HAUTE AUTORITÉ DE SANTÉ

The legally binding text is the original French version

TRANSPARENCY COMMITTEE

Opinion

23 July 2014

VELETRI 0.5 mg, powder and solvent for solution for infusion

B/1 (CIP: 34009 585 763 3 1)

VELETRI 1.5 mg, powder and solvent for solution for infusion

B/1 (CIP: 34009 585 765 6 0)

Applicant: ACTELION

INN	epoprostenol
ATC code (2013)	B01AC09 (antithrombotic agents, platelet aggregation inhibitors)
Reason for the request	**Inclusion**
List concerned	**Hospital use (French Public Health Code L.5123-2)**
Indications concerned	**"VELETRI is indicated for:** **- Pulmonary Arterial Hypertension** **VELETRI is indicated for the treatment of pulmonary arterial hypertension (PAH) (idiopathic or heritable PAH and PAH associated with connective tissue diseases) in patients with WHO Functional Class III–IV symptoms to improve exercise capacity.** **- Renal Dialysis** **VELETRI is indicated for use in haemodialysis in emergency situations when use of heparin carries a high risk of causing or exacerbating bleeding or when heparin is otherwise contraindicated."**

Actual Benefit	**The actual benefit of VELETRI is substantial in PAH.**
Improvement in Actual Benefit	**<u>In PAH:</u> VELETRI (epoprostenol), a hybrid medicine based on FLOLAN and its generics which has a new pharmaceutical form extending the stability of the solution at room temperature, does not provide any improvement in actual benefit (level V, non-existent) in comparison with these proprietary medicinal products.**
Therapeutic use	**2nd line in patients in functional class III 1st line in patients in functional class IV**
Recommendations	**The Transparency Committee recommends inclusion on the list of medicines approved for hospital use.**

01 ADMINISTRATIVE AND REGULATORY INFORMATION

Marketing Authorisation (procedure)	Date initiated (decentralised procedure): 20 March 2013 Rapporteur state: Netherlands ANSM [French National Agency for Medicines and Health Products Safety] has requested specific measures for preventing and monitoring catheter-related infections in patients treated for PAH with VELETRI.
Prescribing and dispensing conditions /special status	List I Medicine for hospital prescription only. Prescription restricted to certain specialists (cardiologists and pulmonologists specialising in PAH). Hybrid medicine based on FLOLAN and its generics.
ATC Classification	2013 B: Blood and blood forming organs B01: Antithrombotic agents B01A: Antithrombotic agents B01AC: Platelet aggregation inhibitors, excl. heparin B01AC09 epoprostenol

02 BACKGROUND

This is an application for inclusion of the proprietary medicinal product VELETRI, powder and solvent for solution for infusion (epoprostenol) on the list of medicines approved for hospital use. VELETRI was granted Marketing Authorisation on 20 March 2013 and ANSM has requested specific measures for preventing and monitoring catheter-related infections in patients treated for PAH with VELETRI.

VELETRI, powder and solvent for solution for infusion is a hybrid version of FLOLAN and its generics, developed with a new formulation containing different excipients, different buffering agents and a different pH to FLOLAN and its generics, keeping the solution stable for longer at room temperature (48 hours).

VELETRI is also indicated in haemodialysis; the company is not applying for reimbursement in this indication but it will nonetheless be discussed in this opinion (see paragraph 09).

03 THERAPEUTIC INDICATIONS

"VELETRI is indicated for:

- Pulmonary Arterial Hypertension
  VELETRI is indicated for the treatment of pulmonary arterial hypertension (PAH) (idiopathic or heritable PAH and PAH associated with connective tissue diseases) in patients with WHO Functional Class III–IV symptoms to improve exercise capacity (see section 5.1 of the SPC).

- Renal Dialysis
  VELETRI is indicated for use in haemodialysis in emergency situations when use of heparin carries a high risk of causing or exacerbating bleeding or when heparin is otherwise contraindicated (see section 5.1 of the SPC)."

04 DOSAGE

See the SPC.

05 THERAPEUTIC NEED

There are five types of pulmonary hypertension. These include pulmonary arterial hypertension (PAH), which can be idiopathic, inherited (familial), drug or toxin-associated, or a complication of certain diseases (chronic respiratory diseases, connective tissue disease, congenital heart disease, portal hypertension, HIV infection, etc.).

Pulmonary hypertension is defined as a mean pulmonary artery pressure ≥ 25 mmHg at rest, measured during right heart catheterisation, and a pulmonary capillary wedge pressure (PCWP) ≤ 15 mmHg.

Pulmonary arterial hypertension is a rare and serious pulmonary vascular disease defined as an increase in pulmonary vascular resistance leading to right-sided heart failure. Symptoms mainly occur on exertion and include dyspnoea, weakness, chest pain, presyncope and syncope. It has a prevalence of 15 cases per million adults.

In addition to a combination of several specific medicinal products and surgical interventions, therapeutic management of pulmonary arterial hypertension includes general measures (sporting activities where possible, prevention of infections) and associated treatments such as anticoagulants, diuretics and oxygen therapy.
The use of specific medicines depends on arterial vasoreactivity (nitric oxide test during catheterisation) and on the severity of the disease according to the 1998 WHO functional classification (see Table 1).

The specific treatments recommended for class I to III PAH with arterial vasoreactivity are calcium channel blockers.[2] If there is no pulmonary arterial vasoreactivity or if calcium channel blockers fail, the treatments used are:

- prostacyclins (and analogues): epoprostenol, treprostinil, iloprost
- endothelin receptor antagonists: bosentan, ambrisentan
- phosphodiesterase type 5 inhibitors: sildenafil, tadalafil.

The treatment algorithm is described in Table 1.[2]
If treatment fails again, a combination of therapies will be discussed.

In cases of severe PAH that is insufficiently improved by maximum medical treatment, a lung transplant or atrioseptostomy pending transplant may be an alternative, last-resort therapy.[3]

Table 1. Algorithm for the therapeutic management of PAH according to WHO class with a **negative** vasoreactivity test, based on the best level of evidence.

WHO functional class		Treatment
I	PAH with no functional limitations; normal physical activity does not lead to dyspnoea, excessive fatigue, chest pain or presyncope.	No treatment consensus
II	PAH with slight functional limitations; physical activity leads to dyspnoea, excessive fatigue, chest pain or presyncope. These patients have no symptoms at rest.	Ambrisentan, bosentan, sildenafil, tadalafil. *Combination with other medicines from a different class should be discussed.*
III	PAH with significant functional limitations; even light physical activity leads to dyspnoea, excessive fatigue, chest pain or presyncope. These patients have no symptoms at rest.	Ambrisentan, bosentan, sildenafil, tadalafil. **Second-line therapies:** IV epoprostenol, inhaled iloprost, treprostinil. *Combination with other medicines from a different class should be discussed.*
IV	PAH preventing any physical activity and/or with signs of right-sided heart failure. Dyspnoea and/or fatigue may occur even at rest. Disability is increased by any form of physical activity.	IV epoprostenol combined with the other treatments above.

A response to treatment for pulmonary hypertension is indicated by an increase in the distance covered during the 6-minute walk test (> 380 or 440 m), a return to functional class I or II, normalisation of haemodynamic and ultrasound parameters, BNP levels, and maximum oxygen consumption > 15 ml/min/kg.[1]

[1] McLaughlin VV, Gaine SP, Howard LS et al. Treatment goals of pulmonary hypertension. J Am Coll Cardiol 2013. 24; 25 Suppl: D73-81.

06 CLINICALLY RELEVANT COMPARATORS

VELETRI (epoprostenol) is a hybrid medicine based on the proprietary medicinal product FLOLAN and its generics.

06.1 Medicinal products

In patients with PAH in functional class III, the clinically relevant comparators for VELETRI are the specific medicines for PAH, namely prostacyclin analogues administered as a second-line treatment in addition to supportive treatments such as anticoagulants and diuretics, as well as oxygen therapy or oral medicines specifically for PAH.
In patients with PAH in functional class IV, FLOLAN and its generics (see Table 2).

Table 2: Prostacyclin analogues in PAH

NAME (INN) *Company*	Indication	Date of TC opinion	AB	IAB (Wording)	Reimbursed
Prostacyclin analogues					
REMODULIN (treprostinil) *Bioprojet Pharma*	Treatment of primary pulmonary arterial hypertension to improve exercise capacity and symptoms of the disease in patients in NYHA (New York Heart Association) functional class III.	05/01/2011 (PAH re-assessment)	Moderate	The Transparency Committee considers that the REMODULIN medicinal products provide a minor improvement in actual benefit (level IV) in the treatment of idiopathic pulmonary arterial hypertension in patients in functional class III.	**Yes (hospital use)**
FLOLAN and its generics (epoprostenol) *GlaxoSmithKline*	FLOLAN is indicated for long-term treatment, by means of continuous infusion, of pulmonary arterial hypertension (PAH): - idiopathic, familial or sporadic pulmonary arterial hypertension - pulmonary arterial hypertension associated with systemic collagen disease in patients in functional clinical stage III or IV (on the severity scale of the New York Heart Association).	05/01/2011 (PAH re-assessment)	Substantial	Given the known and demonstrated effect of FLOLAN on survival and its role in the therapeutic strategy, namely in patients with PAH in functional class IV, the Transparency Committee considers that FLOLAN provides a substantial improvement in actual benefit (level II) in the management of patients with idiopathic PAH or PAH associated with connective tissue disease, who are in functional class III or IV.	**Yes (hospital use)**
VENTAVIS (iloprost) *Bayer HealthCare*	Treatment of primary PAH to improve exercise capacity and symptoms in patients in functional class III.	05/01/2011 (PAH re-assessment)	Moderate	The Transparency Committee considers that the proprietary medicinal product VENTAVIS provides a minor improvement in actual benefit (level IV) in the treatment of idiopathic pulmonary arterial hypertension in patients in functional class III.	**Yes (hospital use)**

Note that endothelin receptor antagonists and phosphodiesterase type 5 inhibitors may be offered as a first- or second-line treatment as part of combination therapy (see Table 3).

Table 3: Other medicines for PAH

NAME (INN) *Company*	Indication	Date of TC opinion	AB	IAB (Wording)	Reimbursed
Endothelin receptor antagonists					
TRACLEER (bosentan) *Actelion Pharmaceuticals France*	Treatment of pulmonary arterial hypertension (PAH) to improve exercise capacity and symptoms in patients in WHO functional class III. Efficacy has been shown in: - primary (idiopathic and familial) pulmonary arterial hypertension - pulmonary arterial hypertension secondary to scleroderma without significant associated interstitial disease - pulmonary arterial hypertension associated with congenital systemic-to-pulmonary shunts and Eisenmenger physiology. Some improvements have also been shown in patients with pulmonary arterial hypertension (PAH) in WHO functional class II.	05/01/2011 (PAH re-assessment)	Moderate	In view of the available data and clinical experience, the Transparency Committee considers that TRACLEER provides a moderate improvement in actual benefit (level III) in the management of idiopathic PAH or PAH associated with connective tissue disease or with congenital heart disease in patients in functional class II or III.	**Yes (hospital use)**
VOLIBRIS (ambrisentan) *GlaxoSmithKline*	VOLIBRIS is indicated for the treatment of adult patients with pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease.	05/01/2011 (PAH re-assessment)	Moderate	The Transparency Committee considers that the VOLIBRIS proprietary medicinal products provide a minor improvement in actual benefit (level IV) in the treatment of idiopathic PAH or PAH associated with systemic collagen tissue disease in patients in functional class II or III.	**Yes (hospital use)**
Phosphodiesterase inhibitors					
REVATIO (sildenafil) *Pfizer*	Treatment of patients with pulmonary arterial hypertension classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in primary pulmonary hypertension and pulmonary hypertension associated with connective tissue disease.	05/01/2011 (PAH re-assessment)	Moderate	The Transparency Committee considers that the proprietary medicinal product REVATIO provides a minor improvement in actual benefit (level IV) in the treatment of idiopathic PAH or PAH associated with systemic collagen tissue disease in patients in functional class II or III.	**Yes (hospital use)**

NAME (INN) *Company*	Indication	Date of TC opinion	AB	IAB (Wording)	Reimbursed
	Treatment of paediatric patients aged 1 year to 17 years old with pulmonary arterial hypertension. Efficacy in terms of improvement of exercise capacity or pulmonary haemodynamics has been shown in primary pulmonary hypertension and pulmonary hypertension associated with congenital heart disease.	06/06/2012 (extension of the paediatric indication)	Moderate	The use of extemporaneous preparations made from sildenafil tablets is common in current clinical practice, and this is justified by the lack of treatment alternatives suitable for use in paediatrics. The pharmaceutical forms available and developed for the REVATIO proprietary medicinal products meet the quality and safety requirements for administration to children and adolescents. However, in the absence of data with a sufficient level of evidence, the Transparency Committee considers that: - REVATIO 20 mg, film-coated tablet, does not provide any improvement in actual benefit (level V) in the management of pulmonary arterial hypertension in children and adolescents aged from 1 to 17 years with PAH; - REVATIO 10 mg/ml, powder for oral suspension, is an addition to the range which is useful for the treatment of PAH in children and adolescents aged from 1 to 17 years with PAH and in adults unable to swallow film-coated tablets.	**Yes (hospital use)**
ADCIRCA (tadalafil) *Lilly France*	ADCIRCA is indicated in adults for the treatment of pulmonary arterial hypertension (PAH) classified as WHO functional class II and III, to improve exercise capacity. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH related to collagen vascular disease.	05/01/2011 (PAH re-assessment)	Moderate	The Transparency Committee considers that the proprietary medicinal product ADCIRCA provides a minor improvement in actual benefit (level IV) in the treatment of idiopathic PAH or PAH associated with systemic collagen tissue disease in patients in functional class II or III.	**Yes (hospital use)**

06.2 Other health technologies

A lung transplant or atrioseptostomy pending transplant may be offered as a last-resort therapy if the above treatments fail.

◗ Conclusion

The other prostacyclin analogues are the clinically relevant comparators for VELETRI.

07 INTERNATIONAL INFORMATION ON THE MEDICINAL PRODUCT

Country	REIMBURSEMENT	
	YES/NO If no, why not	Population(s) Marketing Authorisation or restricted population
Belgium	Under assessment	Treatment of PAH. Dispensed via hospital pharmacies.
Great Britain	Yes	Treatment of PAH. Dispensed via hospital pharmacies.
Netherlands	Yes	Treatment of PAH. Dispensed via hospital and community pharmacies.

08 ANALYSIS OF AVAILABLE DATA

08.1 Efficacy

8.1.1 PAH

Insofar as VELETRI is a hybrid medicine based on the proprietary medicinal product FLOLAN, the available data primarily come from a phase I, open-label, pharmacokinetic and pharmacodynamic study (AC-066-102) which aimed to compare VELETRI with FLOLAN in terms of the above parameters in 40 healthy volunteers.
This study demonstrated equivalence between both treatments on the pharmacokinetic parameters studied (C_{max}, AUC, T1/2, etc.) and on the pharmacodynamic parameters (cardiovascular parameters: cardiac index, cardiac output, heart rate and blood pressure).

The company has also reported a phase IIIb, open-label, prospective, exploratory study (EPITOME-2) which aimed to evaluate the effect of VELETRI 3 months after it was substituted for FLOLAN, in 41 patients with idiopathic PAH, PAH associated with drugs or toxins or PAH associated with connective tissue disease who had been treated with FLOLAN for at least 12 months (stable for at least 3 months).
This study observed the evolution of:

- efficacy, namely through haemodynamic endpoints (right heart catheterisation), 6-minute walk distance (6MWD), dyspnoea (Borg Scale), PAH functional class (cf. NYHA), etc.
- quality of life (TSQM-9)
- safety.

The authors concluded that substituting FLOLAN with VELETRI did not lead to any significant change in the above parameters.
Given the methodology of this study, which is prospective, open-label and descriptive, its results should be interpreted with caution.

8.1.2 Renal dialysis

The clinical data available for this indication are consistent with those obtained with FLOLAN and are summarised in the SPC for VELETRI.

08.2 Adverse effects

According to the SPC, the most commonly observed adverse effects (> 10%) are: headaches, facial flushing (observed even in anaesthetised patients), nausea, vomiting, diarrhoea, jaw pain and pain (unspecified).

08.3 Data on the pharmaceutical form

Epoprostenol is a synthetic prostacyclin with a short half-life (6 minutes) used as a continuous intravenous infusion via a central catheter. The stability of the proprietary medicinal products currently available (FLOLAN and its generics) is short (12 hours for the ready-to-use solution at room temperature), requiring the medicine to be prepared and the cassette changed twice a day.

VELETRI (epoprostenol) has a different formulation to FLOLAN and its generics in terms of excipients, buffering agents and the pH of the reconstituted, ready-to-use solution. The SPC states, “The pH value of VELETRI is higher than the pH of other epoprostenol products. Compared to other epoprostenol diluted solutions, which are buffered with glycine, VELETRI contains l-arginine, at lower buffering capacity. This leads to a broader range of pH values of the diluted solution. The pH of VELETRI decreases with dilution from 12.0 at a concentration of 90,000 ng/ml, 11.7 at a concentration of 45,000 ng/ml to 11.0 at a concentration of 3000 ng/ml.”
In addition, “VELETRI when administered chronically, should be prepared in a drug delivery reservoir appropriate for the infusion pump. Only extension sets with an in-line 0.22 micron filter placed between the infusion pump and the central catheter must be used. It is recommended to use filters with a hydrophilic polyethersulfone membrane. The extension set and the in-line filter must be changed at least every 48 hours.”

08.4 Summary & discussion

VELETRI (epoprostenol) is a hybrid medicine based on FLOLAN and its generics. The available clinical data primarily come from a phase I pharmacokinetic and pharmacodynamic study (AC-066-102). This study demonstrated equivalence between both treatments on the pharmacokinetic parameters studied (C_{max}, AUC, T1/2, etc.) and on the pharmacodynamic parameters (cardiovascular parameters: cardiac index, cardiac output, heart rate and blood pressure).
The company has also reported a phase IIIb, open-label, prospective, exploratory study (EPITOME-2) which aimed to evaluate the effect of VELETRI 3 months after it was substituted for FLOLAN, in 41 patients with idiopathic PAH, PAH associated with drugs or toxins or PAH associated with connective tissue disease who had been treated with FLOLAN for at least 12 months (stable for at least 3 months).
The authors concluded that substituting FLOLAN with VELETRI did not lead to any significant change in the parameters studied.
Given the methodology of this study, which is prospective, open-label and descriptive, its results should be interpreted with caution.
Epoprostenol is the only active ingredient that has been shown to reduce mortality (studies conducted with FLOLAN). As such, it is the standard treatment in the most severe forms of the disease, i.e. for patients in functional class IV.
According to the SPC, the most commonly observed adverse effects (> 10%) are: headaches, facial flushing (observed even in anaesthetised patients), nausea, vomiting, diarrhoea, jaw pain and pain (unspecified).
VELETRI (epoprostenol) has a different formulation to FLOLAN and its generics in terms of excipients, buffering agents and the pH of the reconstituted, ready-to-use solution.

09 THERAPEUTIC USE

The aim of treatment is primarily to improve the patient's survival and quality of life.
PAH is a serious illness in the short term. Regular follow-up is necessary so that clinical exacerbations can be detected early and therapy can therefore be escalated as soon as possible. Assessing the prognosis plays an important role in choosing the initial treatment and in assessing the response to treatment.

The therapeutic strategy recommended by the Transparency Committee in these opinions and found in the literature is as follows:
Conventional treatment for PAH combines anticoagulants, diuretics, oxygen therapy and calcium channel blockers.

In patients with class III PAH, endothelin receptor antagonists (bosentan or ambrisentan) and phosphodiesterase inhibitors (sildenafil or tadalafil) can be used as an oral first-line treatment.
As second-line therapy (due to contraindication, hepatic intolerance of bosentan or failure of oral treatments), prostacyclin analogues are recommended:

- inhaled iloprost
- intravenous epoprostenol via continuous infusion
- subcutaneous treprostinil. The decision to start treprostinil therapy should take into account the high probability of needing to maintain continuous subcutaneous infusion in the long term.[2]

In patients with class IV PAH, only epoprostenol (FLOLAN and VELETRI) can be used as a 1st-line therapy because this is the only treatment indicated in these severely affected patients and there is no medicinal alternative.

The treatment is assessed 3 to 4 months after its initiation. If the patient has achieved the goals of treatment, it is continued, together with regular follow-up by the reference centre or expert centre.
If monotherapy fails, a combination of therapies will be discussed. In actual fact, data on the efficacy and role of dual therapy and on the choice of combined drugs are limited.[3]

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.

The importance of regular follow-up for these patients should be emphasised, in order to monitor the efficacy of treatment and check for exacerbation on treatment.

Role of VELETRI in the therapeutic strategy:
VELETRI is a hybrid medicine based on the proprietary medicinal product FLOLAN and its generics; it has a different pharmaceutical form, extending the stability of the solution at room temperature (48 hours, which allows the cassette to be changed once a day). As such, it may be an alternative to these therapies in patients with class III or IV PAH.

[2] Haute Autorité de Santé. Hypertension artérielle pulmonaire : Protocole national de diagnostic et de soins pour une maladie rare [Pulmonary arterial hypertension: National diagnosis and treatment protocol for a rare disease]. November 2007.
[3] Haute Autorité de Santé. Réévaluation des traitements de l'hypertension artérielle pulmonaire (HTAP) [Reassessment of treatments for pulmonary arterial hypertension (PAH)]. Opinion of 5 January 2011.

010 TRANSPARENCY COMMITTEE CONCLUSIONS

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

010.1 Actual benefit

Pulmonary arterial hypertension:

◗ PAH is a rare, life-threatening lung disease, which is characterised by an increase in pulmonary artery pressure and by right-sided heart failure. Asthenia, progressive exertional dyspnoea, chest pain and loss of consciousness are the most common clinical signs.

◗ VELETRI is intended as symptomatic treatment.

◗ Its efficacy/adverse effects ratio is high.

◗ In patients with functional class III PAH, epoprostenol (FLOLAN and VELETRI) is a second-line therapy. In these patients, there are treatment alternatives, namely the other prostacyclin analogues: treprostinil (REMODULIN) and iloprost (VENTAVIS).

◗ In patients with functional class IV PAH, only epoprostenol (FLOLAN and VELETRI) can be used as a 1st-line therapy because this is the only treatment indicated in these severely affected patients and there are no treatment alternatives.

◗ 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.

Improvement in the management of patients with pulmonary arterial hypertension is a public health need that is an established priority (Law of 9 August 2004 on public health policy, Rare Diseases Plan).

The available data have established that only epoprostenol has shown a benefit in terms of survival compared with conventional treatments in patients with PAH in functional classes III and IV.

In the current state of knowledge, the public health impact of FLOLAN (epoprostenol) is slight. As such, VELETRI (epoprostenol), a hybrid medicine based on FLOLAN, is unlikely to have an additional impact on public health.

Consequently, the Committee considers that the actual benefit of VELETRI is substantial in the indication "treatment of pulmonary arterial hypertension (PAH) (idiopathic or heritable PAH and PAH associated with connective tissue diseases) in patients with WHO Functional Class III–IV symptoms to improve exercise capacity".

The Committee recommends inclusion of VELETRI on the list of medicines approved for hospital use with the same reimbursement criteria as FLOLAN, i.e. in the indication "treatment of pulmonary arterial hypertension (PAH) (idiopathic or heritable PAH and PAH associated with connective tissue diseases) in patients with WHO Functional Class III–IV symptoms to improve exercise capacity" and at the dosages in the Marketing Authorisation.

Renal dialysis:
VELETRI is a hybrid medicine based on FLOLAN and its generics. The Committee has never assessed FLOLAN in this indication and therefore cannot give a ruling on actual benefit of VELETRI.

◗ **Proposed reimbursement rate: 65%**

010.2 Improvement in actual benefit (IAB)

In PAH:
VELETRI (epoprostenol), a hybrid medicine based on FLOLAN and its generics which has a new pharmaceutical form extending the stability of the solution at room temperature, does not provide any improvement in actual benefit (level V, non-existent) in comparison with these proprietary medicinal products.

010.3 Target population

The target population for VELETRI is patients with functional class III or IV PAH for whom a second-line treatment should be considered.
According to the national pulmonary hypertension register, 3193 patients in France were reported and treated for PAH in 2011, with 75% of patients in class III and IV at the time of diagnosis, i.e. about 2400 patients.
The proportion of patients in class III requiring a second-line treatment is difficult to quantify; therefore, the exact target population for VELETRI cannot be established.

For information, the French PAH register identified 209 newly diagnosed patients treated with FLOLAN and its generics between 2006 and 2010.

011 TRANSPARENCY COMMITTEE RECOMMENDATIONS

◗ **Packaging**
Appropriate for the prescribing conditions as regards indication, dosage and treatment duration.