

Annex II

Scientific conclusions and grounds for the variation to the terms of the Marketing Authorisations

Scientific conclusions

Introduction

FloLAN contains epoprostenol sodium which is the monosodium salt of epoprostenol, a naturally occurring prostaglandin produced by the blood vessels. It is a potent inhibitor of platelet aggregation and also a potent vasodilator.

Epoprostenol sodium is indicated for use in renal dialysis when use of heparin carries a high risk of causing or exacerbating bleeding. Epoprostenol sodium is also indicated for the treatment of pulmonary arterial hypertension (PAH).

FloLAN is authorised in the following member states: Austria, Belgium, Czech Republic, Denmark, Estonia, France, Ireland, Italy, Luxembourg, Malta, The Netherlands, Spain and United Kingdom and in Norway.

FloLAN has been included in the list of products for Summary of Product Characteristics (SmPC) harmonisation in accordance with Article 30(2) of Directive 2001/83/EC. Due to the divergent national decisions taken by Member States concerning the authorisation of the above-mentioned products (and its associated names), the European Commission notified on 15 June 2011 the CHMP/EMA Secretariat of an official referral under Article 30 of Directive 2001/83/EC in order to resolve divergences amongst the nationally authorised SmPCs and thus to harmonise its divergent SmPCs labelling and package leaflet across the European Union.

The CHMP assessed the harmonised Product Information proposed by the marketing Authorisation Holder (MAH) of the product taking into account the current national ones and the existing scientific data and discussed the indications for each individual medical condition. FloLAN is indicated for Pulmonary Arterial Hypertension (PAH) and Renal Dialysis. The available clinical studies on both these indications were presented by the MAH together with post-marketing data and published literature and discussed by the CHMP both regarding the efficacy and safety aspects. The main divergences were the following SmPC sections:

Section 4.1 – Therapeutic indications

This section is one of the identified for harmonisation. The indications authorised in various Member States are: Pulmonary Arterial Hypertension and Renal dialysis. The CHMP was requested to assess the available data on the indications and confirm the wording proposed by the MAH.

The following data from clinical studies have been presented by the MAH and discussed during the assessment of these procedure.

Chronic continuous infusions of epoprostenol in patients with idiopathic or heritable pulmonary arterial hypertension (PAH) were studied in two prospective, open, randomised trials of 8 and 12 weeks' duration (N=25 and N=81, respectively) comparing epoprostenol plus conventional therapy to conventional therapy alone. Conventional therapy varied among patients and included some or all of the following: anticoagulants in essentially all patients; oral vasodilators, diuretics, and digoxin in one half to two thirds of patients; and supplemental oxygen in about half the patients. Except for 2 New York Heart Association (NYHA) functional Class II patients, all patients were either functional Class III or Class IV. As results were similar in the 2 studies, the pooled results are described. The combined baseline 6-minute walk test median values for the conventional therapy group and epoprostenol plus conventional therapy group was 266 meters and 301 meters, respectively.

Improvements from baseline in cardiac index (0.33 vs. -0.12 L/min/m²), stroke volume (6.01 vs. -1.32 mL/beat), arterial oxygen saturation (1.62 vs. -0.85%), mean pulmonary artery pressure (-5.39 vs.

1.45 mm Hg), mean right atrial pressure (-2.26 vs. 0.59 mm Hg), total pulmonary resistance (-4.52 vs. 1.41 Wood U), pulmonary vascular resistance (-3.60 vs. 1.27 Wood U), and systemic vascular resistance (-4.31 vs. 0.18 Wood U) were statistically different between patients who received epoprostenol chronically and those who did not. Mean systemic arterial pressure was not significantly different between the two groups (-4.33 vs. -3.05 mm Hg). These haemodynamic improvements appeared to persist when epoprostenol was administered for at least 36 months in an open, nonrandomized study.

Statistically significant improvement was observed in exercise capacity ($p=0.001$), as measured by the 6 minutes walking test (6MWT) in patients receiving continuous intravenous epoprostenol plus conventional therapy ($N=52$) for 8 or 12 weeks compared to those receiving conventional therapy alone ($N=54$) (combined week 8 and 12 change from baseline – median: 49 vs. -4 meters; mean: 55 vs. -4 meters). Improvements were apparent as early as the first week of therapy. At the end of the treatment period in the 12 weeks study, survival was improved in NYHA functional Class III and Class IV patients. Eight of 40 (20%) patients receiving conventional therapy alone died, whereas none of the 41 patients receiving epoprostenol died ($p=0.003$).

Chronic continuous infusions of epoprostenol in patients with pulmonary arterial hypertension/scleroderma spectrum of diseases (PAH/SSD) were studied in a prospective, open, randomised trial of 12 weeks' duration comparing epoprostenol plus conventional therapy ($N = 56$) to conventional therapy alone ($N = 55$). Except for five NYHA functional Class II patients, all patients were either functional Class III or Class IV. Conventional therapy varied among patients and included some or all of the following: anticoagulants in essentially all patients, supplemental oxygen and diuretics in two thirds of the patients, oral vasodilators in 40% of the patients, and digoxin in a third of the patients. The primary efficacy endpoint for the study was improvement in the 6MWT. The median baseline value for the conventional therapy group and epoprostenol plus conventional therapy group was 240 meters and 270 meters, respectively. A statistically significant increase in cardiac index (CI), and statistically significant decreases in mean pulmonary arterial pressure (PAP_m), mean right atrial pressure (RAP_m), pulmonary vascular resistance (PVR), and mean systemic arterial pressure (SAP_m) after 12 weeks of treatment were observed in patients who received epoprostenol chronically compared to those who did not.

Over 12 weeks, a statistical difference ($p<0.001$) in the change from baseline for the 6MWT was observed in the group receiving epoprostenol and conventional therapy as compared to the group receiving conventional therapy alone (median: 63.5 vs. -36.0 meters; mean: 42.9 vs. -40.7 meters).

Improvements were apparent in some patients at the end of the first week of therapy. Increases in exercise capacity were accompanied by statistically significant improvements in dyspnoea, as measured by the Borg Dyspnoea Index. At week 12, NYHA functional class improved in 21 of 51 (41%) patients treated with epoprostenol compared to none of the 48 patients treated with conventional therapy alone. However, more patients in both treatment groups (28/51 [55%] with epoprostenol and 35/48 [73%] with conventional therapy alone) showed no change in functional class, and 2/51 (4%) with epoprostenol and 13/48 (27%) with conventional therapy alone worsened.

For renal dialysis the MAH presented an overview of 14 clinical studies investigating the use of epoprostenol in renal dialysis: three cross over studies, six major controlled studies and five emergency also known and as expanded access studies.

Two studies (30 and 31) addressed the possibility that patients' platelets may become refractory to repeated use of epoprostenol and thereby compromise dialysis efficiency with prolonged use. Epoprostenol or heparin were used during each dialysis for one month in study 30 and for two months in study 31. There was no indication that efficiency was reduced with repeated use of epoprostenol or

heparin as shown by the intradialytic removal of BUN, creatinine, potassium and changes in body weight.

In major controlled studies and emergency studies, major clotting occurred in approximately 9% (n=56) of all epoprostenol dialyses and in <1% (n=1) of heparin dialyses. Most epoprostenol dialyses (67%) that required replacement of artificial kidney were completed subsequently with epoprostenol without clotting. However, 9 of 27 epoprostenol dialyses were unsuccessful following multiple attempts.

Two major prospectively controlled studies (19 and 27), and 5 emergency studies were conducted to investigate bleeding during dialysis. Patients were assigned to 1 of 4 bleeding risk groups prior to receiving their first study dialysis. Each patient was randomly assigned to a sequence of heparin or epoprostenol dialyses and received up to 6 dialyses per entry in study 19 and up to 3 dialyses per entry in study 27.

Patients at Very High Risk of Haemorrhage were assessed in major controlled studies; 12 patients at very high risk of haemorrhage received 35 epoprostenol dialyses and 11 patients received 28 heparin dialyses. In emergency studies, 16 patients received 24 epoprostenol dialyses. When all dialyses were combined for each treatment (heparin or epoprostenol), more heparin patients bled during the day prior to dialysis (-24-0 hours), dialysis day (0-24 hours) and the day following dialysis (24-48 hours) than epoprostenol patients during the same time periods.

Patients at high risk of haemorrhage just prior to their first study dialysis, but who bled within 3 days prior were classified at high risk of haemorrhage. Nineteen patients received 51 heparin dialyses and 19 received 44 epoprostenol dialyses in major controlled studies. Eight patients received 21 epoprostenol dialyses in emergency studies.

In major controlled studies, when all dialyses were combined, slightly more epoprostenol patients appeared to bleed during the pre-dialysis, dialysis and post-dialysis days compared to heparin patients during the same periods. There was no clear consistent evidence that patients receiving either treatment improved more often or worsened less often.

In emergency studies, compared to each pre-dialysis assessment, incidence of bleeding was generally reduced with each epoprostenol dialysis. Of the patients who continued to bleed, severity generally improved more often and worsened less often in patients receiving heparin in major controlled studies.

Overall, these results indicate that renal dialysis with epoprostenol was consistently beneficial in patients at very high risk of hemorrhage. More patients stopped bleeding with epoprostenol and of those that continued to bleed, bleeding severity improved more often than in patients dialysed with heparin.

Following the discussion on the efficacy and safety data the CHMP agreed in the final indications for Flolan for pulmonary arterial hypertension and renal dialysis as per the wording below:

Flolan is indicated for,

Pulmonary Arterial Hypertension

Flolan 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).

Renal Dialysis

Flolan 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).

Section 4.2 – Posology and method of administration

There were differences in Section 4.2 of the SmPCs across Member States. In some cases these differences are due to the differences in indications. The use of Flolan in children and elderly is not harmonised.

The CHMP assessed the submitted data and recommended the re-arrangement of this section by separating the posology in the administration of epoprostenol for PAH during short-term (acute) dose ranging versus long-term continuous infusion.

For renal dialysis the CHMP recommended the addition to the PI that Flolan is suitable for continuous infusion only, either intravascularly or into the blood supplying the dialyser. It also agreed on the recommended schedule of infusion in adults.

Section 4.3 - Contraindications

There are differences in wording of the contraindications across Member States and detail given with respect to these contraindications.

The CHMP assessed the data from the available clinical studies, post-marketing data and published literature and agreed with the following contraindications:

Flolan is contraindicated in patients with known hypersensitivity to the active substance or to any of the excipients, in patients with congestive heart failure arising from severe left ventricular dysfunction. Flolan must not be used chronically in patients who develop pulmonary oedema during dose-ranging.

Section 4.4 - Special warnings and precaution for use

There are differences in the special warnings and precautions for use included in Section 4.4, and in the detail given with respect to these warnings/precautions. Differences identified include, events occurring during infusion, ischemia in patients with severe angina.

The CHMP agreed on the rearrangement of this section and the addition of the warning on patients with coronary artery disease. The enhanced hypotensive effects of epoprostenol due to the acetate buffer used during renal dialysis was also emphasised in this section.

Other Sections of the SmPC

Section 4.6 – Fertility, Pregnancy and lactation

The CHMP agreed that there is limited amount of data from the use of epoprostenol in pregnant women (Schaefer 2007, Reprotox 2010). This was reiterated in the SmPC section. Also the CHMP agreed that given the absence of alternative medicines, epoprostenol can be used in those women who choose to continue their pregnancy, despite the known risk of pulmonary arterial hypertension during pregnancy. Finally as there are no data on the effects of epoprostenol on fertility in humans this information was introduced in the SmPC together with the information on reproductive studies in animals which have shown no effects on fertility.

Section 4.8 – Adverse events

The proposal for changes in section 4.8 was mainly based on the Core Safety Profile (CSP) which has been agreed in 2009 during the PSUR Worksharing Procedure (IE/H/PSUR/0018/001).

That information was already present in the majority member states, and was in general acceptable. Editorial changes and clarifications were requested by the CHMP in the table of ADRs.

The effect of the overdose on the blood pressure was added in this section.

Section 5.1 – Pharmacodynamic properties

The CHMP has agreed that taking into account the latest SmPC guidelines the long known information from the clinical studies justifying the indications needed to be added in this section.

The MAH was asked to evaluate all other sections of the nationally approved SmPC and suggest appropriate changes in the text where divergences exist. In addition minor typographic errors were corrected. All these changes were accepted by the CHMP.

Labelling

The labelling has been updated according to the latest QRD v8 template.

Package Leaflet

Following all the changes in the SmPC there are several corresponding changes to the Package Leaflet. After the corrections were implemented a Readability Testing was performed which was submitted and assessed during the referral procedure. The final Package Leaflet wording was adopted by the CHMP.

Quality – Module 3

The MAH submitted a proposal for harmonisation of the Quality module. Information on development, manufacture and control of powder and solvent for solution for infusion has been presented in a satisfactory manner. The results of tests carried out indicate satisfactory consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the products should have a satisfactory and uniform performance in the clinic. Based on the review of data the CHMP adopted a harmonised Module 3.

In conclusion, based on the assessment of the MAH proposal and responses and following the discussions of the committee, the CHMP adopted the harmonised product information for Flolan and associated names. In particular, the indications and their associated posology recommendations, the warnings and the information of fertility, pregnancy and lactation were harmonised. A harmonised Module 3 was also adopted. Based on the above, the CHMP considers the benefit/risk ratio of Flolan and associated names to be favourable and the harmonised Product Information documents to be approvable.

Grounds for the variation to the terms of the marketing authorisations

Whereas

- The committee considered the referral under Article 30 of Directive 2001/83/EC
- The committee considered the identified divergences for Flolan and associated names regarding the therapeutic indications, posology, the contraindications and warnings.
- The committee reviewed the data submitted by the MAH from the existing clinical studies, the pharmacovigilance data and the published literature justifying the proposed harmonisation of the Product Information.
- The committee agreed the harmonisation of the summary of product characteristic, labelling and package leaflet proposed by the marketing authorisation holders.

the CHMP has recommended the variation to the terms of the marketing authorisations for which the summary of product characteristics and package leaflet are set out in Annex III for Flolan and associated names (see Annex I).