selected adverse reactions

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.

Syncope is a common symptom of the disease itself, but can also occur under therapy. The increased occurrence of syncope can be related to the deterioration of the disease or insufficient effectiveness of the product (see section 4.4).

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. The occurrence of peripheral oedema can be related to the deterioration of the disease or insufficient effectiveness of the product.

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 Yellow Card Scheme at: www.mhra.gov.uk/yellowcard or search for MHRA Yellow Card in the Google Play or Apple App Store.

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 Iloprost, is a synthetic prostacyclin analogue. The following pharmacological effects have been observed *in vitro*:

- Inhibition of platelet aggregation, platelet adhesion and release reaction.
- 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.

The pharmacological effects after inhalation of Iloprost are:

Direct vasodilatation of the pulmonary arterial bed occurs 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 – 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 III 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 1 – 2 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 adult patients with pulmonary hypertension

A randomised, 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 microgram/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 – 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% vs. baseline, and improvement by at least 1 NYHA class at 12 weeks vs. 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 haemodynamic 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

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 – 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 – 0.8 l/kg in healthy subjects. Total plasma protein binding of iloprost is concentration-independent in the range of 30 – 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 characterised in most cases by a 2-phase profile with mean half-lives of 3 – 5 minutes and 15 – 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 3H-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 randomised, 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 (Cmax) and systemic exposures (AUC (0 – tlast)) increased dose-proportionally.

Cmax and AUC (0 – tlast) 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. Cmax and AUC (0 – tlast) 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 – tlast)) and approximately 30% higher maximum serum concentrations (Cmax) 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.

Other special 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 metabolised 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 2 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 haemodynamic 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.

Continuous intravenous/subcutaneous infusion of iloprost up to 26 weeks in rodents and non-rodents did not cause any organ toxicity at dose levels which exceeded the human therapeutic systemic exposure between 14 and 47 times (based on plasma

levels). Only expected pharmacological effects like hypotension, reddening of skin, dyspnoea, increased intestinal motility were observed.

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 (Cmax, cumulative AUC).

Genotoxic potential, tumourigenicity

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 foetotoxicity 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 haemodynamic alterations in the foetoplacental 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 sensitising 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 sensitisation (maximisation test) and an antigenicity study in guinea pigs showed no sensitising potential.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Ethanol 96%

Trometamol

Sodium chloride

Hydrochloric acid (for pH adjustment)

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

5 years.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

Do not freeze.

6.5 Nature and contents of container

Clear glass ampoule of hydrolytic class No. I with identifying colour rings – red, yellow containing 1.0 ml of solution (extractable volume) in sealed ampoule packed in blister and paper box.

Pack sizes:

30×1 ml (6 blisters with 5 ampoules or 5 blisters with 6 ampoules).

42×1 ml (8 blisters with 5 ampoules and 1 blister with 2 ampoules or 7 blisters with 6 ampoules).

168×1 ml (33 blisters with 5 ampoules and 1 blister with 3 ampoules or 28 blisters with 6 ampoules).

Multipack containing 160 ampoules (4 inner boxes containing 8 blisters with 5 ampoules).

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

For each inhalation session the content of 1 opened ampoule of Iloprost has to be transferred completely into the medication chamber immediately before use.

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.

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

7 MARKETING AUTHORISATION HOLDER

Zentiva Pharma UK Limited
12 New Fetter Lane
London
EC4A 1JP
United Kingdom

8 MARKETING AUTHORISATION NUMBER(S)

PL 17780/0886

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

19/02/2021

10 DATE OF REVISION OF THE TEXT

18/11/2024