The format of this leaflet was determined by the Ministry of Health and its content was checked and approved by it in October 2014.

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).
This medicinal product contains 0.8% ethanol/ampoule.

Excipients List in 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/handling" as an intravenous infusion over 6 hours daily via a peripheral vein or a central venous catheter. The dose is adjusted according to individual tolerability within the range of 0.5 to 2.0 ng iloprost/kg body weight/min.

The infusion solution should be made up freshly each day to ensure sterility.

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

The blood pressure and heart rate must be measured at the start of the infusion and after every increase of the dose.

During the first 2 - 3 days, the individually tolerated dose is established. For this purpose, treatment should be started at an infusion rate to deliver 0.5 ng/kg/min for 30 minutes. The dose should then be increased at intervals of about 30 minutes in steps of 0.5 ng/kg/min up to 2.0 ng/kg/min. The exact infusion rate should be calculated on basis of the body weight to effect an infusion within the range of 0.5 to 2.0 ng/kg/min (see tables below for use with infusion pump or for use with 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 one ampoule. One of these two dilutions is 10 fold less concentrated than the other (0.2 µg/ml versus 2 µg/ml) and may 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®), for instructions for use/handling see section 6.6 "Instructions for use/handling".

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®). For instructions for dilution for use with infusion pump 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 with syringe driver

A syringe driver with a 50-ml injection syringe (e.g. the Perfusor®) may also be used. For instructions for dilution for use with syringe driver 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

- 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 II-IV); severe arrhythmias ;
- Suspected pulmonary congestion;

Hypersensitivity to iloprost or to any of the other ingredients.

4.4 Special warnings and precautions for use

Special Warnings

Surgery should not be delayed in patients requiring urgent amputation (e.g. in infected gangrene). Patients should be 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 care should be taken to avoid further hypotension and patients with significant heart disease should be closely monitored.

The possibility of orthostatic hypotension should be borne in mind in patients getting up from the lying to an upright position after the end of administration.

For patients with a cerebrovascular event [e.g. transient ischemic attack, stroke] within the last 3 months a careful benefit-risk evaluation should be undertaken (see also section 4.3 “Contraindications”: risk of hemorrhage, e.g. intracranial hemorrhage).

Special Precautions

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

The paravascular infusion of undiluted Ilomedin can lead to local changes at the injection site.

Oral ingestion and contact with mucous membranes must be avoided. On contact with the skin, iloprost may provoke long-lasting but painless erythema. Therefore, adequate precautions must be applied to avoid contact of iloprost with the skin. If contact with skin occurs, the area must be immediately washed with plenty of water or saline.

This medicinal product contains 0.8% ethanol (alcohol) which corresponds to 4 mg ethanol/ampoule.

4.5 Interaction with other medicinal products and other forms of interaction

Iloprost may increase the antihypertensive activity of ß-receptor blockers, calcium antagonists, vasodilators and ACE inhibitors. If severe hypotension occurs, it can be corrected by decreasing the dose of iloprost.

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

Oral premedication with acetylsalicylic acid up to 300 mg per day over a period of 8 days had no impact on the pharmacokinetics of iloprost. The results of human studies show that iloprost infusions do 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 via these enzymes by iloprost have to be expected.

4.6 Pregnancy and lactation

Ilomedin must not be used during pregnancy or lactation (see section 4.3 "Contraindications").

- Pregnancy

There are no adequate data from 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 unknown, women of child-bearing potential should use effective contraceptive measures during treatment.

- Lactation

It is not known whether iloprost enters human breast milk. As extremely low levels of iloprost pass into the milk of rats, iloprost should not be administered to nursing women.

4.7 Effects on the ability to drive or use of machines

Not applicable.

4.8 Undesirable effects

The overall safety profile of Ilomedin is based on data from post-marketing surveillance and on pooled clinical trial data. The crude incidences were based on the cumulative database of 3325 patients having received iloprost either in controlled or uncontrolled clinical trials or in a compassionate use program from generally elderly and multimorbid patients with peripheral arterial occlusive disease (PAOD) in its advanced stages III and IV and patients with thromboangitis obliterans (TAO), for details see table 1.

The most frequently observed adverse drug reactions (≥ 10%) in patients receiving iloprost in clinical trials are headache, flushing, nausea, vomiting and hyperhidrosis. These are likely to occur while the dose is titrated at the start of treatment to identify the best tolerable dose for the individual patient. However, all these side effects usually disappear quickly with dose reduction.

Overall, the most serious adverse drug reactions in patients receiving iloprost are cerebrovascular accident, myocardial infarction, pulmonary embolism, cardiac failure, convulsion, hypotension, tachycardia, asthma, angina pectoris, dyspnea and pulmonary edema.

Another group of side effects is related to local infusion site reactions. For example, infusion site redness and infusion site pain may occur or a cutaneous vasodilation may give rise to streaky erythema above the infusion vein.

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

Adverse drug reactions from clinical trials are classified according to their frequencies. Frequency groupings are defined according to the following convention: 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 drug 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, Confusional state	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			Vision blurred, Eye irritation, Eye pain	
Ear and labyrinth disorders				Vestibular disorder
Cardiac disorders		Tachycardia*, Bradycardia, Angina pectoris*	Myocardial infarction* Cardiac failure*, Arrhythmia/ Extrasystoles	
Vascular disorders	Flushing	Hypotension *, Blood pressure increased	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	Diarrhea hemorrhagic, Rectal hemorrhage, Dyspepsia, Rectal tenesmus, Constipation, Eructation, Dysphagia, Dry mouth/ Dysgeusia	Proctitis
Hepato-biliary disorders			Jaundice	
Skin and Subcutaneous tisuue disorders	Hyperhidrosis		Pruritus	
Musculoskeletal and connective tissue disorders		Jaw pain/ Trismus Myalgia/ Arthralgia	Tetany/ muscular spasms, Hypertonia	
Renal and Urinary disorders			Kidney pain, Vesical tenesmus, urine abnormality, Dysuria, Urinary tract disorders	
General disorders and administration site conditions		Pain, Pyrexia / Body temperature increased, feeling hot, Asthenia /Malaise, Chills, Fatigue/Tiredness, Thirst, Infusion site reactions (Infusion site erythema, Infusion site pain, Infusion site phlebitis) .		

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

Iloprost may provoke angina pectoris, especially in patients with coronary artery disease.
The risk of bleeding is increased in patients when inhibitors of platelet aggregation, heparin or anticoagulants of the coumarin-type are given concomitantly.

Reporting of suspected adverse reactions
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form (http://forms.gov.il/globaldata/getsequence/getsequence.aspx?formType=AdversEffectMedic@moh.health.gov.il) or by email (adr@MOH.HEALTH.GOV.IL).

4.9 OVERDOSE

Symptoms
Hypotensive reaction might be anticipated as well as headache, flushing, nausea, vomiting and diarrhea. An increase of blood pressure, bradycardia or tachycardia and limb or back pain might be possible.

Treatment
A specific antidote is not known.

Interruption of iloprost administration, monitoring and symptomatic measures are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

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

Iloprost is a prostaciclin analogue. The following pharmacological effects have been observed:

Inhibition of platelet 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 endothelial and decreased release of oxygen free radicals.

The exact mechanism of action is unknown.

5.2 Pharmacokinetic properties

- Distribution

The medicinal product reaches equilibrium in plasma at 10 - 20 minutes after the start of the intravenous infusion. Plasma concentrations at steady state bear a linear relationship with the rate of infusion. With an infusion rate of 3 ng/kg/min, plasma concentrations of approximately 135 ± 24 pg/ml are obtained. The plasma concentration of iloprost decreases very rapidly after the end of infusion due to its high rate of metabolism. The metabolic clearance of the drug substance from the plasma

is 20 ± 5 ml/kg/min approximately. The terminal phase half-life of plasma availability is 0.5 so that the concentration decreases to less than 10% of the equilibrium concentration within two hours after the end of infusion.

It is unlikely that pharmacological interactions occur at the level binding to plasma proteins, given that most of the iloprost binds to plasma albumin (protein binding: 60%) and only very low concentrations of free iloprost are reached. It is also very unlikely that iloprost therapy modify the biotransformation of other drugs considering the metabolic pathways involved and that the absolute dose is low.

- Metabolism and elimination

Iloprost is metabolised primarily by the beta -oxidation of the carboxyl side chain. No portion of the drug substance is eliminated unchanged. The main metabolite is tetranor-iloprost, present in urine in free and conjugated form in 4 diastereoisomers. Tetranor-iloprost has no pharmacological activity. 80% of iloprost metabolites are excreted by the kidneys and 20% in the bile. Metabolites are removed from the plasma and urine in two phases, for which a calculated half-lives of approximately 2 and 5 hours (plasma) and from 2 to 18 hours (urine).

- Special populations

The pharmacokinetic characteristics of iloprost are independent of the patient age or sex. However, in patients with liver cirrhosis and in those with chronic renal failure requiring dialysis, iloprost clearance is 2-4 times lower.

5.3 Preclinical safety data

Preclinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity, carcinogenic potential. Preclinical effects were observed only at exposures considered sufficiently in excess of the maximum human exposure indicating little relevance to clinical use.

- Systemic toxicity

In view of studies in animals, the risk of acute toxicity in humans appears to be low if the total absolute dose administered to patients during treatment and the maximum amount of substance that contains each ampoule is considered, bearing in mind that the medicinal product is administered in the clinical setting.

In systemic toxicity studies, in which an iv infusion was repeatedly administered (continuous), there was a slight decrease in blood pressure at doses higher than 14 ng/min and only serious side effects (such as hypotension, impaired respiratory function) were observed after administration of very high doses (two orders of magnitude above therapeutic) doses compared to the therapeutic dose.

- Genotoxic potential, carcinogenicity

In vitro and in vivo studies on genotoxic effects have provided no evidence of a mutagenic potential.

In carcinogenicity studies conducted in rats and mice no carcinogenicity potential was observed for iloprost.

- Reproduction toxicology

In embryo- and fetotoxicity studies in rats, continuous intravenous administration of iloprost led to abnormalities in single phalanges of the forepaws in a few fetuses/pups in a not dose-dependent manner.

These alterations are not considered as true teratogenic effects, but are most likely related to iloprost induced growth retardation in late organogenesis due to hemodynamic alterations in the fetoplacental unit. It can be assumed that this growth retardation is widely reversible during the post natal development. In comparable embryotoxicity studies in rabbits and monkeys no such digit anomalies or other gross-structural abnormalities were observed even after considerably higher dose levels which exceeded the human dose multiple times.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Hydrochloric acid
Ethanol
Sodium chloride
Water for Injection
Trometamol

6.2 Incompatibilities

No data available for other than those medicinal products described under section "Instructions for use/handling".

6.3 Shelf-life

Do not use after the expiration date shown on the pack.
The expiration date is based on a stability period of 4 years.

6.4 Special precautions for storage

Store below 30ºC.

6.5 Nature and contents of container

- Ampoule 1 ml containing 0.5 ml concentrate for solution for infusion;
Colourless, glass type I ,Ph.Eur

6.6 Instructions for use/handling

Ilomedin should be used only after dilution.
Because of the possibility of interactions, no other drug 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 should be mixed thoroughly.

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

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

7. Manufacturer

BerliMed S.A.,Madrid, Spain

8. Registration Holder

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