Prescribing Information

1. NAME OF THE MEDICINAL PRODUCT
Ilomedin

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

0.5 ml aqueous solution contains 67 microgram iloprost trometamol (equivalent to 50 microgram iloprost).
Excipient with known effect:
The 0.5 mL ampoule contains 4.05 mg of ethanol
For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Concentrate for solution for infusion.: clear, without particles

4. CLINICAL PARTICULARS

4.1 Therapeutic indication(s)

Peripheral arterial occlusive disease (stage 3 and 4 of Fontaine's Classification) in advanced arteriosclerosis, in whom surgery or angioplasty therapy is not possible.
Thromboangitis obliterans (Buerger's disease) with critical limb ischemia in cases where revascularisation is not indicated and Severe disabling Raynaud's phenomenon.

4.2 Dosage and method of administration

Ilomedin should be used only under strict monitoring in hospitals or out-patient clinics with adequate facilities.

In women, pregnancy should be excluded before initiating treatment.

Ilomedin is administered after dilution as described in section 6.6 "Instructions for use andhandling" as an intravenous infusion over 6 hours daily through a peripheral vein or central venous catheter. The dose is adjusted according to individual tolerance within the range of 0.5 to 2.0 ng iloprost/kg body weight/min.

The solution for infusion must be prepared daily to ensure sterility.

The contents of the ampoule and the diluent should be mixed thoroughly.

Blood pressure and heart rate must be checked at the start of the infusion and whenever the dose is increased.

During the first 2-3 days, the dose that the patient can tolerate is established .For this purpose, treatment should be initiated at an infusion rate of 0.5 ng/kg/min for 30 minutes. The dose should then be increased by 0.5 ng/kg/min at intervals of approximately 30 minutes each until the patient is receiving 2.0 ng/kg/min.
The exact infusion rate must be calculated based on the patient's body weight to deliver an infusion within the range of 0.5 to 2.0 ng/kg/min (see tables below for use with an infusion pump or syringe driver).

Depending on the occurrence of side effects such as headache and nausea or an undesired drop of blood pressure, the infusion rate should be reduced until the tolerable dose is found. If the side effects are severe, the infusion should be interrupted. The treatment should then be continued-usually for 4 weeks - with the dose found to be tolerated in the first 2 to 3 days.

Depending on the infusion technique there are two different dilutions of an ampoule. One of these two dilutions is 10 fold less concentrated than the other (0.2 µg/ml versus 2 µg/ml) and should only be applied with an infusion pump (e.g. Infusomat®). In contrary the higher concentrated solution is applied via a syringe driver (e.g. the Perfusor®), **Infusion rates [ml/h] for different doses for use with infusion pump**

In general, the ready-to-use infusion solution is infused intravenously by means of an infusion pump (e.g. Infusomat®). See section 6.6 "Instructions for use/handling".
In the case of an Ilomedin concentration of 0.2 µg/ml, the required infusion rate should be determined according to the above described scheme to effect a dose within the range of 0.5 to 2.0 ng/kg/min.

The following table can be used to calculate the infusion rate corresponding to the individual weight of the patient and the dose to be infused. Please interpolate to match the patient's actual body weight, then set the infusion rate to the target dose in ng/kg/min.

	Dose [ng/kg/min.]			
	0.5	**1.0**	**1.5**	**2.0**
Body weight [kg]	**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 rates [ml/h] for different doses for use withsyringe driver

A syringe driver with a 50-ml injection syringe (e.g. the Perfusor®) may also be used: See 6.6 , "Instructions for use/handling".

In the case of an Ilomedin concentration of 2 µg/ml, the required infusion rate should be determined according to the above scheme to effect a dose within the range of 0.5 to 2.0 ng/kg/min.

The following table can be used to calculate the infusion rate corresponding to the individual weight of the patient and the dose to be infused. Please interpolate to match the patient's actual body weight, then set the infusion rate to the target dose in ng/kg/min.

	Dose **[ng/kg/min.]**			
	0.5	1.0	1.5	2.0
Body weight [kg]	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 duration of treatment is up to 4 weeks. Shorter treatment periods (3 to 5 days) are often sufficient in Raynaud's phenomenon to achieve improvement over several weeks.

Continuous infusion over several days is not recommended because of the possible development of tachyphylaxis of platelet effects and the possibility of rebound platelet hyperaggregability at the end of treatment, although no clinical complications associated with these phenomena have been reported.

- Patients with renal or hepatic impairment

In patients with renal failure requiring dialysis and in patients with liver cirrhosis, iloprost elimination is reduced. In these patients a dose reduction (e.g. half the recommended dose) is necessary.

4.3 Contraindications

- **-** Hypersensitivity to active ingredient or to any of the excipients listed in section 6.1.
- Pregnancy;
- Lactation;

- Conditions where the effects of Ilomedin 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; acute or chronic congestive heart failure (NYHA classes II-IV); severe arrhythmias ;

- Suspected pulmonary congestion.

4.4 Special warnings and precautions for use

Special Warnings

Surgery should not be delayed in patients requiring urgent amputation (for example in infected gangrene).

Patients should be strongly advised to quit smoking.

Iloprost elimination is reduced in patients with hepatic dysfunction and in patients with renal failure requiring dialysis (see section 4.2 "Dosage and method of administration").

In patients with low blood pressure special care should be taken to avoid greater hypotension and patients with significant heart disease should be closely monitored.

The possibility of orthostatic hypotension should be kept in mind in patients going from lying down to standing up after the infusion is completed.

In patients who have had a stroke (for example, a transient ischemic attack or acute cerebrovascular accident) within the last three months, a careful benefit-risk assessment must be performed (see section 4.3, “Contraindications”).

Special Precautions

Currently only sporadic reports of use in children and adolescents are available.

Paravascular infusion of undiluted Ilomedin solution can cause local changes at the injection site.

Oral ingestion and contact with mucous membranes should be avoided. On contact with the skin, iloprost can cause long-lasting but painless erythema. Therefore, adequate precautions should be taken to avoid iloprost coming into contact with the skin. If this occurs, the affected area must be washed immediately with copious amounts of water or saline.

Excipients
This medication contains 4.05 mg of alcohol (ethanol) in each ampoule. The amount of this medication is equivalent to less than 1 mL of beer or wine. The small amount of alcohol this medication contains does not produce any perceptible effects.

This medication contains less than 1mmol of sodium (23 mg) per ampoule; making it essentially 'sodium-free'.

4.5 Interaction with other medications and other forms of interaction

Iloprost can increase the antihypertensive activity of beta blockers, vasodilators, calcium antagonists, and ACE inhibitors. If significant hypotension occurs, it can be corrected by reducing the dose of iloprost.

Because iloprost inhibits platelet function, its use with anticoagulants (such as heparin, coumarin-type anticoagulants), or other function inhibitors (such as acetylsalicylic acid, non-steroidal anti-inflammatory medications, phosphodiesterase inhibitors and nitro vasodilators such as molsidomine) can increase the risk of bleeding.

Oral premedication with up to 300 mg of acetylsalicylic acid per day over a period of eight days had no effect on the pharmacokinetics of iloprost. The results of a study of human subjects showed that iloprost does not affect the pharmacokinetics of multiple oral doses of digoxin in patients and iloprost has no impact on the pharmacokinetics of co- administered t-PA.

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 through these enzymes by iloprost have to be expected.

4.6 Fertillity, pregnancy and lactation

Ilomedin must not be administreted during pregnancy or breastfeeding (see section 4.3 "Contraindications").

- Pregnancy

There is insufficient data on the use of iloprost in pregnant women. Preclinical studies have shown evidence of fetotoxicity in rats, but not in rabbits and monkeys (see section 5.3 " Preclinical safety data").

As the potential risk of the therapeutic use of iloprost during pregnancy is not known, women of childbearing age should use effective contraceptive method during treatment.

- Lactation

It is not known whether iloprost passes into human breast milk. Because extremely low quantities of iloprost do pass into the milk of rats, iloprost should not be administered to women who are lactating.

4.7 Effects on the ability to drive and use machinery

Not applicable.

4.8 Adverse reactions

Ilomedin's overall safety profile is based on data from post-marketing trail surveillance and on pooled clinical trial data. Incidences were calaulated based on cumulative data from 3325 patients who had received iloprost in controlled or uncontrolled clinical trials or in a compassionate- use program, generally elderly or multimorbid patients with advanced-stage (III or IV) peripheral arterial occlusive disease (PAOD) and in patients with thromboangitis obliterans (TAO), See table 1 for more information.

The most frequently observed adverse reactions (≥ 10%) in patients who have received iloprost in clinical trials are headache, flushing, nausea, vomiting and hyperhidrosis. These reactions typically occur at the start of treatment as the dose is being adjusted to identify the dose best tolerated by the patient. However, all these side effects usually disappear quickly with dose reduction.

In general, the most serious adverse reactions in patients treated with iloprost are cerebrovascular accident, myocardial infarction, pulmonary embolism, heart failure, convulsion, hypotension, tachycardia, asthma, angina pectoris, dyspnea and pulmonary edema.

Another group of adverse reactions is tied to local reactions at the infusion site. For example, reddening and pain can occur at the infusion site or a cutaneous vasodilation may lead to linear erythema above the infusion vein.

The adverse reactions observed with ilomedin are presented in the table below. They are classified according to System Organ Class (MedDRA version 14.1). The most appropriate MedDRA term is used to describe each spesific reaction and its synonyms and related conditions.

Adverse reactions in clinical trials are classified according to their frequency. Frequency groupings are defined as follows: very common ≥1/10, common ≥1/100 to <1/10, uncommon ≥ 1/1,000 to <1/100 and rare ≥1/10,000 to <1/1,000.

Table 1: Adverse reactions reported in clinical trials or during post-marketing surveillance in patients treated with Ilomedin

System Organ Class (MedDRA*)	Very common	Common	Uncommon	Rare
Blood and lymphatic system disorders			Thrombocytopenia	
Immune system disorders			Hypersensitivity	
Metabolism and nutrition disorders		Decreased appetite		
Psychiatric disorders		Apathy, Confusion	Anxiety, depression, hallucinations	
Nervous system disorders	Headache	Dizziness Vertigo, Paresthesia/ Throbbing sensation Hyperesthesia/ Burning sensation, Restlessness Agitation, Sedation, Drowsiness	Convulsion*, Syncope, Tremor, Migraine	
Eye disorders			Blurred vision Eye irritation Eye pain	
Hearing and ear disorders				Vestibular disorder
Cardiac disorders		Tachycardia*, Bradycardia, Angina pectoris*	Myocardial infarction* Heart failure*, Arrhythmia/ extrasystoles	
Vascular disorders	Flushing	Hypotension *, Increased blood pressure	Cerebrovascular accident*/ cerebral ischemia, Pulmonary embolism*, Deep vein thrombosis	
Respiratory, thoracic and mediastinal disorders		Dyspnea*	Asthma*, Pulmonary edema*	Cough

System Organ Class (MedDRA)	Very common	Common	Uncommon	Rare
Gastrointestinal disorders	Nausea, Vomiting	Diarrhea, Abdominal discomfort/ abdominal pain	Hemorrhagic diarrhea Rectal bleeding Dyspepsia, Rectal tenesmus, Constipation, Eructation, Dysphagia, Dryness of the mouth Dysgeusia	Proctitis
Hepato-biliary disorders			Jaundice	
Skin and Subcutaneous tissue disorders	Hyperhidrosis		Pruritus	
Musculoskeletal and connective tissue disorders		Mandibular pain Trismus Myalgia Arthralgia	Tetany Muscle spasms. Hypertonia.	
Renal and Urinary disorders			Kidney pain. Vesical tenesmus. Uniary changes , Dysuria, Urinary tract disorders	
General disorders and change at the site of administration		Pain, Pyrexia/ increased body temperature Sensation of heat Asthenia General malaise. Chills. Fatigue / tiredness. Thirst Erythema, pain and phlebitis at the infusion site,		

*** life-threatening and/or fatal cases have been reported**

Iloprost can cause angina pectoris, especially in patients with heart failure.

The risk of bleeding increases in patients being treated concomitantly with platelet aggregation inhibitors, heparin or coumarin-type anticoagulants.

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. Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form:

https://sideeffects.health.gov.il/

4.9 OVERDOSE

Symptoms of overdose

Hypotensive reaction as well as headache, flushing, nausea, vomiting and diarrhea. Increased blood pressure, bradycardia or tachycardia and pain in the extremities or back are also possible.

Treatment of overdose

A specific antidote is not known.

Suspension of the administration of iloprost, monitoring and symptomatic measures are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antithrombotic agents: platelet aggregation inhibitors , excluding heparine.
ATC Code: B01 AC.

Iloprost is a prostacyclin analog. The following pharmacological effects have been observed:

Inhibition of aggregation, platelet adhesion and degranulation, dilatation of arterioles and venules, increased capillary density and reduction of increased vascular permeability in the microcirculation; activation of fibrinolysis, inhibition of adhesion and migration of leukocytes after injury to endothelial tissue and diminished release of oxygen-containing free radicals.

The exact mechanism of action is unknown.

5.2 Pharmacokinetic properties

- Distribution

Steady-state plasma levels of the drug are achieved in as little as 10-20 minutes after the start of an intravenous infusion. Steady- state plasma concentrations are linearly related to the infusion rate.. An infusion rate of 3 ng/kg/min obtains plasma concentrations of approximately 135 ± 24 pg/mL. . The plasma concentration of iloprost drops very rapidly after infusion is completed due to its high metabolism rate. Metabolic clearance of the substance from plasma is approximately 20 ± 5 ml/kg/min. The plasma terminal half-life is 0.5 hours, , so the concentration falls to less than 10% of the stead- state concentration two hours after the end of infusion.

Interactions with other medications at the level of plasma protein binding are unlikely because most of the iloprost binds to the albumin in blood plasma (protein binding: 60 %) and only extremely low concentrations of free iloprost are achieved. It is also highly unlikely for iloprost to modify the biotransformation of other drugs due to the low absolute dose and the metabolic pathways involved.

- Metabolism and elimination

Iloprost is metabolised mainly through beta oxidation of the carboxyl side chain. No unchanged fraction of the substance is eliminated.. The main metabolite is tetranor-iloprost, present in urine in free form and conjugated form as four diastereoisomers. Tetranor-iloprost is pharmacologically inactive. 80% of iloprost's metabolites are excreted through the kidneys and 20% through the liver. Metabolites are eliminated from blood plasma and through the urine in two phases, for which half-lives of approximately two and five hours (plasma) and two and 18 hours (urine) have been calculated.

- Special populations

The pharmacokinetic characteristics of iloprost are not affected by a patient's age or sex. However, in patients with cirrhosis of the liver and in those with chronic renal insufficiency requiring dialysis, iloprost clearance is 2-4 times less.

5.3 Preclinical safety data

Preclinical data reveal no special risks to humans beings according to conventional studies of drug safety, , repeated dose toxicity, genotoxicity, and carcinogenic potential. Preclinical effects were observed only at exposures sufficiently exceeding maximum exposure in humans indicating little relevance in clinical use.

- Systemic toxicity

In light of studies conducted in animals, the risk of acute toxicity in human beings seems to be low when taking into account the total absolute dose administered to patients during treatment and the maximum quantity of substance each ampoule contains
especially if one takes into account that the preparation is only administered in a clinical setting.

In systemic toxicity studies, where a repeated (continuous) intravenous infusion was administered , a slight drop in blood pressure was observed at doses above than 14 ng/min and serious side effects (hypotension, changes in respiratory function) only appeared after administration of very high doses (twice that of the therapeutic does) in comparison to the therapeutic dose.

- Genotoxic potential, carcinogenicity

In vitro and in vivo studies on genotoxic effects have not produced any evidence of mutagenic potential.

In carcinogenicity studies performed on rats no carcinogenicity potential was observed whatsoever for iloprost.

- Reproduction toxicology

In embryotoxicity and fetotoxicity studies preformed on rats, continuous intravenous administration of iloprost caused isolated anomalies in the phalanges of the forepaws of some of the pups regardless of the dose.

These abnormalities are not considered true teratogenic effects, but are most likely related to iloprost induced growth retardation in late organogenesis due to hemodynamic changes in the fetoplacental unit. It can be assumed that this growth retardation is easily reversible during the postnatal development. In comparable embryotoxicity studies conducted on rabbits and monkeys, neither digital abnormalities nor other macroscopic structural abnormalities were observed even after the administration of considerably higher doses exceeding the human dose several times over.

6. PHARMACEUTICAL Data

6.1 List of excipients

Water for Injection
Sodium chloride
Ethanol
Hydrochloric acid
Trometamol

6.2 Incompatibilities

No data are available except for those medications described in section 6.6 "Instructions for use andhandling". Therefore, this medication should not be mixed with others except those mentioned in section 6.6 “Instructions for use and handling".

6.3 Shelf life

Four years in the packaging material provided for sale.

6.4 Special precautions for storage

No special storage conditions are required.

6.5 Nature and contents of container

1 transparent type I glass ampoule containing 0.5 mL of concentrate for solution for infusion

6.6 Special precautions for disposal and other handling

Ilomedin should only be used afte it is diluted.
Because of the possibility of interactions, no other substance should be added to the ready- to-use infusion solution.
The ready- to-use infusion solution must be freshly prepared each day in order to guarantee the sterility.

- Instructions for dilution

The contents of the ampoule and the diluent must be mixed thoroughly.

Dilution of Ilomedin for use with an infusion pump:
For this purpose, the contents of an 0.5 ml ampule of Ilomedin (i.e. 50 µg) are diluted with 250 ml of a sterile saline physiological serum or a 5% glucose solution.

Dilution of Ilomedin for use with a syringe driver:
In this case, the contents of a 0.5 ml ampoule of Ilomedin (i.e., 50 µg) are diluted with 25 ml of sterile saline physiological serum or 5% glucose solution.

7. **Manufacturer**

BerliMed S.A.,Madrid, Spain

8. **Registration Holder**

Bayer Israel Ltd, 36 Hacharash St., Hod Hasharon 45240

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