SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT
Iloprost Pharmamentum 50 micrograms/0.5 ml concentrate for solution for infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION
0.5 ml of aqueous solution contains 67 micrograms of Iloprost trometamol (equivalent to 50 micrograms of iloprost).
For a full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM
Concentrate for solution for infusion. Clear, colourless solution with no visible particles.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications
Treatment of advanced thromboangiitis obliterans (Buerger’s disease), with severe circulation disturbances, in cases where revasculariation is not indicated.

4.2 Posology and method of administration
The treatment with Iloprost Pharmamentum should be performed under strict monitoring in hospitals or clinics that have suitable equipment.
Before initiating the treatment in women, pregnancy must be ruled out.

Iloprost Pharmamentum is administered after dilution, as described in section 6.6 “Special precautions for disposal”, as an intravenous infusion, for a period of 6 hours/day, through a peripheral vein or a central catheter into a vein. The dose will be adjusted according to the individual tolerability within a dosage range of 0.5 to 2.0 ng iloprost/kg of body weight/min.

The solution for infusion should be prepared daily to ensure its sterility.
The content of the ampoule and solvent must be completely mixed.

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

During the first 2 to 3 days the dose tolerated by the patient will be determined. In order to do this, the treatment should start with an infusion rate that supplies a dose of 0.5 ng/kg/min, for 30 minutes. Following, the dose should be gradually increased, in intervals of about 30 minutes, in stages of 0.5 ng/kg/min. to 2.0 ng/kg/min. The exact infusion rate should be calculated based on the body weight, in order to obtain an infusion between 0.5 and 2.0 ng/kg/min (see tables with the use of an infusion pump or a bypass system).
If side effects occur, such as headaches, nausea or blood pressure decrease, the infusion rate should be decreased until a tolerable dose is established. If severe side effects are present, the infusion should be interrupted. Treatment should continue, usually for a period of 4 weeks, with the dose that had been well tolerated in the first 2 to 3 days.

Depending on the infusion technique, there are two different dilutions of the ampoule. One of these dilutions is 10 times less concentrated than the other (0.2 µg/ml versus 2 µg/ml) and may only be used with an infusion pump (e.g. Infusomat). On the contrary, the solution with the highest concentration is administered through a bypass system (e.g. Perfusor). For instructions on use and handling, see section 6.6 “Special precautions for disposal”.

Infusion rate (ml/hour) for different doses using an infusion pump

Generally, the solution ready for infusion is intravenously administered through an infusion pump (e.g. Infusomat). For instructions on dilution and use with an infusion pump, see section 6.6 “Special precautions for disposal”.

In case of a concentration of Iloprost Pharmamentum of 0.2 µg/ml, the necessary infusion rate should be calculated according to the scheme described below, in order to obtain a dose between 0.5 and 2.0 ng/Kg/min.

The following table can be used to calculate the infusion rate corresponding to the patient’s individual weight and the infusion rate. Please, check the current body weight of the patient and determine the infusion rate for the wanted dose, in ng/Kg/min.

<table>
<thead>
<tr>
<th>Body Weight (Kg)</th>
<th>Dose (ng/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>Infusion rate (ml/h)</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>6.0</td>
</tr>
<tr>
<td>50</td>
<td>7.5</td>
</tr>
<tr>
<td>60</td>
<td>9.0</td>
</tr>
<tr>
<td>70</td>
<td>10.5</td>
</tr>
<tr>
<td>80</td>
<td>12.0</td>
</tr>
<tr>
<td>90</td>
<td>13.5</td>
</tr>
<tr>
<td>100</td>
<td>15.0</td>
</tr>
</tbody>
</table>
Infusion rate (ml/hour) for different doses using a bypass system.

A bypass system can also be used with a 50 ml injection syringe (e.g. Perfusor). For instructions for dilution on use with a bypass system, see section 6.6 “Special precautions for disposal”.

In case of a concentration of Iloprost Pharmamentum of 2 µg/ml, the required infusion rate should be determined according to the following scheme, in order to obtain a dose between 0.5 and 2.0 ng/Kg/min.

The following table can be used to calculate the infusion rate corresponding to the patient’s individual weight and the infusion dose. Please, check the current body weight of the patient and determine the infusion rate for the required dose, in ng/Kg/min.

<table>
<thead>
<tr>
<th>Body Weight (Kg)</th>
<th>Dose (ng/kg/min)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.5</td>
</tr>
<tr>
<td>Infusion rate (ml/h)</td>
<td></td>
</tr>
<tr>
<td>40</td>
<td>0.60</td>
</tr>
<tr>
<td>50</td>
<td>0.75</td>
</tr>
<tr>
<td>60</td>
<td>0.90</td>
</tr>
<tr>
<td>70</td>
<td>1.05</td>
</tr>
<tr>
<td>80</td>
<td>1.20</td>
</tr>
<tr>
<td>90</td>
<td>1.35</td>
</tr>
<tr>
<td>100</td>
<td>1.50</td>
</tr>
<tr>
<td>110</td>
<td>1.65</td>
</tr>
</tbody>
</table>

The treatment duration is 4 weeks.

Due to possible occurrences of tachyphylaxis of the platelet effect and a possible platelet hyperaggregation rebound at the end of the treatment, a continuous infusion for several days is not advised, even though no clinical complications were reported due to these manifestations.

- Patients with renal or hepatic failure
It should be taken into account that, in patients with renal failure undergoing dialysis, as well as in patients who suffer from hepatic cirrhosis, iloprost elimination is reduced. In these patients, it is required to reduce the dose (e.g., half of the recommended dose).

4.3 Contraindications
- Hypersensitivity to iloprost or to any of the excipients
- Pregnancy;
- Breastfeeding;
- Situations in which the effect of Iloprost Pharmamentum on platelets might increase the risk of haemorrhages (e.g. active peptic ulcers, traumas, intracranial haemorrhages);
- Severe coronary heart disease or unstable angina pectoris;
- Myocardial infarction in the past 6 months;
- Chronic or acute cardiac failure (NYHA II-IV);
- Severe arrhythmias;
- Suspicion of pulmonary congestion;

4.4 Special warnings and precautions for use

Special warnings

A surgical intervention should not be postponed in patients who need to be submitted to an urgent amputation (e.g. in case of infected gangrene).

The patients should be strongly advised to stop smoking.

The elimination of iloprost is reduced in patients with hepatic or renal failure who require dialysis (see section 4.2 “Posology and method of administration” and 5.2 “Pharmacokinetic properties”).

Caution is advised in hypotensive patients, to avoid a worsening of this situation. Patients with relevant cardiac conditions should be carefully monitored.

Attention should be exercised due to the possible occurrence of orthostatic hypotension in patients who switch from lying down to standing straight, at the end of the infusion.
For patients with cerebrovascular disorders (transient ischaemic attack, stroke) in the past 3 months, a rigorous risk-benefit assessment should be performed (see also 4.3 “Contraindications: risk of haemorrhage, e.g. intracranial haemorrhage”).

Special precautions
Currently, there are only sporadic reports available on the use in children and adolescents.
Paravascular infusion of undiluted Iloprost Pharmamentum may cause changes in the injection site.

Oral ingestion and contact with mucous membranes should be avoided. When in contact with the skin, iloprost can cause persistent but painless erythema. Thus, the appropriate measures to avoid skin contact with iloprost must be taken. If such contact happens, the affected area should be rinsed immediately with plenty of water or saline solution.

4.5 Interaction with other medicinal products and other forms of interaction
Iloprost can increase the anti-hypertensive activity of β-receptor blockers, calcium antagonists, vasodilators and ACE inhibitors. If significant hypotension is seen, the dose of iloprost should be reduced.

Given that iloprost inhibits platelet aggregation, its simultaneous use with anticoagulants (such as heparin, coumarin derived anticoagulants) or other platelet aggregation inhibitors (such as acetylsalicylic acid, non-steroidal anti-inflammatory drugs, phosphodiesterase inhibitors and nitrovasodilators, e.g. molsidomine), may increase the risk of haemorrhage. If haemorrhages occur, the administration of iloprost should be interrupted.

Oral pre-medication with acetylsalicylic acid up to 300 mg daily for 8 days did not have impact on the pharmacokinetics of iloprost. In an animal study, it was discovered that iloprost may result in a reduction of the steady-state of t-PA (plasminogen activator) plasma concentration. The results of human studies show that iloprost infusions do not affect the pharmacokinetics of multiple oral doses of digoxin in patients and iloprost does not have any impact on the pharmacokinetics of the co-administered t-PA.

During animal experiments, it was seen that the vasodilator effect of iloprost is reduced when the animals are previously treated with glucocorticoids, without alteration of its antiplatelet action. The significance of this is still unknown in humans.

Although clinical trials were performed, in vitro studies to investigate the inhibitory potential of iloprost in the enzymatic activity of the cytochrome P450 have revealed that a relevant inhibition of the metabolism of drugs by this enzymatic pathway is not expected by iloprost.

4.6 Fertility, pregnancy and lactation
Iloprost Pharmamentum should not be administered to pregnant women or during breastfeeding (see section 4.3. “Contraindications”).

- Pregnancy
There are no adequate data on the use of iloprost on pregnant women. Pre-clinical studies have shown evidence of foetotoxicity in mice, but not in rabbits or monkeys (see section 5.3. “Preclinical safety data”). Given that the risk of the therapeutic use of iloprost during pregnancy is unknown, women of childbearing potential should take effective contraceptive measures during treatment.

**- Breastfeeding**
It is unknown if iloprost passes into human breast milk. Given that in mice iloprost passes, in very small doses, into breast milk, it should not be administered to breastfeeding women.

**4.7 Effects on ability to drive and use machines**
Not applicable.

**4.8 Undesirable effects**
The pharmacological action of iloprost is reflected on very common side effects such as headaches (68.8%) or vasodilatation leading to redness (58%) or gastrointestinal symptoms (up to 29.7%). These effects may occur when the dose is titrated in the beginning of the treatment for the identification of the dose better tolerated by the patient. However, these side effects usually disappear rapidly with dose reduction.

Other group of side effects is related to infusion site local reactions. For example, the infusion site may present redness and pain, or a skin vasodilatation that can lead to erythema with striae at the site of the infusion vein.

The frequencies of the adverse effects are referred in the following table (very common = 1/10, common = 1/100 to 1/10, uncommon = 1/1000 to <1/100, rare = 1/10,000 to <1/1000, very rare <1/10,000), are based on pooled data.

In the following table, the adverse effects were selected according to the incidence in the iloprost groups (553 patients) compared to the placebo groups (507 patients) in controlled clinical trials and the effective incidences based on cumulative data of 3325 patients to whom iloprost was administered, whether in controlled or uncontrolled trials, or in compassionate use programs.

**Adverse effects**

<table>
<thead>
<tr>
<th>System organ class (MedDRA* (v. 8.0))</th>
<th><strong>Very common</strong> ≥ 1/10</th>
<th><strong>Common</strong> ≥ 1/100 to ≤ 1/10</th>
<th><strong>Uncommon</strong> ≥ 1/1000 to ≤ 1/100</th>
<th><strong>Rare</strong> ≥ 1/10,000 to ≤ 1/1000</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Metabolism and nutrition disorders</th>
<th>Anorexia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Psychiatric disorders</td>
<td>Apathy</td>
</tr>
<tr>
<td></td>
<td>Anxiety</td>
</tr>
<tr>
<td></td>
<td>Depression</td>
</tr>
<tr>
<td></td>
<td>Hallucinations</td>
</tr>
<tr>
<td>Nervous system disorders</td>
<td>Headaches</td>
</tr>
<tr>
<td></td>
<td>Dizziness, vertigo</td>
</tr>
<tr>
<td></td>
<td>Paraesthesia/ Pins and needles</td>
</tr>
<tr>
<td></td>
<td>Palpitations, Hyperaesthesia, Burning sensation</td>
</tr>
<tr>
<td></td>
<td>Restlessness, Agitation</td>
</tr>
<tr>
<td></td>
<td>Sedation, Drowsiness</td>
</tr>
<tr>
<td></td>
<td>Tremor</td>
</tr>
<tr>
<td></td>
<td>Migraine</td>
</tr>
<tr>
<td></td>
<td>Faint/Syncope</td>
</tr>
<tr>
<td>Eye disorders</td>
<td>Abnormal vision</td>
</tr>
<tr>
<td></td>
<td>Blurred vision</td>
</tr>
<tr>
<td></td>
<td>Eye irritation</td>
</tr>
<tr>
<td></td>
<td>Eye pain</td>
</tr>
<tr>
<td>Ear and labyrinth disorders</td>
<td>Bradycardia</td>
</tr>
<tr>
<td></td>
<td>Arrhythmia</td>
</tr>
<tr>
<td></td>
<td>Extrasystoles</td>
</tr>
<tr>
<td></td>
<td>Myocardial infarction</td>
</tr>
<tr>
<td>Cardiac disorders</td>
<td>Redness</td>
</tr>
<tr>
<td></td>
<td>Hypotension</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular accident</td>
</tr>
<tr>
<td></td>
<td>Cerebrovascular ischaemia</td>
</tr>
<tr>
<td></td>
<td>Deep vein thrombosis</td>
</tr>
<tr>
<td></td>
<td>Pulmonary embolism</td>
</tr>
<tr>
<td>Vascular disorders</td>
<td>Asthma</td>
</tr>
<tr>
<td></td>
<td>Cough</td>
</tr>
<tr>
<td>Respiratory, thoracic and mediastinal disorders</td>
<td></td>
</tr>
<tr>
<td>Gastrointestinal disorders</td>
<td>Nausea Vomiting</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-----------------</td>
</tr>
<tr>
<td>Hepatobiliary disorders</td>
<td></td>
</tr>
<tr>
<td>Skin and subcutaneous tissue disorders</td>
<td>Sweating</td>
</tr>
<tr>
<td>Musculoskeletal and connective tissue disorders</td>
<td>Jaw pain Myalgia, Trismus Arthralgia</td>
</tr>
<tr>
<td>Renal and urinary disorders</td>
<td></td>
</tr>
</tbody>
</table>
The most appropriate MedDRA terms are used to describe the listed reactions. Synonyms or related pathologies are not listed, but should also be taken into consideration.

In addition, the adverse reactions were allergic reactions, confusion states, tachycardia and blood pressure increase. Isolated cases of dyspnoea and individual cases of pulmonary oedema or heart failure were registered in elderly patients with advanced arteriosclerosis. Iloprost can cause angina, especially in patients with coronary disease. Hypotension has been noticed after the administration of low doses of Iloprost Trometamol.

The risk of haemorrhage increases in patients who are receiving concomitant administration of platelet aggregation inhibitors, heparin or coumarin derived anticoagulants.

Data from post-marketing studies:

- Nervous system disorders
  Very rare: convulsions.

4.9 Overdose
- Symptoms
  An hypotensive reaction may be expected, as well as headaches, redness, nausea, vomiting and diarrhoea. A blood pressure increase, bradycardia or tachycardia and limb or back pain increase are also possible.

- Therapy
No specific antidote is known. The interruption of Iloprost administration, monitoring and symptomatic measures are recommended.

5. PHARMACOLOGICAL PROPERTIES
5.1 Pharmacodynamic properties
Pharmacotherapeutic group: Antithrombotic agents. Platelet aggregation inhibitors excl. heparin.

ATC Code: B01A C11
Iloprost is a synthetic prostacyclin analogue. The following pharmacological properties were observed:

- 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;
- anti-inflammatory effects, such as inhibition of leukocyte adherence following endothelial lesion, leukocyte accumulation in injured tissue and decrease of the release of tumoral necrosis factor.

5.2 Pharmacokinetic properties

Distribution
The steady state plasma levels are reached 10 to 20 minutes after the beginning of the intravenous infusion. The steady state plasma levels present a linear relation to the infusion rate. With an infusion rate of 3 ng/kg/min, plasma levels of 135 ± 24 ng/ml are obtained. Once the infusion is finished, a very fast decrease of plasma concentration of iloprost is verified, as a consequence of the high metabolisation rate. The metabolic clearance rate of the substance, from plasma, is approximately 20 ± 5 ml/Kg/min. The half-life of the terminal plasma disposition phase is 0.5 hours, so the substance levels decrease to less than 10% of the balance concentration 2 hours after the end of the infusion.

Any interactions with other medicinal products, on the level of plasma protein binding, seem highly unlikely, given that the iloprost concentrations reached are very low and, besides, a predominant part of iloprost is bound to the blood plasma albumin (protein binding: 60%). Similarly, any therapy effect with iloprost on the biotransformation of other medicinal products is highly unlikely given the nature of the metabolic routes and the presence of low absolute doses.

Metabolism
Iloprost is extensively metabolised via β-oxidation of the carboxyl side chain. No unchanged substance is eliminated. The main metabolite is tetranor-iloprost, which is found in the urine in the free and conjugated form of 4 diastereoisomers. Tetranor-iloprost is pharmacologically inactive as shown in animal studies. In
vitro studies suggest that iloprost metabolism in the lungs is similar after intravenous administration or inhalation.

**Elimination**

In patients with normal renal and hepatic function, the elimination of iloprost following intravenous infusion is characterised in most cases by a two-phase profile with mean half-lives of 3 to 5 minutes and 15 to 30 minutes. The total clearance of iloprost is about 20 ml/kg/min, which indicates an extra-hepatic contribution to the metabolism of iloprost.

A mass-balance study was performed using 3H-iloprost in healthy subjects. Following intravenous infusion, the total recovery of radioactivity is 81% and the recoveries in urine and faeces are 68% and 12%, respectively. 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.

**Characteristics in patients**

**Renal failure**

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/minute/kg) than patients with renal failure not undergoing intermittent dialysis treatment (mean CL = 18±2 ml/minute/kg).

**Hepatic failure**

Since iloprost is extensively metabolised by the liver, the plasma levels of the drug are influenced by changes in the 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/minute/kg.

**Age and gender**

Age and gender are not clinically relevant in the pharmacokinetics of iloprost.

**5.3 Preclinical safety data**

Pre-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated dose toxicity, genotoxicity and carcinogenic potential. Toxic effects were only observed at exposures considered sufficiently greater than the maximum human exposure indicating little relevance in clinical use. These effects were predominantly related to the excessive pharmacological action.

In embryo- and foetotoxicity studies in rats, continuous intravenous administration of iloprost led to abnormalities in the phalanges of the rear paws in a few foetuses, without dose dependence.
These changes are not considered as true teratogenic effects, but are most likely related to iloprost induced growth retardation in late organogenesis, due to haemodynamic changes in the foetoplacental unit. In comparable embryotoxicity studies in rabbits and monkeys no such finger abnormalities or other gross-structural abnormalities were observed even after dose levels considerably higher than the therapeutic dose.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Trometamol
Each 0.5 ml ampoule contains 4050 µg of ethanol 96%
Sodium chloride
1N Hydrochloric acid
Water for injections

6.2 Incompatibilities
There are no data available for medicinal products other than those described in section 6.6. “Special precautions for disposal”.

6.3 Shelf life
24 months.
The physical and chemical stability of the solution ready for infusion (diluted in saline solution or in glucose solution) was demonstrated for 6 hours, at 25°C.
From a microbiological point of view, the medicinal product must be used immediately. If not used immediately, in-use storage times and the conditions prior to use are the responsibility of the user and should normally not be longer than 24 hours at 2 to 8°C, unless dilution has taken place in controlled and validated aseptic conditions.

6.4 Special precautions for storage
This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container
Colourless, 1.5 ml, type I, glass ampoules containing 0.5 ml of concentrate for solution for infusion.

Presentations
Package with 1 ampoule containing 0.5 ml of concentrate for infusion.
Package with 5 ampoules containing 0.5 ml each of concentrate for infusion.
Package with 20 ampoules containing 0.5 ml each of concentrate for infusion.

6.6 Special precautions for disposal
Iloprost Pharmamentum should only be administered after dilution.
Given the possibility of drug interactions, other drugs should not be mixed with the solution ready for infusion. The solution for infusion should be prepared daily to ensure its sterility.

Instructions for dilution
The content of the ampoule and the solvent must be completely mixed.

Dilution of Iloprost Pharmamentum to use with infusion pump:

The content of one 0.5 ml ampoule (i.e. 50 µg) of Iloprost Pharmamentum should be diluted in 250 ml of saline solution or glucose 5% solution.

Dilution of Iloprost Pharmamentum to use with bypass system:

In this case, the content of one 0.5 ml ampoule (i.e. 50 µg) of Iloprost Pharmamentum should be diluted in 25 ml of saline solution or glucose 5% solution.

Handling
The storage conditions of the medicinal products should be respected, and the products should be kept out of sight and reach of children.

7. MARKETING AUTHORISATION HOLDER
Pharmamentum Aps
Jaegersborg Allé 164, DK-2820 Gentofte
Denmark

8. MARKETING AUTHORISATION NUMBER(S)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

10. DATE OF REVISION OF THE TEXT