**TRASPARRENCY COMMITTEE**

**Opinion**  
2 April 2014

**REMODULIN 1 mg/ml, solution for infusion (intravenous route)**  
1 20-ml glass vial (CIP: 34 009 368 161-5 2)

Applicant: BIOPROJET PHARMA

<table>
<thead>
<tr>
<th>INN</th>
<th>treprostinil sodium</th>
</tr>
</thead>
<tbody>
<tr>
<td>ATC code (2014)</td>
<td>B01AC21 (prostacyclin)</td>
</tr>
<tr>
<td>Reason for the request</td>
<td>Inclusion</td>
</tr>
<tr>
<td>List concerned</td>
<td>Hospital use (French Public Health Code L.5123-2)</td>
</tr>
<tr>
<td>Indication concerned</td>
<td>&quot;Treatment of idiopathic or hereditary pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms of the disease in patients in NYHA (New York Heart Association) functional class III.&quot;</td>
</tr>
<tr>
<td>Actual Benefit</td>
<td>Insufficient to justify reimbursement by National Health Insurance in the treatment of idiopathic or hereditary PAH in functional class III patients</td>
</tr>
<tr>
<td>----------------------------------------</td>
<td>-----------------------------------------------------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Improvement in Actual Benefit</td>
<td>Not applicable</td>
</tr>
<tr>
<td>Therapeutic Use</td>
<td>This proprietary medicinal product has no role in the therapeutic strategy (see section 012.1)</td>
</tr>
<tr>
<td>Recommendations:</td>
<td>The Transparency Committee does not recommend inclusion of REMODULIN 1 mg/ml on the list of medicinal products approved for hospital use, by intravenous administration, in the treatment of idiopathic or hereditary PAH in order to improve exercise capacity and symptoms of the disease in patients in functional class III (indication of the Marketing Authorisation).</td>
</tr>
</tbody>
</table>
01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)  
Date (mutual recognition procedure) 29 March 2013  
Conditional Marketing Authorisation associated with an RMP for the new intravenous administration route.

Prescribing and dispensing conditions/special status  
List I  
Medicine for hospital prescription only, with prescription restricted to specialists and/or hospital departments specialising in respiratory medicine or cardiology.

ATC Classification  
2014  
B Blood and blood forming organs  
B01 Antithrombotic agents  
B01A Antithrombotic agents  
B01AC Platelet aggregation inhibitors excl. heparin  
B01AC21 treprostinil

02 BACKGROUND

In the first application for inclusion for hospital use, REMODULIN, a subcutaneous prostacyclin analogue, was indicated in the treatment of pulmonary arterial hypertension, PAH (TC Opinion of 20 July 2005). The Committee granted a substantial AB and an IAB II (sharing the IAB granted to VENTAVIS in 2004) in the population of patients with a contraindication for or hepatic intolerance to bosentan (TRACLEER) and in whom the administration of epoprostenol (FLOLAN) was not appropriate. For other patients, an IAB V relative to TRACLEER was given.

In 2010, the Transparency Committee set itself the task of re-assessing the AB and IAB of all medicinal treatments indicated in PAH.  
In its re-assessment of 5 January 2011, it granted subcutaneous REMODULIN a moderate AB and an IAB IV in the treatment of idiopathic pulmonary arterial hypertension in patients of functional class III.

This proprietary medicinal product has been sold in France since 2006 for ambulatory subcutaneous infusion in four doses (1 mg/ml, 2.5 mg/ml, 5 mg/ml and 10 mg/ml).

Bioprojet Pharma has requested inclusion of a new form of REMODULIN for intravenous administration for a single dose of 1 mg/ml with the following justification:  
"Although it allows simplified treatment relative to intravenous infusions, the main limit to subcutaneous infusion is the appearance of intolerance at the infusion site (pain, induration) leading to treatment discontinuation for a significant number of patients. The use of IV treprostinil is intended for patients already stabilised by subcutaneous infusion but who have had intolerable local reactions."
03 THERAPEUTIC INDICATION

“Treatment of idiopathic or hereditary pulmonary arterial hypertension to improve exercise capacity and symptoms of the disease in patients in NYHA (New York Heart Association) functional class III.”

04 DOSAGE

“REMODULIN is administered as a continuous subcutaneous or intravenous infusion. Due to the risks associated with indwelling central venous catheters, in particular serious systemic infections, subcutaneous infusion (undiluted) is the recommended administration route and continuous intravenous infusion should only be considered in patients stabilised by subcutaneous infusion of treprostinil but who can no longer tolerate subcutaneous administration and if the level of risk incurred by intravenous administration is deemed acceptable.

The treatment should be initiated and monitored by a physician experienced in managing pulmonary hypertension.

**Adults**

**Initiation of treatment in patients not previously treated by prostacyclins:**

The treatment should be initiated under close medical supervision within a medical establishment with intensive care facilities.

The recommended rate of infusion for starting treatment is 1.25 ng/kg/min. If this initial dose is poorly tolerated, the infusion rate will be reduced to 0.625 ng/kg/min.

**Adjusting the dosage:**

The infusion rate is increased under medical supervision in steps of 1.25 ng/kg/min per week during the first 4 weeks of treatment, and then by 2.5 ng/kg/min per week.

The dosage is adjusted individually under medical supervision in order to achieve a dose for long-term treatment that will ensure improvement of symptoms with a tolerability that is acceptable to the patient.

In the principal studies lasting 12 weeks, efficacy was only maintained by increasing the dose 3 to 4 times per month on average. The objective of long-term dosage adjustment is to establish the dose with which an improvement of the pulmonary arterial hypertension symptoms is obtained while minimising excessive pharmacodynamic effects.

Adverse effects such as flushing, headache, hypotension, nausea, vomiting and diarrhoea are generally dependent on the dose of treprostinil administered. Symptoms may resolve with continued treatment, but if they persist or are intolerable for the patient, the infusion rate should be reduced to decrease their intensity.

During the follow-up phases of the clinical trials, the mean doses achieved were 26 ng/kg/min after 12 months of treatment, 36 ng/kg/min after 24 months and 42 ng/kg/min after 48 months.

For obese patients (30% heavier than the theoretical ideal weight), the initial dose and subsequent dose increases should be based on the theoretical ideal weight.

---

1The NYHA classification (New York Heart Association Functional Classification) is based on the functional capacity of the patient. It divides patients into four classes:

- **Class I:** no limit to physical activity. No dyspnoea and no fatigue during everyday activities.
- **Class II:** moderate limit to physical activity. Discomfort during strenuous physical activities. No discomfort at rest.
- **Class III:** clear limit to physical activity. Discomfort during even moderate everyday activities. No discomfort at rest.
- **Class IV:** Unable to undertake most everyday activities without considerable discomfort. Discomfort at rest.
Suddenly stopping or decreasing the REMODULIN infusion may induce rebound pulmonary arterial hypertension. Therefore it is recommended not to interrupt REMODULIN infusion and to start it again as soon as possible after a sudden or accidental decrease or interruption. In this case, the procedures for re-initiating the infusion will be determined case by case by qualified personnel. In the majority of cases, if the duration of the interruption is limited to a few hours, the infusion may be restarted at the same rate. Longer interruptions may require a new initiation and dose adjustment phase.

**Elderly**
Clinical studies performed with REMODULIN have not included a sufficient number of patients aged 65 or older to determine if the treatment response is different in the elderly. The results of a population pharmacokinetic analysis showed a 20% reduction in plasma clearance of treprostinil in the elderly. Generally, due to the frequency of hepatic, renal or cardiac function impairment, intercurrent diseases or associated medical treatments, the dose should be adjusted with extreme caution in the elderly.

**Children and adolescents**
Few data exist concerning patients below age 18. From the clinical studies available it is impossible to determine whether the efficacy and safety of the dosage regimen recommended in adults can be extrapolated to children and adolescents.

**Hepatic impairment**
Systemic exposure to treprostinil measured by the area under the curve (AUC) of the plasma concentrations over a given period increases by 260% to 510% in subjects with mild to moderate hepatic impairment (stage A to B of the Child-Pugh classification). A reduction in plasma clearance of treprostinil of up to 80% was observed in subjects with mild to moderate hepatic impairment. In hepatic impairment, caution is recommended due to the risk of increased systemic exposure that could lead to reduced tolerability and an increase in dose-dependent adverse effects. Consequently, the REMODULIN initiation dose will be decreased to 0.625 ng/kg/min and the greatest caution is recommended for each dose increase.

**Renal impairment**
In the absence of studies in patients with renal impairment, modalities for use in these subjects have not been established. Given that treprostinil and its metabolites are essentially excreted in the urine, caution is recommended in cases of renal impairment to prevent detrimental consequences related to a possible increase in systemic exposure.

**Switching to treatment with intravenous epoprostenol**
When it is necessary to switch to treatment with intravenous epoprostenol, the REMODULIN transition phase should be done with close medical supervision appropriate to each case. The following regimen is recommended as a guide. In the first step, treprostinil infusion will be slowly decreased to 2.5 ng/kg/min. After maintenance of this new dose for at least one hour, the intravenous epoprostenol treatment may be initiated at the maximum dose of 2 ng/kg/min. The treprostinil dose will then be decreased at successive intervals of at least 2 hours while progressively increasing the dose of epoprostenol after having maintained the initiation dose for at least one hour.

**Method of administration**

**Continuous intravenous infusion**
REMODULIN is administered by continuous intravenous infusion by a central venous catheter using an ambulatory infusion pump. Temporarily, it can also be administered through a peripheral vein using a large calibre vein. An increased risk of thrombophlebitis is observed in extended use of peripheral venous infusion.
REMODULIN must be diluted in sterile water for injection or in a 0.9% sodium chloride solution for infusion and administered in continuous infusion by an indwelling central venous catheter, surgically placed or, temporarily, through a peripheral vein using an intravenous infusion pump.
Instructions for patients treated with continuous intravenous infusion:
Patients should be fully trained and comfortable with the handling and operation of the infusion device being used. Patients should receive appropriate and personalised instructions, and be assisted by caregivers until they are completely ready to change the infusion devices, adjust the rate/dose according to the prescription, and manage the situation if pump alarms go off. They should also receive all the instructions necessary for preparing the dilute solution, filling the pump reservoir, and connecting and starting up the infusion circuit under rigorous hygienic and aseptic conditions. Pump usage documentation should be provided to the patient by an instruction manual from the pump manufacturer or in the form of specific advice prepared by the prescribing physician. The documentation should describe all the operations in common practice for administration of the medicine, the steps to take to deal with the occurrence of an infusion system blockage or other malfunctions reported by the pump alarms and the contact information for the person to call in the event of an emergency.

Measures for minimising the risk of systemic infections induced by the catheter:
Close attention must be paid to the recommendations (see section 4.4 of the SPC) to reduce the risk of systemic infections caused by the catheter in patients treated with REMODULIN by intravenous infusion. This information comes from the recommendations currently in effect for improving practices and preventing systemic infections by catheters (see SPC).

05 Therapeutic need

The objective of management is primarily to improve the patient's survival and quality of life. Since PAH is a progressive disease over the short term, regular follow-up is necessary for early detection of clinical exacerbation and also to enable therapy to be escalated as soon as possible. Assessment of the prognosis has an important place in the choice of initial treatment and in assessment of the response to treatment.

The therapeutic strategy recommended by the Transparency Committee in these opinions found in the literature3,4,5 and updated in December 20136 is as follows:

- Conventional treatment for PAH combines anticoagulants, diuretics, oxygen therapy, and calcium inhibitors.
- In patients with PAH of functional class III in particular, the following can be used:
  - oral endothelin antagonists (bosentan and ambrisentan), and phosphodiesterase inhibitors (sildenafil or tadalafil)
  - inhaled iloprost (VENTAVIS), in cases of a contraindication to or hepatic intolerance of bosentan
  - continuous subcutaneous treprostinil (REMODULIN), which can be offered for the same reasons as iloprost (VENTAVIS). The decision to embark on treprostinil therapy must consider the high probability of the need to maintain continuous subcutaneous infusion for the long term.
  - continuous intravenous infusion of epoprostenol (FLOLAN).

A lung or heart-lung transplant is the last-resort treatment. It is generally considered in patients who have not improved after 3 months of medical treatment. TRACLEER (bosentan), VOLIBRIS (ambrisentan), ADCIRCA (tadalafil) and REVATIO (sildenafil) are indicated in the management of PAH patients in functional class II.

New substances have obtained a Marketing Authorisation (macitentan) or are in the process of doing so (riociguat) in the treatment of PAH and are under assessment.

Treatment is assessed 3 to 4 months after initiation. If the patient has achieved the therapeutic objectives established, the treatment is continued in association with regular follow-up by the centre of competence.

The importance of regular follow-up of these patients must be emphasised in order to monitor treatment efficacy or, conversely, detect any exacerbation during treatment.

In patients in functional class III or IV, treatment with intravenous prostacyclin (epoprostenol) results in significant improvement in functional and haemodynamic parameters. The results obtained with iloprost are, unfortunately, somewhat disappointing. Practically speaking, epoprostenol is a treatment that is complex to manage and restrictive for patients (indwelling central venous catheter, twice-daily preparation of the product, portable pump). These are the drawbacks that led to the development of analogues administered subcutaneously or by inhalation. However, treprostinil, which is administered subcutaneously, is very frequently associated with pain at the injection site (more than 85% of patients) which is the main limiting factor for dose increases and leads to treatment discontinuation in 8% to 40% of cases.

No data permits the therapeutic choice to be guided more towards one class than another in first-line treatment. Nevertheless, in patients in functional class III, the prostacyclins are not used as first-line treatment although they have a Marketing Authorisation for this type of patient, but are administered following the failure of oral treatments. In practice, if oral treatment fails (mainly with bosentan), epoprostenol is directly administered without trying iloprost or treprostinil, which are infrequently used in practice.

Several open-label studies suggest that a combination of the substances indicated in PAH could enable a synergistic therapeutic effect to be obtained. These combinations are currently used frequently in cases where monotherapy has failed. However these data are still limited and the role of bitherapies remains to be defined, particularly the choice of the therapeutic combination and the optimal time for its initiation, by means of 2 trials satisfying current methodological requirements. However, treatment combinations have become common practice in many PAH centres of competence despite the absence of short and long-term efficacy and safety data or data being assessed. They are suggested in cases of inadequate clinical response to monotherapy treatments (no improvement in functional class, clinical deterioration, clinical signs of right ventricular failure, etc.).

**06 CLINICALLY RELEVANT COMPARATORS**

*The clinically relevant comparators of the medicinal product assessed are medicinal products available at the same stage of the therapeutic strategy and intended for the same population, on the date of the assessment.*

---

These include prostacyclins indicated after failure of oral treatments in patients with functional class III PAH.

### 06.1. Medicinal products

<table>
<thead>
<tr>
<th>INN</th>
<th>Same TC*</th>
<th>Name (Company)</th>
<th>Date of opinion</th>
<th>AB</th>
<th>IAB</th>
<th>Reimbursement</th>
</tr>
</thead>
<tbody>
<tr>
<td>iloprost inhalation (nebulisation)</td>
<td></td>
<td>VENTAVIS (Bayer Santé)</td>
<td>5 January 2011 (re-assessment of AB and IAB)</td>
<td>moderate</td>
<td>IAB IV</td>
<td>Yes</td>
</tr>
<tr>
<td>treprostineil SQ infusion</td>
<td>Yes</td>
<td>REMODULIN (Bioprojet)</td>
<td></td>
<td></td>
<td></td>
<td>Approved for hospital use</td>
</tr>
<tr>
<td>epoprostenol IV (central catheter)</td>
<td></td>
<td>FLOLAN (GSK)</td>
<td></td>
<td>substantial</td>
<td>IAB II, especially considering the known and proven effect on survival</td>
<td></td>
</tr>
</tbody>
</table>

*therapeutic category

### 06.2. Other health technologies

In the event of disease resistant to any pharmacological agent, the patient is assessed for possible surgical treatment: atrioseptostomy or heart-lung transplant.

**Conclusion**

All the comparators listed are clinically relevant.

### 07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

REMODULIN for intravenous administration was approved in the US in 2004 and obtained a Marketing Authorisation in all European Union countries in 2011 (except for Ireland, Spain and the United Kingdom where it has compassionate use status).

In Europe, reimbursement by health insurance systems is being assessed.\(^\text{10}\)

### 08 ANALYSIS OF AVAILABLE DATA

#### 08.1 Efficacy

The company has not filed clinical data in support of its application to assess the efficacy of REMODULIN for intravenous administration.

The SPC specifies that subcutaneous and intravenous administration of REMODULIN has proven to be bioequivalent at equilibrium with a dose of 10 ng/kg/min in terms of area under the curve and maximum plasma concentrations.

\(^\text{10}\)REMODULIN is currently reimbursed in Germany and the Netherlands.
08.2 Safety/Adverse effects

8.2.1 SPC Data
These data, for intravenous administration, refer to the existing data for subcutaneous administration.

"Nervous system disorders: very common: headaches, common: dizziness
Cardiovascular disorders: very common: vasodilation, common: hypotension
Gastrointestinal disorders: very common: diarrhoea, nausea
Cutaneous and subcutaneous disorders: very common: rash, common: pruritus
Musculoskeletal, connective tissue and bone disorders: very common: jaw pain
General disorders and local problems at the infusion site: very common: pain at the infusion site, local reaction at the infusion site, bleeding or haematoma, common: oedema.

Adverse events related to the intravenous administration system:
The following adverse events have been identified since REMODULIN has been sold. Since these effects arise from spontaneous reports, their relative frequency in the entire treatment population cannot be determined with certainty.
These adverse effects are: thrombophlebitis in cases of peripheral intravenous infusion, systemic infection, sepsis, infection related to the central venous catheter, local infection and abscess at the subcutaneous infusion injection site, thrombocytopenia, bleeding at the infusion injection site and bone pain.
A retrospective study was performed by the CDC (Centers for Disease Control) at seven sites in the United States that used REMODULIN intravenously for treatment of pulmonary arterial hypertension. The results of this study found an incidence rate of systemic infections related to the catheter of 1.10 events per 1000 catheter days. Given the risk of contamination by a broad spectrum of Gram negative or Gram positive bacteria with dilute REMODULIN solution administered long-term by central venous line, administration of undiluted REMODULIN by continuous subcutaneous infusion should be preferred.
In addition, cases of generalised rash with a macular or papular appearance, as well as cases of cellulitis have been reported rarely."

8.2.2 Risk Management Plan (RMP)
The company is committed to setting up measures for risk management and minimisation, notably including a caregiver staff and patient information programme on good practice for preparation and administration of the dilute REMODULIN solution and specific pharmacovigilance measures for monitoring the risk of systemic or catheter infection with REMODULIN.

09 SUMMARY & DISCUSSION

There are no clinical data supporting the efficacy and safety of intravenous administration of REMODULIN.
A randomised, double-blind, placebo-controlled study designed to evaluate this new administration method was discontinued after recruiting 45 patients out of the 126 planned in the protocol due to many tolerability problems.

The only data available and assessed by the Committee are those relating to subcutaneous administration.

A meta-analysis evaluating the efficacy and safety of prostacyclins included 9 randomised and controlled trials, with a duration of between 3 days and 1 year and including 1175 patients. The

authors concluded that efficacy was shown by prostacyclins administered intravenously, epoprostenol (improvement of 90 m in distance walked in the 6-minute test compared with conventional PAH treatment in four trials), or administered subcutaneously (median improvement of 16 m with treprostinil compared with placebo in 2 studies) and by inhaled prostacyclin (improvement of 36 m in one study versus placebo). However, the studies were of short duration for the most part and included a small number of patients. The symptomatic benefit is modest and based on an intermediate endpoint, except for FLOLAN, for which a proven effect on survival is known and established in controlled studies.

The efficacy of different prostacyclins is variable. In the absence of studies comparing these different substances, none of them can be recommended preferentially. However, FLOLAN is considered, in practice, as the first-line prostacyclin due to its symptomatic efficacy and the demonstration of its effect on survival. In the majority of clinical trials, one of the chief limitations is that patients remain symptomatic with a non-optimum quality of life, despite the treatments. The clinical benefit provided to patients by these different treatments is difficult to estimate. It has not been demonstrated that the currently available PAH treatments, except for FLOLAN, decrease mortality or delay disease progression. On the basis of intermediate endpoints, the symptomatic benefit is modest.

For subcutaneous REMODULIN, there are long-term data with a positive impact on survival, but these data have a limited level of evidence. There are no data on the time to clinical worsening, the most relevant clinical endpoint. Its use in practice is very limited due to its cutaneous tolerability. In fact, pain at the injection site is observed in approximately 85% of patients and is responsible for discontinuation of treatment in approximately 8% of patients. This intolerance is dose-dependent. In practice, the dose used can be reduced, but may sometimes be insufficient. It should be emphasised that in practice, with the anti-pain protocols recently developed with healthcare professionals by Bioprojet, and which are routinely used, local intolerance is much less common.

According to the SPC, "special warnings and precautions for use section," the decision to embark on REMODULIN treatment must take account of the high probability of it being necessary to persist with continuous infusion over a prolonged period. Thus it is appropriate to perform a careful assessment of the patient's ability to accept and monitor an indwelling catheter and infusion pump. The benefit of treatment with REMODULIN has not been established in patients with the most severe stages of pulmonary arterial hypertension (NYHA functional classification stage IV). The efficacy/safety ratio for REMODULIN has not been studied in pulmonary arterial hypertension associated with a left-right cardiac shunt, portal hypertension or HIV infection. Patients should be fully trained and comfortable with the handling and operation of the infusion device being used.

Close attention must be paid to the recommendations (see section 4.4 of the SPC) to reduce the risk of systemic infections caused by the catheter in patients treated with REMODULIN by intravenous infusion. Thus, due to the risks associated with indwelling central venous catheters, in particular serious systemic infections, subcutaneous infusion (undiluted) is the recommended administration route and continuous intravenous infusion should only be considered in patients stabilised by subcutaneous infusion of treprostinil but who can no longer tolerate subcutaneous administration and if the risk incurred by central intravenous administration is deemed acceptable.

The company is only requesting inclusion for a single dose of 1 mg/ml, which is the weakest and least used according to hospital sales data for the year 2013 for subcutaneous administration. For patients treated at high doses, the option of switching to this presentation is not justified.

R.J. Barst et al. Long-term Outcome in Pulmonary Arterial Hypertension Patients Treated With Subcutaneous Treprostinil. European Respiratory Journal 2006; 28; 1195-1203
In practice, in view of the existing alternatives (epoprostenol - FLOLAN and generics) this IV presentation of treprostinil does not meet a need (expert opinion).

**010 PLANNED STUDIES**

A trial evaluating an oral form of treprostinil is in progress.

**011 THERAPEUTIC USE**

Not applicable (see section 012.1.)

---

15 Usage data for REMODULIN administered SQ in hospital (GERS [Partnership to Collect and Prepare Statistics] – units sold in 2013): 191 vials for REMODULIN 1 mg/ml, 627 for REMODULIN 2.5 mg/ml, 605 for REMODULIN 5 mg/ml, 317 for REMODULIN 10 mg/ml.
012 TRANSPARENCY COMMITTEE CONCLUSIONS

In view of all the above information, and following the debate and vote, the Committee’s opinion is as follows:

012.1. Actual Benefit

PAH is a rare, life-threatening lung disease, which is characterised by progressive obstruction of small pulmonary arteries leading to a progressive increase in pulmonary arterial pressure and right heart failure. PAH is defined as an increase, found on right cardiac catheterisation, in the mean pulmonary arterial pressure (mPAP) greater than or equal to 25 mmHg at rest without an increase in pulmonary capillary pressure. Asthenia, dyspnoea, chest pain, and loss of consciousness are the most common clinical signs. The median survival with symptomatic treatment is around 2.5 years for patients with PAH in functional class III.7

Intravenous administration of REMODULIN 1 mg/ml is intended as symptomatic therapy.

In the absence of clinical data, its efficacy cannot be established and its use entails an increased risk of infection (systemic infections, bacteraemia, septicaemia, etc.) related to its administration route. The SPC specifies that subcutaneous administration should be preferred. There is nothing to suggest a clinical benefit for patients. For these reasons, the efficacy/adverse effects ratio for REMODULIN 1 mg/ml for intravenous administration cannot be qualified.

In practice, physicians specialising in the management of PAH do not need this new route of administration, especially in view of serious adverse effects, because they already have an intravenous prostacyclin, epoprostenol (FLOLAN) and its generics. Due to discontinuations of subcutaneous REMODULIN treatment for intolerance, epoprostenol is prescribed.16 It is also commonly administered directly to patients without trying subcutaneous REMODULIN because epoprostenol is more effective and its use is widely known and established. Thus, REMODULIN for intravenous administration has no role in the therapeutic strategy. Remember that when initiating PAH treatment, patients must be educated and monitored by the referral centre or in a French PAH network centre of competence for this type of treatment.

Public health benefit:
Although pulmonary arterial hypertension is a serious and life threatening clinical situation, the public health burden of this disease is low due to the small number of patients concerned. The improvement of the management of pulmonary arterial hypertension patients is a public health need which is an established priority.17 Given the absence of data to document, in particular, the impact on disease progression, REMODULIN treatment by the intravenous route is not expected to have a populational impact on morbidity, mortality and quality of life, associated with this disease. Therefore, this proprietary medicinal product is not expected to impact public health.

Consequently, the Committee considers that the actual benefit of REMODULIN, 1 mg/ml by intravenous administration in the treatment of idiopathic or hereditary PAH in patients of functional class III is insufficient for reimbursement by National Health Insurance.

---

16In general, patients are already on multiple oral therapies when resorting to prostacyclins.
17Act of 9 August 2004 on public health policy, Rare Diseases Plan.
012.2. Improvement in actual benefit (IAB)

Not applicable.

013 TARGET POPULATION

Not applicable.

TRANSPARENCY COMMITTEE RECOMMENDATIONS

The Transparency Committee does not recommend inclusion of REMODULIN 1 mg/ml on the list of medicines approved for hospital use, by intravenous administration, in the treatment of idiopathic or hereditary PAH in order to improve exercise capacity and symptoms of the disease in patients of functional class III (indication of the Marketing Authorisation).