SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

DIVODIN 20 mcg/ml I.V. Solution for Infusion
Sterile

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 1 mL of solution contains:
Active substance:
Iloprost 20 mcg (equivalent to 27 mcg iloprost trometamol)

Excipient(s):

Ethanol	1.62 mg
Sodium chloride	9 mg

For list of excipients see 6.1.

3. PHARMACEUTICAL FORM

Clear, colourless solution for intravenous (i.v.) infusion.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

• Treatment of advanced thromboangiitis obliterans (Buerger's disease) cases with critical limb ischemia where revascularization is not indicated.
• Treatment of patients with severe peripheral arterial occlusive disease (PAOD), especially those at risk of amputation and in whom surgical intervention or angioplasty is not possible.
• Treatment of patients with Raynaud's phenomenon who do not respond to other treatments and who experience severe limitations.

4.2 Posology and method of administration

Posology/frequency and duration of administration
DIVODIN should only be used in hospitals under careful supervision or in outpatient clinics with adequate facilities.

In women, pregnancy must be ruled out before treatment begins.

DIVODIN is administered as an intravenous infusion over 6 hours via a peripheral vein or central venous catheter after dilution. The dose is adjusted within the range of 0.5–2 ng iloprost/kg body weight/min according to individual tolerance.

Blood pressure and heart rate should be measured at the start of the infusion and after each dose increase.

The individually tolerable dose is determined within the first 2–3 days. For this purpose, treatment should be started with an infusion rate of 0.5 ng/kg/min for 30 minutes. After that, the dose should be increased in increments of 0.5 ng/kg/min at approximately 30-minute intervals up to 2 ng/kg/min. The appropriate infusion rate should be determined based on body weight within the range of 0.5–2 ng/kg/min (see the tables below for infusion pump or automatic injector use).

Depending on the occurrence of side effects such as headache, nausea, or an unwanted drop in blood pressure, the infusion rate should be reduced until a tolerable dose is determined. If side effects are severe, the infusion should be discontinued. Treatment should then be continued with the tolerated dose found in the first 2 to 3 days, usually for a period of 4 weeks.

Depending on the infusion technique, an ampoule is diluted in two ways. One of these is 10 times less concentrated than the other (0.2 mcg/mL vs. 2 mcg/mL) and can only be administered with an infusion pump (e.g., Infusomat). In contrast, the high-concentration solution is administered using an automatic injector (e.g., Perfusor). For instructions on use and preparation, see the section entitled "Method of administration" under heading 4.2. Posology and method of administration.

Infusion rates (mL/hour) for different doses when using an infusion pump:
In general, the ready-to-use infusion solution is administered intravenously using an infusion pump (e.g., Infusomat). For dilution instructions when using an infusion pump, see the section "Method of administration" under 4.2. Posology and method of administration.

If DIVODIN is to be used at a concentration of 0.2 mcg/mL, the infusion rate should be determined according to the plan described above in order to administer a dose between 0.5 and 2 ng/kg/min.

The following table can be used to calculate the infusion rate that corresponds to the patient's body weight and the dose to be administered. Please select the number range that corresponds to the patient's current weight, then adjust the infusion rate according to the target dose in ng/kg/min.

Body Weight (kg)	Dose (ng/kg/min)			
	0,5	1	1,5	2
	Infusion rate (mL/h)			
40	6	12	18	24
50	7,5	15	22,5	30
60	9	18	27	36
70	10,5	21	31,5	42
80	12	24	36	48
90	13,5	27	40,5	54
100	15	30	45	60
110	16,5	33	49,5	66

Infusion rates (mL/h) for different doses when using an automatic injector: A 50 mL automatic injector (e.g., Perfusor) can also be used. When using an automatic injector, refer to the "Method of administration" section under heading 4.2. Posology and method of administration for dilution instructions.

In the case of a DIVODIN concentration of 2 mcg/mL, the infusion rate required should be determined in accordance with the above plan to produce a dose of 0.5-2 ng/kg/min.

The following table can be used to calculate the infusion rate that corresponds to the patient's body weight and the dose to be administered. Please select the range of numbers that corresponds to the patient's current weight, then adjust the infusion rate according to the target dose in ng/kg/min.

Body Weight (kg)	Dose (ng/kg/min)			
	0,5	1	1,5	2
	Infusion rate (mL/h)			
40	0,6	1,2	1,8	2,4
50	0,75	1,5	2,25	3
60	0,9	1,8	2,7	3,6
70	1,05	2,1	3,15	4,2
80	1,2	2,4	3,6	4,8
90	1,35	2,7	4,05	5,4
100	1,5	3	4,5	6
110	1,65	3,3	4,95	6,6

Treatment can last up to 4 weeks. In Raynaud's phenomenon, shorter treatment periods (3-5 days) are usually sufficient to achieve healing that lasts for weeks.

Continuous infusion over several days is not recommended because of the possibility of developing tachyphylaxis to platelet effects—although no clinical complications related to this phenomenon have been reported to date—and the risk of rebound platelet hyperaggregation at the end of treatment.

Method of administration
After dilution, DIVODIN is administered as an intravenous infusion through a peripheral vein or a central venous catheter for 6 hours per day.

DIVODIN should only be used after dilution.

Due to the possibility of interactions, no other drugs should be added to the ready-to-use infusion solution.

To ensure sterility, the ready-to-use infusion solution must be prepared fresh every day.

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

Dilution for use with a DIVODIN infusion pump:
For this purpose, one ampoule of DIVODIN containing 1 mL (i.e., 20 mcg) is diluted with sterile physiological saline or 5% glucose solution to a final infusion volume of 100 mL.

Dilution of DIVODIN for use with an automatic injector:
For this purpose, one ampoule of DIVODIN containing 1 mL (i.e., 20 mcg) is diluted with sterile physiological saline or 5% glucose solution to a final infusion volume of 10 mL.

Additional information on special population
Kidney/liver impairment:
It should be noted that iloprost elimination is reduced in patients with liver cirrhosis and in patients with kidney impairment requiring dialysis. In these patients, the dose should be reduced (e.g., half the recommended dose).

Pediatric populations:
Only sporadic use is considered in children and adolescents. As there is limited information on how patients under the age of 18 respond to DIVODIN treatment, caution should be exercised when administering it to patients under the age of 18.

4.3 Contraindications

- Pregnancy;
- Lactation;
- DIVODIN should not be used in conditions where its effect on platelets may increase the risk of bleeding (e.g., active peptic ulcer, trauma, intracranial hemorrhage);
- 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 any of the other ingredients of the drug.

4.4 Special warnings and precautions for use

In patients requiring urgent amputation (e.g., infected gangrene), surgery should not be delayed. Patients should be strongly advised to quit smoking.

Iloprost excretion is reduced in patients with hepatic dysfunction or renal impairment requiring dialysis (see "4.2 Posology and method of administration" and "5.2 Pharmacokinetic properties").

Caution should be exercised to avoid further hypotension in patients with low blood pressure, and patients with significant heart disease should be closely monitored.

The possibility of orthostatic hypotension should be considered in patients rising from a supine position after discontinuing medication administration.

A careful benefit-risk assessment should be performed for patients who have had a cerebrovascular accident (e.g., transient ischemic attack, stroke) within the last 3 months (see “4.3 Contraindications” - risk of bleeding, e.g., intracranial hemorrhage).

Currently, there are only sporadic reports of its use in children and adolescents.

Paravascular infusion of undiluted DIVODIN may cause local changes at the injection site.

Avoid oral administration and contact with mucous membranes. If it comes into contact with the skin, iloprost may provoke prolonged but painless erythema. Therefore, appropriate measures should be taken to avoid contact of iloprost with the skin. In the event of such contact, the affected area should be immediately washed with plenty of water or physiological saline.

This medicinal product contains a small amount of ethanol (alcohol), less than 100 mg per mL.

This medicinal product contains less than 1 mmol (23 mg) of sodium per mL. This means it is essentially "sodium-free."

4.5 Interaction with other medicinal products and other forms of interaction

Iloprost may enhance the antihypertensive activity of beta-receptor blockers, calcium channel blockers, vasodilators, and angiotensin-converting enzyme inhibitors. In cases of marked hypotension, the dose of iloprost may be reduced.

Since iloprost inhibits platelet function, concomitant use with anticoagulants (e.g., heparin, coumarin-type anticoagulants) or other platelet aggregation inhibitors (e.g., acetylsalicylic acid, nonsteroidal anti-inflammatory drugs, phosphodiesterase inhibitors, and nitro vasodilators, e.g., molsidomine) may increase the risk of bleeding. In these cases, iloprost administration should be discontinued.

Oral premedication with acetylsalicylic acid up to 300 mg daily for more than 8 days had no effect on the pharmacokinetics of iloprost. An animal study found that iloprost may cause a decrease in the steady-state plasma concentration of t-PA. Results of human studies indicate that iloprost infusion in patients does not affect the pharmacokinetics of multiple oral doses of digoxin and has no effect on the pharmacokinetics of t-PA administered concomitantly with iloprost.

In animal studies, the vasodilatory effect of iloprost was attenuated when the animals were premedicated with glucocorticoids, but its inhibitory effect on platelet aggregation was unchanged. The significance of this finding for human use is unknown.

Although no clinical studies have been conducted, based on the results of *in vitro* studies investigating the inhibitory effect potential of iloprost on cytochrome P450 enzyme system activity, inhibition of drug metabolism by iloprost via these enzymes is not expected.

4.6 Pregnancy and lactation

General Principles
Pregnancy category is X.

Women of child-bearing potential/Birth Control (Contraception)
Because the possible risks of using iloprost for treatment during pregnancy are unknown, women of childbearing potential should use effective contraception during treatment.

Pregnancy
DIVODIN should not be administered to pregnant women. There is insufficient data on the use of DIVODIN in pregnant women. Preclinical studies have shown evidence of fetotoxicity in rats, but not in rabbits and monkeys. (See 5.3 Preclinical safety data).

There is suspicion that iloprost may cause serious birth defects when administered during pregnancy. DIVODIN is contraindicated during pregnancy (see 4.3 Contraindications).

Breast-feeding
DIVODIN should not be administered to breastfeeding women. It is unknown whether iloprost passes into breast milk. Since it passes into rat milk in very small amounts, iloprost should not be administered to breastfeeding women.

4.7 Effects on ability to drive and use machines
Not known.

4.8 Undesirable effects

The overall safety profile of DIVODIN is based on clinical trial data compiled with data from post-marketing surveillance. Crude incidences are based on a cumulative database of 3,325 patients who received iloprost in controlled or uncontrolled studies or through the compassionate use program, which generally included elderly and multimorbid patients with advanced stage III and IV peripheral arterial occlusive disease (PAOD) and thromboangiitis obliterans (TAO).

The most frequently observed adverse drug reactions (≥10%) in patients receiving iloprost in clinical trials were headache, flushing, nausea, vomiting, and hyperhidrosis. These reactions are likely to occur during initial dose titration to identify the optimal patient-tolerant dose. However, all these side effects generally resolve rapidly with dose reduction.

In general, the most serious adverse drug reactions in patients receiving iloprost were cerebrovascular accident, myocardial infarction, pulmonary embolism, heart 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 cutaneous vasodilation may cause mottled erythema overlying the infusion vessel.

Adverse drug reactions observed with DIVODIN are classified by system organ class. The most appropriate MedDRA term is used to describe a particular reaction, synonyms, and associated conditions.

Adverse drug reactions from clinical trials were classified by frequency. Frequency groupings are defined according to the following conventional method: Very common (≥1/10); common (≥1/100, <1/10); uncommon (≥1/1,000, <1/100); rare (≥1/10,000, <1/1,000); very rare (<1/10,000), not known (cannot be estimated from the available data).

Blood and lymphatic system disorders
Uncommon: Thrombocytopenia

Immune system disorders
Uncommon: Hypersensitivity

Metabolic and nutritional disorders
Common: Anorexia

Psychiatric disorders

Common:	Apathy, loss of consciousness
Uncommon:	Anxiety, depression, hallucinations

Nervous system disorders

Very common:	Headache
Common:	Dizziness, vertigo, paresthesia, palpitations, hyperesthesia, burning sensation, restlessness, agitation, sedation, drowsiness
Uncommon:	Convulsion*, syncope, tremor, migraine

Eye Diseases

Uncommon:	Blurred vision, eye irritation, eye pain

Ear and labyrinth disorders

Rare:	Vestibular disorder

Cardiac disorders

Common:	Tachycardia*, bradycardia, angina pectoris*
Uncommon:	Myocardial infarction*, heart failure*, arrhythmia, extrasystoles

Vascular disorders

Very common:	Pronounced redness
Common:	Hypotension*, increased blood pressure
Uncommon:	Cerebrovascular accident*, cerebrovascular ischemia, pulmonary embolism*, deep vein thrombosis

Respiratory, thoracic, and mediastinal disorders

Common:	Dyspnea*
Uncommon:	Asthma*, pulmonary edema*
Rare:	Cough

Gastrointestinal disorders

Very common:	Nausea, vomiting
Common:	Diarrhea, abdominal discomfort, abdominal pain
Uncommon:	Hemorrhagic diarrhea, rectal bleeding, dyspepsia, rectal tenesmus, constipation, eructation, dysphagia, dry mouth, dysgeusia
Rare:	Proctitis

Hepatobiliary disorders

Uncommon:	Jaundice

Skin and subcutaneous tissue disorders

Very common:	Hyperhidrosis
Uncommon:	Pruritus

Musculoskeletal disorders, connective tissue and bone diseases

Common:	Jaw pain, trismus, myalgia, arthralgia
Uncommon:	Tetany, muscle spasms, hypertonia

Kidney and urinary tract disorders

Uncommon:	Kidney pain, vesical tenesmus, urinary disturbance, dysuria, urinary tract disease

General disorders and administration site conditions

Common:	Pain, pyrexia, increased body temperature, feeling of fever, asthenia, malaise, tremor, fatigue, tiredness, thirst, injection site reaction (infusion site erythema, infusion site pain, post-infusion phlebitis)

* Life-threatening and/or fatal cases have been reported.

Iloprost can trigger angina pectoris, especially in patients with coronary artery disease. When administered concomitantly with platelet aggregation inhibitors, heparin, or coumarin-type anticoagulants, the risk of bleeding increases.

<u>Reporting of suspected adverse reactions</u>
Reporting suspected adverse reactions after authorization of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system.

4.9 Overdose

Symptoms
Headache, pronounced redness, nausea, vomiting, and diarrhea may occur, as well as hypotensive reactions. Increased blood pressure, bradycardia or tachycardia, and pain in the extremities or back are also possible.

Treatment
There is no specific antidote. Interruption of the infusion, monitoring, and symptomatic measures are recommended.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Platelet aggregation inhibitors (excluding heparin)
ATC code: B01AC11

Iloprost is a prostacyclin (PGI2) analog.

The following pharmacological effects have been observed:
• Inhibition of platelet aggregation, adhesion, and release reactions
• Dilation of arterioles and venules
• Increased capillary density and increased vascular permeability in the microcirculation caused by mediators such as serotonin or histamine
• Stimulation of endogenous fibrinolytic potential
• Anti-inflammatory effects, such as inhibition of leukocyte adhesion and leukocyte accumulation in damaged tissue after endothelial injury, and reduction of tumor necrosis factor release

5.2 Pharmacokinetic properties

General properties
Absorption:
Not applicable because it is administered intravenously.

Distribution:
Steady-state plasma levels are reached within a short period of 10-20 minutes after the start of intravenous infusion. Steady-state plasma levels are directly proportional to the infusion rate. A plasma concentration of approximately 135 ± 24 pg/mL is achieved at an infusion rate of 3 ng/kg/min. Following discontinuation of the infusion, iloprost plasma concentrations decline rapidly due to high metabolic clearance. The metabolic clearance of the substance in plasma is approximately 20 ± 5 mL/kg/min. The plasma half-life is 0.5 hours, as a result of which the substance level falls below 10% of the equilibrium concentration immediately 2 hours after the end of the infusion.

Since only very low concentrations of iloprost are obtained when high levels of iloprost bind to plasma albumin (protein binding: 60%), interaction with other drugs at the level of plasma protein binding is impossible. The effect of iloprost treatment on the biotransformation of other drugs is also extremely unlikely due to metabolic pathways and low absolute doses.

Biotransformation:
Iloprost is primarily metabolized by β-oxidation of the carboxyl side chain. It is eliminated by conversion to iloprost metabolites. No unchanged substance is excreted. The main metabolite is tetranor-iloprost, which is found in urine in its free form and conjugated with four diastereoisomers. Tetranor-iloprost is pharmacologically inactive, as demonstrated in animal studies. *In vitro* studies have shown that iloprost is metabolized similarly in the lungs after intravenous administration or inhalation.

Elimination:
In individuals with normal renal and hepatic function, after intravenous infusion, iloprost elimination occurs in two phases with half-lives of approximately 3 and 5 hours, and 15 and 30 minutes. Total iloprost clearance is 20 mL/kg/min, indicating extrahepatic contribution to iloprost metabolism.

A mass balance study was conducted in healthy subjects receiving ^{3}H-iloprost. Following intravenous administration, total radioactivity recovery was 81%, with 68% and 12% in urine and feces, respectively. Metabolites are eliminated biphasically from plasma and urine, with half-lives estimated to be 2-5 hours in plasma and 2-18 hours in urine.

Characteristic features in patients
Renal failure:
In a study conducted with intravenous infusion of iloprost, significantly lower clearance was observed in patients with end-stage renal failure undergoing intermittent dialysis (mean 5±2 mL/min/kg) compared to patients with renal failure not undergoing dialysis (mean 18 ± 2 mL/min/kg).

Liver impairment:
Since iloprost is primarily metabolized by the liver, changes in hepatic function affect plasma levels of the drug. In an intravenous study, results were obtained from 8 patients with liver cirrhosis. The average clearance was estimated to be 10 mL/min/kg.

Age and gender:
The pharmacokinetics of iloprost are not dependent on age and gender.

5.3 Preclinical safety data
Preclinical data, based on ongoing studies in humans, do not indicate any specific risk in terms of safety pharmacology, repeated dose toxicity, genotoxicity, or carcinogenic potential. Preclinical effects have been observed at doses well above the highest dose used in humans. This is of little relevance to clinical use.

Systemic toxicity
In acute toxicity studies, single intravenous and oral doses twice the therapeutic intravenous dose of iloprost have been shown to result in severe intoxication or death (intravenous). When evaluating the high pharmacological potency of iloprost and its absolute dose for therapeutic purposes in acute toxicity studies, results indicate that it does not pose a risk of acute side effects in humans. As expected from a prostacyclin, iloprost causes hemodynamic effects (vasodilation, skin redness, hypotension, inhibition of platelet function, respiratory disorders) and general intoxication symptoms such as apathy, gait disturbance, and postural changes.

In repeated systemic toxicity studies with intravenous infusion, a slight decrease in blood pressure occurred at 14 ng/kg/min, and serious adverse effects (hypotension, respiratory distress) occurred only at very high doses.

Repeated i.v./s.c. infusions for more than 26 weeks in rodents/non-rodents at doses exceeding the therapeutic dose in humans by 14 to 47 times (based on plasma blood levels) did not cause organ toxicity. Only the expected pharmacological effects, such as hypotension, skin redness, dyspnea, and increased intestinal motility, were observed.

Genotoxic potential, tumorigenicity
No genotoxic effects that would constitute evidence of mutagenic potential have been observed in *in vitro* and *in vivo* studies.

In tumorigenicity studies, iloprost has not been shown to have tumorigenic potential in rats and mice.

Reproductive toxicology
In embryo and fetotoxicity studies conducted on rats, continuous intravenous administration of iloprost caused single- toe anomalies in the front paws of some puppies, regardless of the dose. Although these changes are not considered true teratogenic effects, they are most likely related to growth retardation resulting from hemodynamic changes in the fetoplacental unit caused by iloprost. The growth retardation during postnatal development is thought to be largely reversible.

In comparative embryotoxicity studies in rabbits and monkeys, no such toe or gross structural abnormalities were observed even at doses many times greater than the human dose.

Very low levels of iloprost have been observed to pass into milk in rats.

6. PHARMACEUTICAL PARTICULARS

6.1 List of Excipients
Ethanol (96% w/v)
Trometamol
Sodium chloride
Hydrochloric acid
Water for injections

6.2 Incompatibilities
There are no data available for medicinal products other than those described in section “4.2 Posology and method of administration”.

6.3 Shelf life
24 months

6.4 Special precautions for storage
It should be stored at room temperature below 30°C.

After dilution with 0.9% sodium chloride solution or 5% glucose solution, it can be stored at room temperature below 25°C for 6 hours.

6.5 Nature and contents of container
1 mL colorless, Type I neutral glass ampoule with a white ring. Presented in a cardboard box with five ampoules in a separator along with package leaflet.

6.6 Special precautions for disposal and other handling of waste of human medicinal product
Any unused product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORIZATION HOLDER

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8. MARKETING AUTHORIZATION NUMBER(S)
2018/40

9. DATE OF FIRST AUTHORIZATION/ RENEWAL OF THE AUTHORIZATION

Date of first authorization: 26.01.2018
Date of renewal:

10. DATE OF REVISION OF THE TEXT