## VI.2 Elements for a Public Summary

### *VI.2.1 Overview of disease epidemiology*

***Thromboangiitis Obliterans (TAO)***[1][2]

TAO, also called Buerger disease, is an inflammatory disease that most commonly affects the small to medium-sized arteries and veins of the extremities. Patients are young smokers who present with distal extremity ischemia, ischemic digit ulcers or digit gangrene. The disease is strongly associated with the use of tobacco products and smoking cessation is important to decrease the risk for amputation.

The prevalence of TAO has decreased over the past decade, partly because the prevalence of smoking has decreased but also because the diagnostic criteria have become more stringent.

Most patients with TAO are aged 20-45 years; the disease does not occur in pediatric or elderly patients. TAO is more common in males; however, the incidence in women is believed to be increasing, probably as a consequence of the growing frequency of smoking among women. The disease is relatively less common in people of northern European descent; natives of India, Korea, and Japan, along with Israeli Jews of Ashkenazi descent, have the highest incidence of TAO.

***Peripheral Arterial Occlusive Disease (PAOD)***[3]

Claudication, which is defined as reproducible ischemic muscle pain, is one of the most common manifestations of PAOD caused by atherosclerosis. Claudication occurs during physical activity and is relieved after a short rest. Pain develops because of inadequate blood flow.

Atherosclerosis affects up to 10% of the Western population older than 65 years. With the elderly population expected to increase 22% by the year 2040, atherosclerosis is expected to have a huge financial impact on medicine.

When claudication is used as an indicator, it is estimated that 2% of the population aged 40-60 years and 6% of the population older than 70 years are affected. Intermittent claudication most commonly manifests in men older than 50 years. Although younger patients may present with symptoms consistent with intermittent claudication, other etiologies of leg pain and claudication (eg, popliteal entrapment syndrome) must be strongly considered. PAOD has no racial predilection.

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[1] Piazza G, Creager M. ***Thromboangiitis Obliterans***. Circulation. 2010 Apr 27; 121(16): 1858–1861

[2] Nassiri N. ***Thromboangiitis Obliterans***. Available from: http://emedicine.medscape.com/article/460027-overview#a5

[3] Rowe V. ***Peripheral Arterial Occlusive Disease***. Available from: http://emedicine.medscape.com/article/460178-overview

### *VI.2.2 Summary of treatment benefits*

A clinical trial placebo-controlled was conducted with TAO patients. Patients were randomised to iloprost or placebo for 8 weeks.

For relief of rest pain without need of analgesics, iloprost was significantly more effective than placebo.[4]

In a prospective study, 158 patients with rest pain and/or ischemic ulcers from 17 clinics were administered iloprost for 28-days. The primary endpoint was complete healing without pain or major amputation at 24 weeks. The secondary endpoints were pain assessment, reduction in ulcer area and reduction of the ulcer size. Complete healing rate was significantly better with iloprost treatment in comparison to the initial values at 24 weeks. The secondary endpoints were also significantly better.

The results of this independent study indicate that intravenous iloprost relieves ischemic symptoms efficiently in the acute phase Buerger's disease patients. Considering unsatisfactory results following surgical revascularisation and sympathectomy in Buerger's disease, prostacyclin analogues might be the first line treatment as long as complete abstinence from smoking is achieved.[5]

### *VI.2.3 Unknowns relating to treatment benefits*

According to the SmPC, there are no sufficient data on the effectiveness of iloprost when used in paediatric populations.

### *VI.2.4 Summary of safety concerns*

**Important identified risks**

| Risk | What is known | Preventability |
|---|---|---|
| Bleeding | Uncommon side effect (can occur in 1 to 10 in 1,000 users): bleeding disorder with symptoms of bruising and easy bleeding (thrombocytopenia).<br>Iloprost Solufarma has an effect on blood clotting: it has a blood-thinning effect. For this reason, using Iloprost Solufarma at the same time as blood thinners (such as | Do not use Iloprost Solufarma if you have a condition where the use of Iloprost Solufarma, due to the effect that the product has on blood clotting, increases the risk of bleeding (for instance, a stomach ulcer, injury or bleeding within the skull). |

[4] ***Oral iloprost in the treatment of thromboangiitis obliterans (Buerger's disease): a double-blind, randomised, placebo-controlled trial. The European TAO Study Group***. Eur J Vasc Endovasc Surg. 1998 Apr;15 (4):300-7.

[5] Bozkurt AK, Cengiz K, Arslan C, Mine DY, Oner S, Deniz DB, Ufuk D. ***A stable prostacyclin analogue (iloprost) in the treatment of Buerger's disease: a prospective analysis of 150 patients***. Ann Thorac Cardiovasc Surg. 2013;19 (2):120-5. Epub 2012 Aug 31.

| Risk | What is known | Preventability |
|---|---|---|
| | heparin and acenocoumarol) may increase the risk of bleeding.<br>Combined use of Iloprost Solufarma and certain painkillers which also have an anti-inflammatory and fever-reducing effect (known as NSAIDs, including acetylsalicylic acid, the active substance of aspirin and ibuprofen) also increases the risk of bleeding, as this group of painkillers also have a blood-thinning effect. | Tell your doctor if you are taking other medicine that make your blood thinner or anti-inflammatory and fever reducing medicines. |

| Risk | What is known | Preventability |
|---|---|---|
| Hypotension | Iloprost Solufarma has an antihypertensive (blood pressure-lowering) effect.<br>The side effects listed below can be life-threatening in severe cases and even fatal:<br>• stroke/cerebral infarction, also known as brain haemorrhage or cerebral infarction (cerebrovascular accident, CVA)<br>• low blood pressure (hypotension) | If you have low blood pressure in the arteries, it must be ensured that your blood pressure does not drop any further.<br>Have special precaution if you have had a stroke in the last 3 months or any other interruption in the blood supply to your brain.<br>After administration of Iloprost Solufarma, you must be careful when getting up from a lying position, on account of hypotension. Your blood pressure may fall if you get up too quickly from a lying or sitting position, which may be accompanied by dizziness.<br>You must tell your doctor if you are already using medicines for high blood pressure (for example, beta-blockers, calcium antagonists, vasodilators or ACE inhibitors), as these agents may increase the antihypertensive effect of Iloprost Solufarma.<br>If you get any of these side effects, tell your doctor or pharmacist immediately. |
| Use during pregnancy and breast-feeding | If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine. | Do not use Iloprost Solufarma if you are pregnant or breast-feeding. |

| Risk | What is known | Preventability |
|---|---|---|
| | If you are pregnant, Iloprost Solufarma must not be used in your case. If you are a woman of childbearing age, you must avoid becoming pregnant.<br>You must not breastfeed during treatment with Iloprost Solufarma. | |

**Important potential risks**

| Risk | What is known (Including reason why it is considered a potential risk) |
|---|---|
| Off label use | Other medicines containing iloprost are approved in other indications, namely treatment of adult patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms.[6] |
| Renal insufficiency | In patients with renal insufficiency requiring dialysis, high levels of iloprost in blood may occur.<br>Have special precaution if you have severe kidney problems.<br>In patients doing dialysis, a reduction in dose is required by commencing with half of the recommended dose. |
| Hepatic disorders | In patients with cirrhosis, high levels of iloprost in blood may occur. Have special precaution if you have severe liver problems.<br>In patients with cirrhosis, a reduction in dose is required by commencing with half of the recommended dose. |
| Acute respiratory distress syndrome | The side effects listed below can be life-threatening in severe cases and even fatal:<br>• sudden and intense attacks of breathlessness, caused by spasm of the airway muscles and swelling of the airway lining (asthma)<br>• shortness of breath (dyspnoea)<br>• fluid accumulation in the lungs (pulmonary oedema), which can lead to severe breathing problems or coughing up blood.<br>If you get any of these side effects, tell your doctor or pharmacist immediately. |

**Missing information**

None proposed.

### *VI.2.5 Summary of risk minimisation measures by safety concern*

All medicines have a Summary of Product Characteristics (SmPC) which provides physicians, pharmacists and other health care professionals with details on how to use the medicine, the risks and

[6] Ventavis: EPAR – Product Information (2014)

recommendations for minimising them. An abbreviated version of this in lay language is provided in the form of the package leaflet (PL). The measures in these documents are known as routine risk minimisation measures.

The Summary of Product Characteristics and the Package leaflet for *Iloprost Solufarma* can be found in the *Iloprost Solufarma*'s EPAR page

This medicine has no additional risk minimisation measures.

### *VI.2.6 Planned post authorisation development plan*

Besides routine pharmacovigilance activities, there are no planned activities in terms of efficacy studies and further investigation of safety concerns.

### *VI.2.7 Summary of changes to the Risk Management Plan over time*

Not applicable.

This is the first EU-RMP for *Iloprost Solufarma*.