Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Iloprost Waymade 100 micrograms/ml concentrate for solution for infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

One ampoule of 0.5 ml contains 67 micrograms of Iloprost trometamol (equivalent to 50 micrograms of iloprost).
Each 1 ml concentrate contains 134 micrograms of Iloprost trometamol (equivalent to 100 micrograms of iloprost).

Excipient(s) with known effect:
Each ampoule of 0.5 ml contains 4.050 mg of 96% ethanol.

For the full list of excipients, see section 6.1.

3 PHARMACEUTICAL FORM

Concentrate for solution for infusion.

Clear colourless solution, free of visible particles.

4 CLINICAL PARTICULARS

4.1 Therapeutic indications

For the treatment of advanced-stage thromboangiitis obliterans (Buerger's disease), with severe circulation disorders, in cases where revascularisation is not indicated.

4.2 Posology and method of administration

Posology
Treatment with Iloprost Waymade must be done under rigorous monitoring in hospitals or clinics that have the proper equipment. Pregnancy must be ruled out before starting treatment in women.

Iloprost Waymade is to be administered after dilution, as described in section 6.6 "Special precautions for disposal and handling," in the form of an intravenous infusion, over a period of 6 hours per day, through a peripheral vein or a central catheter in a vein. The dose is to be adjusted according to the patient's tolerance within a range of 0.5 - 2.0 ng of iloprost per kg of body weight per minute.

The solution for infusion must be prepared daily in order to ensure it is sterile. The contents of the ampoule and the solvent must be thoroughly mixed.

Blood pressure and heart rate must be checked at the start of the infusion and after every dose increase.

The dose tolerated by the patient is to be determined during the first 2 -3 days. To that end, treatment should be started with an infusion rate that provides a dose of 0.5 ng/kg/min. over 30 minutes. Subsequently, the dose should be gradually increased by intervals of approximately 30 minutes, in stages of 0.5 mg/kg/min. - 2.0 ng/kg/min. The exact infusion rate must be calculated based on the patient's body weight so as to obtain an infusion of 0.5 - 2.0 ng/kg/min (see the tables on the use of an infusion pump or a bypass system).

If side effects occur, such as headache, nausea or decreased blood pressure, the infusion rate should be reduced until the tolerated dose is found. If there are severe side effects, the infusion should be discontinued. Treatment should normally proceed over a period of 4 weeks, using the dose that was well tolerated in the first 2 - 3 days.

Depending on the method of infusion, there are two different dilutions for the ampoule.
One of them is 10 times less concentrated than the other (0.2 µl/ml versus 2 µl/ml) and can only be used with an infusion

pump (e.g. Infusomat). In contrast, the solution with the higher concentration is to be administered using a bypass system (e.g. Perfusor). For instructions on use and handling, see section 6.6, Special precautions for disposal".

Speed of infusion (ml/hour) for different doses with the use of an infusion pump
In general, the solution prepared for infusion is to be administered intravenously using an infusion pump (e.g. Infusomat). For instructions for dilution for use with an infusion pump, see section 6.6, "Special precautions for disposal and handling".

For a 0.2 µg/ml concentration of Iloprost Waymade, the infusion rate required must be calculated according to the procedure described below so as to obtain a dose of 0.5 - 2.0 mg/km/min.

The following table may be used to calculate the infusion rate that matches the patient's body weight and the dose for infusion. Please be sure to check the patient's body weight and determine the infusion rate for the desired dose, in ng/kg/min.

Body weight (kg)	Dose (ng/kg/min)			
	0.5	1.0	1.5	2.0
	Infusion rate (ml/h)			
40	6.0	12	18.0	24
50	7.5	15	22.5	30
60	9.0	18	27.0	36
70	10.5	21	31.5	42
80	12.0	24	36.0	48
90	13.5	27	40.5	54
100	15.0	30	45.0	60
110	16.5	33	49.5	66

Infusion rate (ml/h) for different doses using a bypass system.

A bypass system may also be used, with a 50 ml capacity injection syringe (e.g. Perfusor). For dilution instructions for use with a bypass system, see section 6.6, "Special precautions for disposal and handling".

For a 2 µg/ml concentration of Iloprost Waymade, the required infusion rate must be determined according to the following procedure, so as to obtain a dose of between 0.5 and 2.0 ng/kg/min.

The following table may be used to calculate the infusion rate that matches the patient's body weight and the dose for infusion. Please be sure to check the patient's body weight and determine the infusion rate for the desired dose, in ng/kg/min.

Body weight (kg)	Dose (ng/kg/min)			
	0.5	1.0	1.5	2.0
	Infusion rate (ml/h)			
40	0.60	1.2	1.80	2.4
50	0.75	1.5	2.25	3.0
60	0.90	1.8	2.70	3.6
70	1.05	2.1	3.15	4.2
80	1.20	2.4	3.60	4.8
90	1.35	2.7	4.05	5.4
100	1.50	3.0	4.50	6.0
110	1.65	3.3	4.95	6.6

The treatment should last for 4 weeks.

Due to possible tachyphylaxis effects caused by platelets and to a possible rebound platelet hyper-aggregation at the end of treatment, a continuous infusion over several days is not recommended, even if no clinical complications due to such manifestations have been found.

- Patients with renal or hepatic impairment

It must be taken into consideration that the elimination of iloprost is reduced in patients with renal impairment undergoing dialysis, and in patients with hepatic cirrhosis. The dose must be reduced in such patients (e.g. to half the recommended dose).

Method of administration
For instructions on how to dilute this medicinal product before administration, see section 6.6.

4.3 Contraindications

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

- Pregnancy;
- Breast-feeding;
- Situations where the effect of Iloprost Waymade on platelets may increase the risk of haemorrhaging (e.g. active peptic ulcers, trauma, intra-cranial haemorrhaging);
- severe coronary heart disease or unstable angina;
- myocardial infarction in the last 6 months;
- acute or chronic heart failure (NYHA II-IV);
- Severe arrhythmia;
- Suspected lung congestion.

4.4 Special warnings and precautions for use

Special warnings
Surgery should not be postponed in patients who need emergency amputation (e.g. in cases of infected gangrene).

Patients should be strongly advised to stop smoking.

The elimination of iloprost is reduced in patients with hepatic impairment and renal failure who require dialysis (see sections 4.2, "Posology and method of administration" and 5.2 "Pharmacokinetic properties".

Caution should be used in hypotensive patients in order to avoid aggravating this condition. Patients with relevant heart disorders should be carefully monitored.

Attention should be given to the possible occurrence of orthostatic hypotension in patients who change from a prone position to a standing position at the end of the infusion. For patients with cerebrovascular disorders (transitory ischemic attack, stroke) in the last 3 months, a rigorous risk/benefit assessment must be done (also see 4.3, "Contraindications: risk of haemorrhaging, e.g. intra-cranial haemorrhaging.

Special precautions
Only sporadic reports are currently available on use in children and adolescents.

Vascular infusion of undiluted Iloprost Waymade may cause alterations at the injection site.

Oral ingestion and contact with mucous membranes should be avoided. When it comes into contact with the skin, iloprost may cause persistent but painless erythema. The necessary precautions should thus be taken to avoid iloprost coming into contact with the skin. Should this occur, the affected area should immediately be washed with generous amounts of water or saline solution.

Iloprost Waymade, 100 micrograms/ml concentrate for solution for infusion contains ethanol and sodium

This medicinal product contains 4.050 mg of alcohol (96% ethanol) in each 1 ml. The amount in 1 ml of this medicinal product is equivalent to less than 1 ml beer or 1 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects.

This medicinal product contains less than 1 mmol sodium (23 mg) per 1 ml, that is to say essentially 'sodium free'.'

4.5 Interaction with other medicinal products and other forms of interaction

Iloprost may increase the anti-hypertensive action of β-receptor blockers, calcium antagonists, vasodilators and ACE inhibitors. If significant hypotension is observed, the dose of iloprost must be reduced.

Since iloprost inhibits platelet aggregation, its simultaneous use with anticoagulants (such as heparin and anticoagulants derived from coumarin), or other platelet aggregation inhibitors (such as acetylsalicylic acid, NSAID's, phosphodiesterase inhibitors, and nitro vasodilators, e.g. moisidomine), may increase the risk of haemorrhaging.

If haemorrhaging occurs, the administration of iloprost must be discontinued.

Oral pre-medication with acetylsalicylic acid up to 300 mg per day for a period of 8 days had no effect on the pharmacokinetics of iloprost. In a study with animals, it was found that iloprost may cause a reduction in the steady-state plasma concentration of t-PA (a plasminogen activator). The results of studies in humans showed that infusions of iloprost do not affect the pharmacokinetics of multiple oral doses of digoxin in patients and that iloprost has no effect on the pharmacokinetics of co-administered t-PA.

During experiments with animals, it was found that the vasodilator effect of iloprost is attenuated if the animals were treated previously with glucocorticoids, with no change in their platelet anti-aggregation action. The significance of this datum in relation to humans is still unknown.

Although clinical studies have not been conducted, in vitro studies to investigate the potential inhibitive effect of iloprost on the enzyme activity of the P-450 cytochrome showed that no relevant inhibition by iloprost of drug metabolism by this enzymatic path is to be expected.

4.6 Fertility, pregnancy and lactation

Iloprost Waymade must not be administered to women who are pregnant or breast feeding (see section 4.3, "Contraindications").

- Pregnancy
There are not sufficient data on the use of iloprost in pregnant women. Pre-clinical studies have shown evidence of foetal toxicity in rats, but not in rabbits or monkeys (see section 5.3, "Preclinical safety data"). Since the risk of therapeutic use of iloprost during pregnancy is unknown, women of child-bearing age should use an effective means of contraception during their treatment.

- Breast-feeding
It is not known whether iloprost is excreted into breast milk. Since in rats, iloprost is excreted into mother's milk in very small amounts, it should not be administered to women who are breast feeding.

4.7 Effects on ability to drive and use machines

Not relevant.

4.8 Undesirable effects

The pharmacological action of iloprost results in very common side effects, such as headache (68.8%) or vasodilation that causes flushing (58%), or gastrointestinal symptoms (up to 29.7%). These effects may occur while the dose is being adjusted, at the start of treatment, in order to determine the dose that the patient tolerates the best. However, these side effects usually disappear quickly after dose reduction.

Another group of side effects is related to local reactions at the site of the infusion. For example, redness or pain may occur at the infusion site, or a cutaneous vasodilation that causes striated erythema at the site of the vein used for infusion. The frequency of occurrence of the adverse effects are shown in the following table (very common (≥1/10), common (≥1/100 and <1/10); uncommon (≥1/1,000 and <1/100); rare (≥1/10,000 and <1/1,000); and very rare (<1/10,000) or unknown (cannot be estimated based on the data available).

In the following table, the adverse effects were chosen according to their rate of occurrence in the iloprost groups (553 patients) compared with the placebo groups (507 patients) in controlled clinical studies, and the effective rates of occurrence based on cumulative data in 3,325 patients to whom iloprost was administered, whether in controlled or uncontrolled studies, or in programs of compassionate use.

Adverse effects

Adverse effects				
System Organ Class (MedDRA* (v.8.0))	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
Metabolism and nutrition disorders		Anorexia		
Psychiatric disorders		Apathy	Anxiety Depression Hallucinations	
Nervous system disorders	Headache	Dizziness, Vertigo, Paraesthesia/ Tingling Palpitations Hyperaesthesia, A burning sensation, Restlessness, Agitation, Sedation, Sleepiness	Tremor Migraine Fainting/Syncope	
Eye disorders			Abnormal vision Cloudy vision Eye irritation Eye pain	
Ear and labyrinth disorders				Vestibular disorders
Cardiac disorders		Bradycardia	Arrhythmia Extra-systoles Myocardial infarction	
Vascular disorders	Flushing	Hypotension	Stroke Cerebrovascular ischemia Deep-vein thrombosis Pulmonary embolism	
Respiratory, thoracic and mediastinal disorders			Asthma	Cough
Gastrointestinal disorders	Nausea Vomiting	Diarrhoea Abdominal discomfort Abdominal pain	Dyspepsia Tenesmus Obstipation Burping Dysphagia Diarrhoea Rectal haemorrhaging Dry mouth Changes in taste	Proctitis
Hepatobiliary disorders			Jaundice	
Cutaneous and subcutaneous tissue disorders	Sudation		Pruritus	
Musculoskeletal and connective tissue disorders		Jaw pain, Myalgia, Lockjaw Arthralgia	Tetany Cramps Hypertonia	
Renal and urinary disorders			Renal pain Tenesmus -urogenital Abnormal urine Dysuria	

			Urinary tract disorders	
General disorders and alterations at the site of administration		Localised pain/Generalised pain Fever/High body temperature General sensation of heat Weakness General discomfort Chills Fatigue/Tiredness Thirst Reaction at the injection site (erythema, pain, phlebitis)		

* The most suitable MedDRA terms are used to describe the reactions listed. Synonymous or related pathologies are not listed, but should also be taken into consideration.

In addition, adverse reactions found include: allergic reactions, states of confusion, tachycardia and increased blood pressure. Isolated cases of shortness of breath (dyspnea) and individual cases of pulmonary oedema or heart failure in elderly patients with advanced-stage arteriosclerosis. Iloprost may cause chest pain due to angina, especially in patients with coronary disease. Hypotension has been reported after the administration of low doses of Iloprost Trometamol.

The risk of haemorrhaging increases in patients with the concomitant administration of platelet aggregation inhibitors, heparin or anticoagulants derived from coumarin.

Post-marketing study data:
- Nervous system disorders
Very rare: Seizures

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, Website: www.hpra.ie.

4.9 Overdose

- Symptoms
The following may be expected: hypotensive reaction, headache, flushing, nausea, vomiting and diarrhoea. Also possible are increased blood pressure, bradycardia or tachycardia, and pain in the limbs and back.

- Treatment
No specific antidote is known.
It is recommended that the administration of iloprost be discontinued, the patient be monitored, and symptomatic measures taken.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: 4.3.1.4 - Platelet anti-aggregants.
ATC code: B01A C11

Iloprost is a synthetic analogue of prostacyclin. The following pharmacological properties have been found:

- Inhibition of platelet aggregation and adhesion, and of the release reaction;

- dilation of arterioles and venules, increased capillary density and decrease in elevated vascular permeability caused by mediators such as serotonin or histamine in the microcirculation system;
- stimulation of the endogenous fibrinolytic potential;
- anti-inflammatory effects, such as inhibited adhesion of leukocytes after endothelial lesions, the accumulation of leukocytes in damaged tissue and reduced release of the tumoral necrosis factor.

5.2 Pharmacokinetic properties

Distribution
Steady-state plasma levels are achieved in 10 - 20 minutes after intravenous infusion starts. Steady-state plasma levels show a linear relationship with the infusion rate. With an infusion rate of 3 ng/kg/min, one obtains plasma levels of 135 + 24 µg/ml. After the infusion is finished, a quick drop is found in the plasma concentration of iloprost as a result of its high rate of metabolisation. The metabolic clearance rate of the substance from plasma is approximately 20 + 5 ml/kg/min. The half-life of the plasma terminal disposal phase is 0.5 hours, so the levels of the substance drop to less than 10% of the equilibrium concentration 2 hours after the infusion ends. Any interactions with other medicinal products in terms of plasma protein binding seem to be quite unlikely since the concentrations of iloprost attained are very low, and since a major part of the iloprost is bound to blood plasma albumin (protein binding: 60%). Likewise, it is deemed quite unlikely that treatment with iloprost will have any effect on the biotransformation of other medicinal products, due to the nature of the metabolic pathways and the presence of low absolute doses.

Biotransformation
Iloprost is extensively metabolised, especially via β-oxidation of the carboxyl side chain. There are no reports of any later elimination of unaltered substance. The main metabolite is tetranor-iloprost, which is found freely in the urine and is combined with 4 diastereoisomers. The tetranor-iloprost is pharmacologically inactive, as has been demonstrated in animal studies. The in vitro studies suggest that metabolism of iloprost in the lungs is similar after both intravenous administration and inhalation.

Elimination
In people with normal renal and hepatic function, the elimination of iloprost after intravenous infusion is characterised most of the time by a profile with two phases, with median half-lives of 3 - 5 minutes and of 15 - 30 minutes. Total iloprost clearance is around 20 ml/kg/min., which indicates there is an extra-hepatic contribution to the metabolism of iloprost.

A weight-balance study was done using 3H-iloprost in healthy subjects. After intravenous infusion, total recovery of the radioactivity was 81%, and the respective recovery rates in the urine and faeces were 68% and 12%. The metabolites are eliminated from the plasma and urine in 2 phases, for which the half-lives are calculated to be approximately 2 - 5 hours for plasma and 2 - 18 hours for the urine.

Characteristics in patients

Renal impairment.
In a study with intravenous infusion of iloprost, those patients with terminal-phase renal impairment subjected to intermittent dialysis were found to have significantly lower clearance (mean CL=5±2 ml/min/kg) than the patients with renal impairment not undergoing intermittent dialysis (mean CL=18±2 ml/min/kg).

Hepatic impairment
Since iloprost is extensively metabolised in the liver, plasma levels of the drug are influenced by changes in hepatic function. In an intravenous study, results were obtained involving 8 patients with hepatic cirrhosis. The mean clearance of iloprost was estimated to be 10 ml/min/kg.

Age and gender
Age and gender have no clinical relevance in the pharmacokinetics of iloprost.

5.3 Preclinical safety data

Preclinical data based on conventional studies of pharmacological safety, acute toxicity, repeated-dose toxicity, genotoxicity and carcinogenic potential, showed no special dangers for humans. Toxic effects were only found with exposure rates considered to be sufficiently greater than the maximum exposure rate in humans, indicating little relevance in clinical use. These effects were predominantly related to excessive pharmacological action.

In embryo-toxicity and foeto-toxicity studies in rats, continuous intravenous administration of iloprost resulted in abnormalities in the phalanges of the front paws in some foetuses, independent of the dose.

These alterations are not considered true teratogenic effects, but are most likely related to delayed growth in later organogenesis induced by iloprost, due to haemodynamic changes in the foeto-placenta unit. In comparative embryo-toxicity studies in rabbits and monkeys, these abnormalities of the toes were not found, nor were other major structural changes, not even after dose levels substantially higher than the therapeutic doses.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol
Sodium chloride
Hydrochloric acid
Water for injection
Ethanol 96 % (v/v)

6.2 Incompatibilities

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

6.3 Shelf life

Before opening:
4 years.

After opening and dilution:
The physical and chemical stability of the solution prepared for infusion (diluted in saline solution or glucose solution) has been demonstrated in an assay of 6 hours at 25°C. From a microbiological point of view, this medicine should be used immediately. If not used immediately, the user will be responsible for period of time and conditions of use, which should normally not exceed 24 hours at a temperature of 2°C - 8°C, unless the dilution was prepared under controlled and validated aseptic conditions.

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions. For storage conditions after dilution and first opening of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Type I, colourless glass ampoules of 1 ml, containing 0.5 ml of concentrate for solution for infusion.
Pack sizes: 1, 5 or 20 glass ampoules, each with 0.5 ml concentrate for solution for infusion.
Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Iloprost Waymade must be administered only after dilution.

Given the possibility of drug interactions, no other drugs should be added to the solution prepared for infusion.
The solution for infusion must be prepared daily in order to ensure it is sterile.

Instructions for dilution
The contents of the ampoule and the solvent must be thoroughly mixed.

Dilution of Iloprost Waymade for use with an infusion pump:
The contents of one ampoule of 0.5 ml (50 µg) of Iloprost Waymade must be diluted in 250 ml of 5% saline solution or glucose solution.

Dilution of Iloprost Waymade for use with a bypass system:
In this case, the contents of one ampoule of 0.5 ml (50 µg) of Iloprost Waymade must be diluted in 25 ml of 5% saline solution or glucose solution.

Handling
Do not let iloprost solution come into contact with your skin or eyes. If it does, rinse the skin or your eyes immediately with plenty of water.

Storage conditions for these medicinal products must be complied with, and the products must be kept out of the reach and sight of children.

Any unused medication or waste should be disposed of in accordance with local regulations.

7 MARKETING AUTHORISATION HOLDER

Waymade B.V.
Herikerbergweg 88
Amsterdam
1101 CM
Netherlands

8 MARKETING AUTHORISATION NUMBER

PA22879/006/001

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 14th August 2026

10 DATE OF REVISION OF THE TEXT