22 May 2014
EMA/134160/2014
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ventavis

International non-proprietary name: iloprost

Procedure No. EMEA/H/C/000474/X/43

Note

Assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted

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List of abbreviations

AE Adverse event
AAD Adaptive Aerosol Delivery
AUC Area under the plasma concentration-time curve from zero (start of inhalation) to infinity after single dose
AUC(0-tlast) AUC from time zero (start of inhalation) to the last data point above LLOQ
Cmax Maximum observed drug concentration in plasma after single dose administration
CL Clearance
IV Intravenous
LLOQ Lower limit of quantification
MAH Marketing authorization holder
MMAD Mass median aerodynamic diameter
NYHA New York Heart Association
PAH Pulmonary arterial hypertension
PBT persistent, bioaccumulative and toxic
PK Pharmacokinetic(s)
PPH Primary pulmonary hypertension
PSUR Periodic Safety Update Report
SAE Serious adverse event
SPC Summary of product characteristics
tmax Time to reach maximum observed drug concentration in plasma after single dose
US, USA United States of America
WHO World Health Organization

1. Background information on the procedure

1.1. Submission of the dossier

The applicant submitted on 06 June 2013 an extension application for Marketing Authorisation to the European Medicines Agency (EMEA) for Ventavis, 20 microgram / ml nebuliser solution, through the centralised procedure falling within the Article 19 (1) and Annex I (point 2 intend C) of the Commission Regulation (EC) No 1234/2008.

Bayer Pharma AG is already the Marketing Authorisation Holder for Ventavis, 10 microgram / ml nebuliser solution.

The applicant applied for the following indication Treatment of patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms.

The legal basis for this application refers to:

The application submitted is composed of administrative information, complete quality data and at least a bioequivalence study with the reference medicinal product Ventavis 10 µg/ml instead of non-clinical and clinical unless justified otherwise.

Information on Paediatric requirements

Not applicable

Information relating to orphan market exclusivity

Similarity

Pursuant to Article 8 of Regulation (EC) No. 141/2000 and Article 3 of Commission Regulation (EC) No 847/2000, the applicant did submit a critical report addressing the possible similarity with authorised orphan medicinal products.

Licensing status

Ventavis 10 µg/ml has been given a Marketing Authorisation in the EU on 16 September 2003.

Ventavis 20 µg/ml has been given a Marketing Authorisation in the USA in 2009.

1.2. Manufacturers

Manufacturer responsible for batch release

Berlimed S.A.
Poligono Industrial Santa Rosa s/n
E-28806 Alcalá de Henares

Madrid
Spain

1.3. Steps taken for the assessment of the product

The Rapporteur appointed by the CHMP was:

Rapporteur: Dr Pierre Demolis

- The application was received by the EMA on 06 June 2013.
- The procedure started on 24 July 2013.
- The Rapporteur's first Assessment Report was circulated to all CHMP members on 18 October 2013.
- The PRAC rapporteur`s first Assessment Report was circulated to all PRAC members on 28 October 2013 and the PRAC advice was issued on 7 November 2013.
- During the meeting on 18-21 November 2013, the CHMP agreed on the consolidated List of Questions to be sent to the applicant. The final consolidated List of Questions was sent to the applicant on 21 November 2013.
- The applicant submitted the responses to the CHMP consolidated List of Questions on 15 January 2014.
- The summary report of the inspection carried out at the following site(s) Analytical Lab, Wegenerstr. 13 D-89231 Neu-Ulm Germany between 09 and 12 September 2013 was issued on 13 December 2013.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 23 February 2014.
- The PRAC rapporteur circulated the first Assessment Report on 21 February 2014; the PRAC RMP Advice and assessment overview was adopted by PRAC on 14 March 2014.
- The CHMP adopted a report on similarity of Ventavis with Volibris, Revatio, Opsumit, Adempas on 22 May 2014.
- During the CHMP meeting on 20 March 2014, the CHMP agreed on a list of outstanding issues to be addressed in writing by the applicant.
- The applicant submitted the responses to the CHMP List of Outstanding Issues on 16 April 2014.
- The PRAC rapporteur circulated the first Assessment Report on 30 April 2014; the PRAC RMP Advice and assessment overview was adopted by PRAC on 8 May 2014.
- The Rapporteurs circulated the Joint Assessment Report on the applicant's responses to the List of Questions to all CHMP members on 02 May 2014.
- During the meeting on 22 May 2014, the CHMP, in the light of the overall data submitted and the scientific discussion within the Committee, issued a positive opinion for granting a Marketing Authorisation to Ventavis 20 µg/ml.

2. Scientific discussion

2.1. Introduction

Pulmonary Arterial Hypertension (PAH) is a chronic and progressive disease of the small pulmonary arteries that is characterised by vascular proliferation and remodelling. It results in increased pulmonary artery pressure and pulmonary vascular resistance and, ultimately, right ventricular heart failure and death.

Ventavis is the trade name for inhaled iloprost, a stable prostacyclin analogue, which has been developed in pulmonary arterial hypertension (PAH) under orphan drug status in Europe as designated by the EU Commission on 29 December 2000. Ventavis was removed from the Community register of orphan medicinal products in September 2013 at the end of the 10-year period of market exclusivity.

The first marketing authorization for Ventavis 10 µg/mL (iloprost) inhalation solution was granted by the European Commission on 16 September 2003 under exceptional circumstances with the specific obligation to gather further data on longer-term safety and efficacy.

On May 2013, the exceptional circumstances status was left and the marketing authorization of Ventavis 10 was renewed. See Procedure EMEA/H/C/000474/R/02

The current indication is: *"Treatment of patients with primary pulmonary hypertension, classified as New York Heart Association (NYHA) functional class III, to improve exercise capacity and symptoms.*

The approved product is dispensed as a ready-to-use 10 µg/ml solution in glass vials of 1 ml and 2 ml containing 10 µg and 20 µg of iloprost, respectively. Patients self-administer the product 6 to 9 times daily.

Ventavis 10 µg/ml is recommended to be used with one of 4 nebulizer systems that were assessed and considered suitable for administration of Ventavis 10 µg/ml: 2 compressed air nebulizer systems: the HaloLite Adaptive Aerosol Delivery (AAD) system and the ProDose AAD system, one ultrasonic battery powered nebulizer: the Venta-Neb and one portable vibrating mesh technology nebulizer system: the I-Neb AAD system.

The devices were approved as suitable ones to deliver the approved dose of either 2.5 or 5 µg iloprost ex-mouthpiece with estimated inhalation times comprised between 4 to 10 minutes (depending on the nebulizer systems and dose to be inhaled). But in practice, some patients require prolonged inhalation time, frequently exceeding 15 minutes, to inhale the 5 µg dose using Ventavis 10. The sponsor received reports from physicians who were concerned that the effectiveness of Ventavis 10 µg/ml treatment may be reduced in patients who require long inhalation times to achieve the recommended dose of 5 µg. Physicians had expressed particular concern for patients with long inhalation times who fail to receive their required Ventavis doses and for whom compliance is poor. It was postulated that a 20 µg/mL solution of iloprost administered in the approved breath-actuated nebulisers would require half the volume to administer the same 5 µg dose, and could be inhaled with half the number of breaths compared to the 10 µg/mL concentration of Ventavis 10 solution. The expected result for patients who experience prolonged inhalation times (>15 min) was a drug delivery that approaches the intended dosing rate of 5 µg inhaled within approximately 8 – 10 minutes.

The 20 mcg/ml ampoules containing 1 ml solution (i.e. 20 µg of iloprost) was approved by the FDA in August 2009. Actelion is the NDA holder for Ventavis in the USA and Bayer cooperation partner. It is marketed in USA since September 2009 for patients who are maintained at the 5 µg dose and who have repeatedly experienced extended treatment times with Ventavis 10 µg/ml. It is recommended to be administered using exclusively the I-Neb AAD System using a smaller medication chamber (0.25 ml

nebulized volume instead of 0.5 mL) specifically designed with gold color coded latch to achieve the 5 μg dose with this higher concentration. The manufacturer of I-Neb AAD system Philips Respironics delivers only I-Neb devices equipped with power level 6 discs to all US patients to be treated with Ventavis.

The present application is for a line extension to Europe for the double concentration for Ventavis 20μg/mL nebulizer solution provided in 1 ml glass ampoules containing 20 μg of iloprost with the same quality of excipients as Ventavis 10 microgram / ml. In Europe, the "Ventavis discs" provided to patients by Philips Respironics have a power level 10 setting.

2.2. Quality aspects

2.2.1. Introduction

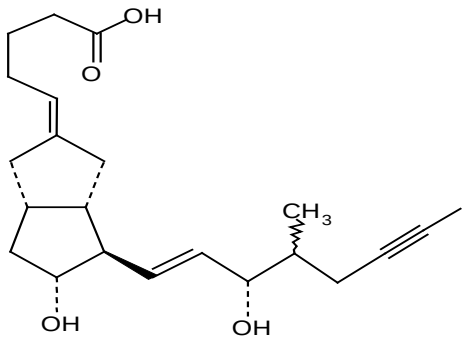
The finished product is presented as a nebuliser solution containing 20 μg/ml of iloprost (as iloprost trometamol) as active substance.

Other ingredients are: trometamol, ethanol 96%, sodium chloride, hydrochloric acid (for pH adjustment), water for injections.

The product is available in 1-ml ampoules, colourless, glass type I, containing 1 ml nebuliser solution, ring coded with two coloured rings (yellow-red).

2.2.2. Active Substance

The chemical name of iloprost is : 5-{(E)-(1S,5S,6R,7R)-7-Hydroxy-6-[(E)-(3S,4RS)-3-hydroxy-4-methyl-1-octen-6-ynyl]-bicyclo[3.3.0]oct-3-ylidene}-pentanoic acid. Iloprost has the following structure:



The active substance used in the 20 μg/ml nebuliser solution is the same active substance as the one approved for the currently authorised strength Ventavis 10 μg/ml. The drug substance is manufactured

according to the approved manufacturing process. An additional manufacturing site has been introduced for the final process step. The synthetic route, operating procedures and process parameters remain unchanged. Comparative results between two batches produced at the site approved for the 10 µg/ml strength and three batches produced at the new site show that the batches are of the same quality.

2.2.3. Finished Medicinal Product

Pharmaceutical Development

Iloprost 20 µg/ml was designed for patients who are maintained at the 5 µg dose and have repeatedly experienced extended treatment times with Ventavis 10 µg/ml, which could result in incomplete inhalation. It enables to shorten inhalation times by inhaling only 0.25 ml of the iloprost 20 µg/ml formulation instead of the 0.5 ml of the currently approved 10 µg/ml formulation.

A parenteral solution of iloprost 20 µg/ml is already marketed for many years. The formulation of 20 µg/ml iloprost nebuliser solution is identical to the formulation of 20 µg/ml iloprost parental therefore a formulation development for iloprost solution 20 µg/ml nebuliser solution was not carried out.

Ventavis 20 µg/ml has the same qualitative composition than Ventavis 10 µg/ml.

The 20 µg/ml and 10 µg/ml formulations contain the functional excipients ethanol 96 % and trometamol in the same ratio to the drug substance. The formulation used during clinical studies is the same that the used for marketing.

Comparative *in vitro* data of the nebulised aerosol generated by Ventavis 10 µg/ml versus Ventavis 20 µg/ml solutions have been provided using the I-neb AAD system device equipped with power disk 10. A higher mean emitted dose was observed for Ventavis 20 µg/ml as compared to approved Ventavis 10µg/ml i.e. 5 µg compared to 4.1 µg respectively. But results showed similar particle size distribution between Ventavis 10 and Ventavis 20 based on MMAD, mean (GSD) and FPF (< 4.7µm) with a shorter delivery rate with Ventavis 20 as compared to Ventavis 10. All batches used for in vitro tests and for the PK study comply with the specifications, especially with regard to drug content. As an aqueous solution, all batches will provide equivalent aerosolisation. The clinical impact of the differences on the *in vitro* characteristics of the aerosols generated by Ventavis 20 as compared to Ventavis 10 are discussed below in Clinical Part.

The primary packaging is 1-ml ampoules, colourless, glass type I, ring coded with two coloured rings (yellow-red). The material complies with Ph.Eur. and EC requirements. The choice of the container closure system has been validated by stability data and is adequate for the intended use of the product.

Adventitious agents

No excipients derived from animal or human origin have been used.

Manufacture of the product

The manufacturing process consists of the following main steps: dissolution of trometamol and sodium chloride in water for injection, dissolution of iloprost in ethanol and a mixing of the 2 phases, followed by pH adjustment, volume adjustment, and a filtration on a 0.2 µm filter. After filling of the solution, the ampoules are sealed and sterilized at 121°C for 20 min, and visually checked. The process is the same as the process used for Ventavis 10. The process is considered to be a standard manufacturing process taking into account the applicant's experience for iloprost solution manufacture.

For the critical steps, the in-process controls performed are: control of pH and iloprost content for bulk solution, filter integrity test, filled weight check and extractable volume, control of sterilization conditions. The in-process controls are considered adequate for this type of manufacturing process.

Major steps of the manufacturing process have been validated by a number of studies. The validation was performed prospectively with three consecutive batches at commercial scale of 100 kg at the current manufacturing site. It has been demonstrated that the manufacturing process is capable of producing the finished product of intended quality in a reproducible manner.

Product specification

The finished product release specifications include appropriate tests for this kind of dosage form. At release, the product is examined for appearance of the solution: colour and clarity (visual / EP 2.2.1), pH (potentiometry), extractable volume (gravimetry), identification of iloprost and trometamol (TLC and HPLC), sterility. The assay of iloprost and determination of impurities are performed by validated HPLC methods.

Identical specifications are applied at release and end of shelf life.

Batch analysis results are provided for 4 commercial scale batches confirming the consistency of the manufacturing process and its ability to manufacture to the intended product specification.

The finished product is released on the market based on the above release specifications, through traditional final product release testing.

Stability of the product

Iloprost solution 20 µg/ml 1 ml for inhalation has the same composition and manufacturing process than the drug product iloprost solution 20 µg/ml for infusion (ILOMEDIN 20). Therefore the available stability data of iloprost solution 20 µg/ml for infusion (ILOMEDIN 20) have been presented and are considered as representative for iloprost solution 20 µg/ml 1 ml for inhalation.

Stability data of 3 production scale batches of finished product stored 60 months under long term conditions (at 25 ºC / 60% RH and 30 ºC / 65% RH) and for up to 6 months under accelerated conditions at 40 ºC / 75% RH according to the ICH guidelines were provided. The batches of ILOMEDIN 20 are representative to those proposed for marketing and were packed in the primary packaging proposed for marketing.

Samples were tested according to iloprost solution 20 µg/ml 1 ml for inhalation release specifications. The analytical procedures used are stability indicating.

The product complies with the requirements of the specification through 60 months at 25 °C/60 % RH, and 30 °C/65 % RH and 6 months at 40 ºC / 75 % RH.

On-going stability studies on two validation batches (production scale) of iloprost solution 20 µg/ml solution for infusion, 1 ml ampoules (ILOMEDIN 20) have been performed and 36-months data at 25 °C/60 % RH are reported. Results comply with specifications. A commitment is made to continue stability studies for iloprost solution 20 µg/ml 1 ml in glass ampoules post approval through the proposed shelf life.

Furthermore a commitment is made to start ICH stability studies for iloprost solution 20 µg/ml 1 mL for inhalation in glass ampoules through the proposed shelf life.

Thermal stress testing on iloprost solution 20 µg/ml 1 ml was performed using temperatures up to 80°C up to 31 days. Assay, Z-Isomers, polar and non-polar related substances impurities/degradation products were investigated. Severe thermal stress conditions lead to an increase of impurities. As a conclusion iloprost solution 20 µg/ml is stable when stored at temperatures up to 40 °C.

In addition, a photostability study conducted on one batch of iloprost solution 10 µg/ml for inhalation showed that light exposure (overall irradiation of more than 1.2 million lux hours as defined in the ICH Guideline on Photostability Testing of New Drug Substances and Products) has no effect on ilosprost solution. It is considered that the results can be extended to iloprost solution 20 µg/ml 1 ml for inhalation. Indeed according to literature it is stated that a concentrated solution is likely to be more stable than the same product in a diluted form.

Based on available stability data, the shelf-life as stated in the SmPC is acceptable.

2.2.4. Discussion on chemical, pharmaceutical and biological aspects

Information on development, manufacture and control of the active substance and finished product has been presented in a satisfactory manner. The results of tests carried out indicate consistency and uniformity of important product quality characteristics, and these in turn lead to the conclusion that the product should have a satisfactory and uniform performance in clinical use.

2.2.5. Conclusions on the chemical, pharmaceutical and biological aspects

The quality of this product is considered to be acceptable when used in accordance with the conditions defined in the SmPC. Physicochemical and biological aspects relevant to the uniform clinical performance of the product have been investigated and are controlled in a satisfactory way.

2.2.6. Recommendation(s) for future quality development

N/A

2.3. Non-clinical aspects

No new data are provided in addition to the data provided for Ventavis 10 µg/ml. This is acceptable as the dose, indication and target population claimed for Ventavis 20 µg/ml are identical to that of Ventavis 10 µg/ml.

2.3.1. Ecotoxicity / environmental risk assessment

Regarding this application for line extension, the applicant has performed an environmental risk assessment to meet the requirements of Directive 2004/27/EC.

The applicant has determined iloprost PEC surface water of 0.000225 µg/L, based on a maximum recommended daily dose of iloprost of 9 x 5µg, equivalent to 45 µg (0.045 mg) administered as aerosol by a nebulizer and a default Fpen of 1. In addition, a logKow of 1.6 was measured by the applicant based on a study performed with the flask-shaking method following OECD guideline 107. Therefore, iloprost PEC surface water value is below the action limit of 0.01 µg/L and is not a PBT substance as log Kow does not exceed 4.5.

The newly available strength/potency is not expected to result in an increased risk to the environment.

2.3.2. Conclusion on the non-clinical aspects

The non-clinical aspects are sufficiently covered. No further data is required for the purpose of the present application.

2.4. Clinical aspects

2.4.1. Introduction

GCP

The Clinical trials were performed in accordance with GCP as claimed by the applicant.

The applicant has provided a statement to the effect that clinical trials conducted outside the community were carried out in accordance with the ethical standards of Directive 2001/20/EC.

- Tabular overview of clinical studies

Type of Study Clinical Phase	Study No. Report No.	Objective(s) of the Study	Study Design and Type of Control	Test Product(s) Dosage Regimen Route of Administration	Numbers of Subjects	Healthy Subjects or Diagnosis of Patients	Study Status Type of Report	Location of Study Report
I	15762 A59983	To compare the PK of iloprost following inhalation of the 10 µg/mL iloprost (Ventavis 10) with the PK of iloprost following inhalation of the 20 µg/mL iloprost (Ventavis 20) using the I-Neb nebulizing system in subjects with an extended inhalation time To monitor acute safety and tolerability	Single-center, cross-over study with 2 periods (1 single dose per period); randomized order of treatment (Ventavis 10 or Ventavis 20) Comparison of 2 admin. methods (5 µg as a 10 µg/mL or 20 µg/mL solution)	BAY q 6256 / Iloprost / Ventavis 5 µg (10 µg/mL solution or 20 µg/mL solution) Inhalation	21 subjects included in safety evaluation 19 subjects included in PK analysis	Healthy male volunteers	Completed Final report	5.3.3.1 A55983

2.4.2. Pharmacokinetics

The systemic exposure to iloprost following administration of Ventavis 20 has been investigated and compared to that observed after administration of Ventavis 10 using the Ineb-AAD nebulizer power disk 10 in Study 15762 (CSR A59983).

This study was conducted in healthy volunteers, according to a single-center (Germany), randomized, open-label, cross-over design. The study drug was administered as two single inhalations of 5 µg iloprost using one of two different formulations (10 µg/mL or 20 µg/mL iloprost) separated by a washout period of at least 24 h. Adequate analytical and statistical methods have been used in this study.

The outcome of the study showed that AUC and Cmax are respectively approximately 10% and 27 % higher with Ventavis 20 as compared to Ventavis 10 in healthy volunteers dosed with a single 5µg iloprost dose. In response to the CHMP Day 80 LOQ, the applicant has provided the results from study 15762 based on the 90% confidence intervals for the ratio of the population geometric means for AUC and Cmax according to CPMP/EWP/QWP/1401/98/Rev.1/Corr. Results are as follows:

. 90% CI for AUC (0-tlast) was 1.094 [0.941; 1.272],
. 90% CI for Cmax was 1.271 [1.173; 1.377]

Ventavis 10 and Ventavis 20 are not bioequivalent with respect to Cmax and the upper limit of AUC (1.272) is slightly above the 90% CI limit of 1.25 as defined in the bioequivalence guideline CPMP/EWP/QWP/1401/98/Rev.1/Corr. The slightly higher systemic exposure with Ventavis 20 could be explained by the shorter mean inhalation time (i.e.: 12 minutes versus 17 minutes) in this PK study and by taking into account the *in vitro* data showing a higher drug delivery rate (i.e.: 1.62 µg/minutes versus 0.48 µg/minutes *in vitro*) and a higher emitted dose (5.0 µg versus 4.1 µg *in vitro*) with Ventavis 20 as compared to Ventavis 10 (see Quality part above). The differences in systemic exposure between Ventavis 20 as compared to Ventavis 10 can however, be considered as weak. As a reminder, it is noticed that the plasma concentrations curve of iloprost observed in this study is superimposable to that observed in a previous PK study conducted in 2007 with a single dose of 5 µg of Ventavis 10 µg/ml using the I-Neb nebuliser (Study 310932 (CSR A36582)) which is currently approved in the SmPC of Ventavis 10.

2.4.3. Pharmacodynamics

No new pharmacodynamic study is provided in support of Ventavis 20 application.

This is acceptable as same indication and posology are claimed for this line extension as compared to Ventavis 10µg/ml.

2.4.4. Conclusions on clinical pharmacology

Ventavis 10 and Ventavis 20 are not bioequivalent with respect to Cmax and the upper limit of AUC (1.272) is slightly above the 90% CI limit of 1.25. The slightly higher systemic exposure with Ventavis 20 could be explained by the shorter mean inhalation time. The differences in systemic exposure between Ventavis 20 as compared to Ventavis 10 can however, be considered as weak, and it is worth mentioning that the plasma concentrations curve of iloprost observed in this study is superimposable to that observed in a previous PK study conducted in 2007 with a single dose of 5 µg of Ventavis 10 µg/ml using the I-Neb nebuliser (Study 310932 (CSR A36582)) which is currently approved in the SmPC of Ventavis 10. The CHMP therefore considers that the bioavailability is sufficiently addressed with no outstanding issues.

2.5. Clinical efficacy

No controlled clinical efficacy study was conducted with Ventavis 20 µg/ml. No efficacy end point was defined in the 2 *in vivo* trials using Ventavis 20 µg/ml, the PK study 15762 (A59983) and the phase 4 retrospective study (CONVERT, AC-063A407).

2.5.1. Discussion on clinical efficacy

The efficacy of inhaled iloprost was primarily based on the results of two studies that were submitted within the original dossier for Ventavis 10 µg/ml. These data consisted of a phase 2 randomized controlled study ME98008 (report A02237) including 63 PAH patients, and a phase 3 placebo controlled study ME97218 (AIR) (report A02997) including 203 PAH patients. These studies used the air-compressed nebulising device HaloLite. The two air-compressed nebulising devices, Halolite and its successor Prodose were mentioned in the initial SmPC as suitable nebuliser systems for the administration of Ventavis 10 µg/ml. In July 2005, a portable, hand-held ultrasonic nebuliser Venta-Neb-ir was approved as a third suitable nebuliser based on in vitro data which showed superimposable characteristics of the aerosol output measurement and droplet sizes distribution with Ventavis 10 µg/ml as compared to Prodose nebuliser system. The fourth additional nebulising device I-Neb, a vibrating mesh technology nebuliser system, was approved and mentioned in the SmPC as suitable for Ventavis 10µg/ml in March 2006 (EMEA/H/C/00474/II/006). The *in vitro* data provided were not superimposable compared to ProDose®. The results of a post commitment PK study (310932-CSRA36582) comparing a single dose of 5 µg iloprost administered using Ventavis 10 µg/ml solution via the I-Neb nebulising system equipped with power disk 10 versus the ProDose® system (the successor of Halolite which was no more available) showed a higher Cmax and AUC (0-tlast) as well as shorter Tmax following Ventavis 10 inhalation via I-Neb nebulizer as compared to the ProDose nebulizer. The estimated inhalation times were 3.2 minutes and 6.5 minutes for 2.5 µg and 5 µg of iloprost delivered at the mouth piece, respectively. However, in practice, patients may experience longer time of inhalation.

The available data with Ventavis 20 do not suggest any loss of efficacy as compared to the approved Ventavis 10 currently used in Europe. The *in vitro* comparative data showed a higher emitted dose with Ventavis 20 as compared to Ventavis 10 using I-Neb equipped with power disk 10 (i.e.: 5.0 µg and 4.1 µg/ml, respectively), with similar particle size distribution based on MMAD and FPF measurements (See Quality part). These results strongly suggest that lung deposition will be similar and that equal (or even higher) doses of iloprost will reach the targeted pulmonary vasculature to exert the vasodilatating effect on pulmonary arteries.

In addition to the sought higher delivery rate showed *in vitro* with Ventavis 20 as compared to Ventavis 10 (i.e.: 1.62µg/minutes as compared to 0.48 µg/minute, respectively*),* the PK study 15762 showed a shorter inhalation time with Ventavis 20 as compared to Ventavis 10 (i.e.: 12 minutes versus 17 minutes = approximately 30 % shorter time) while slightly higher systemic exposure was observed with Ventavis 20 as a demonstration that at least the same dose of iloprost had been inhaled during this time.

2.5.2. Conclusions on the clinical efficacy

No controlled clinical efficacy study has been conducted with Ventavis 20 µg/ml. This is acceptable as it can be agreed that based on the available data (*in vitro* measurement and the comparative PK study) the efficacy of Ventavis 20 µg/ml with I-Neb system equipped with power disk 10 will not be less than the efficacy of the Ventavis 10 µg/ml currently approved in Europe.

In addition, it is assumed that adding Ventavis 20 µg/ml would give patients who are taking a maintenance dose of 5 µg and experiencing compliance issues and withdrawal due to extended inhalation duration using the 10 µg/mL concentration, the option of shortening their drug delivery time aiming at achieving the targeted drug exposure within the intended inhalation time.

2.6. Clinical safety

Clinical safety results specifically obtained with Ventavis 20 µg/ml and submitted by the applicant in support of the present application are from:

1. the clinical pharmacology/pharmacokinetic study no.15762 conducted in Germany in 21 healthy male subjects aged from 18 to 45 years (also described in section 2.1. Pharmacokinetics above).
2. a phase 4 retrospective, multicenter study of 19 PAH patients who converted from the Ventavis 10 to the Ventavis 20 inhalation solution using the I-Neb AAD System conducted in USA from July 2010 to August 2011 sponsored by Actelion (NDA holder in USA) after launch of Ventavis 20 in USA (CONVERT study, report study dated on 7 February 2013, no: AC-063A407, document no. D-12.584).
3. post-marketing data following marketing authorization in the USA obtained for a 3 year period from 01 Sep 2009 (date of first launch in USA) through 31 Oct 2012 (estimated patients exposure 3633 patients).

Patient exposure

1. Clinical pharmacokinetic study no 15762 (A59983) entitled "A randomised, open- label, single center crossover study to compare the pharmacokinetics of iloprost following inhalation of Ventavis 10 or Ventavis 20 solution with the I-Neb nebulising device in healthy male volunteers under the condition of an extended inhalation time." was conducted from May 2012 to June 2012 by Bayer Health Care in one center in Germany (study report signed on 17 April 2013). The objectives of the study were to compare the pharmacokinetics (PK), acute safety and tolerability of single dose inhalations of 5 µg iloprost using Ventavis 10µg/ml and using Ventavis 20µg/ml both via the I-Neb AAD system equipped with power disk 10 in 21 adult healthy male subjects under condition of extended inhalation time.

The 21 subjects included were told to inhale with the same breathing pattern during both treatment periods as determined during a previous training for an extended inhalation time between 15 to 20 minutes achieved with the I-Neb nebulizer with the purple chip (5 µg / Ventavis 10). All 21 subjects received one single dose of 5 µg using Ventavis 20 µg/ml.

One subject prematurely discontinued after period 1 (Ventavis 20) due to an adverse event (presyncope). Consequently, only 20 subjects received the second single dose of 5 µg using Ventavis 10.

In this study the median durations of inhalation of 5 µg iloprost according to the predefined extended inhalation scheme were 17 minutes [min: 5 minutes; max: 40 min] and 12 min [min: 5 minutes; max: 17 minutes] with Ventavis 10 and Ventavis 20 respectively. This corresponds to approximately 30% reduction in the mean inhalation time when using Ventavis 20.

Systemic exposure was slightly higher with Ventavis 20 as compare to Ventavis 10 (Cmax and AUC were respectively 30% and 10 % higher with Ventavis 20 µg/ml as compared to Ventavis 10 µg/ml (see PK Section above).

2. Phase 4 Study no.AC-063A407 (CSR: D-12.584) was entitled *"A phase 4, retrospective, multicenter study of patients with pulmonary arterial hypertension treated with iloprost (inhalation) evaluating inhalation times, compliance, safety and tolerability when converting from the iloprost inhalation solution 10 µg/ml to the 20 µg/ml with the I-Neb AAD system and power disk-6".* It was conducted by Actelion (NDA holder of Ventavis in USA) from July 2010 to August 2011 after launch of Ventavis 20 in USA (study report dated on 7 February 2013).

For this study PAH patients were identified retrospectively by reviewing the medical charts and related information of patients who had completed at least 28 days of dosing with Ventavis 20 µg/ml. Patients were considered evaluable if they had received at least 28 days each of Ventavis 10 (Period 1) and Ventavis 20 (Period 2) at 5 µg/dose) administered by the I-Neb AAD system using PD-6. Iloprost inhalation data were captured electronically by a memory chip in the I-neb® AAD® device used to deliver iloprost by the INSIGHT software in the hand-piece, which supports a Patient Logging System (PLS). The primary objective was to compare the inhalation times between the Ventavis 10 in Period 1 (i.e. the last 28 days on Ventavis 10 prior to the 1st shipment of Ventavis 20) and the Ventavis 20 in Period 2 (i.e. the last 28 days on Ventavis 20 prior to entry into the study). Secondary objectives were to evaluate iloprost dosing compliance (dose frequency and percentage of complete doses) during Period 1 (28 days with Ventavis 10) and Period 2 (28 days with Ventavis 20), to collect treatment-emergent AEs and SAEs associated with the use of iloprost inhalation solution 20 mcg/mL concentration occurring in Period 2 (20 mcg/mL), vital signs (systolic and diastolic blood pressure, heart rate) measured at the in-clinic visit.

Patients served as their own control for comparing inhalation time and compliance between Period 1 (28 days with Ventavis 10) and Period 2 (28 days with Ventavis 20).

Nineteen (19) adult patients (mean age : 60.6 years ranging from 24 to 86 years) with the different types of PAH belonging to Dana Point classification Group 1 were enrolled in 4 study sites in US.

The average inhalation time was lower with the 20 mcg/mL iloprost (5.5 minutes) than with the 10 mcg/mL iloprost (11.1 minutes). The mean decrease after switching from the 10 mcg/mL to the 20 mcg/mL was 5.6 minutes and statistically significant ($P < 0.0001$). Their reduction in average inhalation time observed during Post-Switch (just after switch to 20 mcg/mL) was maintained during Period 2 (20 mcg/mL) i.e. average inhalation time increased slightly and non-significantly from Post-Switch (20 mcg/mL) to Period 2 (20 mcg/mL), from 4.4 to 4.8 minutes ($P = 0.596$).

The average number of daily doses was similar between Period 1 (10 mcg/mL) and Period 2 (20 mcg/mL): 4.8 (range: 1.5–6.7) and 4.6 doses (range: 1.8–6.1), respectively ($p= 0.501$), and between Pre-Switch (10 mcg/mL) and Post-Switch (20 mcg/mL): 5.2 and 5.3 doses, respectively ($p = 0.720$).

The percentage of patients with complete doses (100% complete doses during the 28 days as recorded on the memory chip in the I-neb® AAD® system. was higher in Period 2 : 94.3% (20 mcg/mL) than in Period 1: 89.6%, (10 mcg/mL), but the difference was not statistically significant ($p = 0.205$). Similarly, the percentage of total inhalations that were considered complete (100%, full) doses was slightly higher in Period 2 (20mcg/mL) compared to Period 1 (10 mcg/mL): 96.1% and 90.0%, respectively. The percentage of patients with complete doses was statistically significantly higher during Post-Switch (20 mcg/mL just after switching from Ventavis 10 to Ventavis 20) compared to Pre-Switch (10 mcg/mL, just before switching from Ventavis 10 to Ventavis 20): 98.0% and 90.2%, respectively ($P = 0.012$). Similarly, the percentage of total inhalations that were considered complete (100%, full) doses was higher in Post-Switch (20mcg/mL) compared to Pre-Switch (10 mcg/mL): 98.3% and 90.0%, respectively.

3. Post marketing reports from US:

As Ventavis 20 has been approved and marketed in US since 1st September 2009 by Actelion Pharmaceuticals Inc., post marketing of Ventavis 20 and Ventavis 10 data for a 3-year period from 01 Sep 2009 through 31Oct 2012 has been submitted in support of the present application.

As per the pharmacovigilance agreement with the license partner Actelion Pharmaceuticals, Bayer Health Care holds the Global Pharmacovigilance Safety Database and all US Ventavis case reports are being forwarded by Actelion to Bayer HealthCare and entered into the Global Pharmacovigilance Safety Database.

Based on the amount of vials of the inhalation solution distributed in the US market through October 31, 2012, the US patient exposure of Ventavis 20 µg/ml can be estimated to be 3633 patients (assuming 7.5 vials per day for 6 month per patient). The US patient exposure of Ventavis 10 is estimated to be 1481 patients during the same period. Thus, more than 70% of the patients were treated with Ventavis 20 µg/ml during this 3-year period.

According to the report, the majority of the US adverse events for Ventavis are received either through an organized data collection/patient contact program by specialty pharmacies in place for all patients, or from an additional voluntary patient support program in the United States sponsored by Actelion Pharmaceuticals US, Inc, or from registries, funded by Actelion Pharmaceuticals US,Inc.

In the US both concentrations of Ventavis (10 and 20 µg/mL) are exclusively administered with the I Neb nebulizer (Power Chip 6).

Adverse events

Clinical pharmacology/pharmacokinetic study no 15762 (A59983) in healthy volunteers.
No deaths or other SAEs occurred in this study.

There was one event of presyncope (rated as 'moderate' "vasovagal reaction without loss of consciousness" that began 13 minutes after the start of his inhalation of Ventavis 20 (with an inhalation duration of 16 minutes) systolic blood pressure dropped from 110 to 86 mmHg and diastolic blood pressure dropped from 53 to 37 mmHg during vasovagal reaction. The patient withdrawn prematurely from the study and did not received Ventavis 10.

The number of treatment emergent adverse events (AEs) following Ventavis 20 treatment was greater than the number associated with Ventavis 10

Most reports were of 'flushing' for 7 (33%) and 2 (10%) subjects with Ventavis 20 and Ventavis 10 respectively (without evidence for an association of higher frequency with higher C_{max} following treatment with Ventavis 20). All other single case adverse events occurred after treatment with Ventavis 20 only (blood creatinine increase (1), gamma-glutamyltransferase increased (1), headache (1) spontaneous penile erection (1)). All of them were considered related to the study drug except one (headache). All adverse events were rated as 'mild', except for the single case of presyncope (after Ventavis 20), which was rated as 'moderate'. Laboratory events were mild and transient and therefore they can be considered as not being of special concern. There was no clear trend toward any change in systolic or diastolic blood pressure over the period of administration (before dosing as well as 5 and 30 minutes after dosing) either with Ventavis 10 or with Ventavis 20. Six hours after dosing a slight trend towards higher systolic blood pressure was found for both treatments. However, in summary no difference between the two treatments was established.

As conducted with a single dose, this study only allows the assessment of acute tolerance. Moreover, it relates to healthy volunteers with stable hemodynamic status but not to PAH patients prone to frail and unstable hemodynamic status.

In the Phase 4 Study no. AC-063A407 (no. D-12.584)

For the purpose of this study, patients were interviewed at the in-clinic visit for any emergent AEs and SAEs occurring over the last 28 days prior to study entry.

During period 2 (28 days with 20 mcg/mL), 5 of 19 patients (26.3%) reported 7 AEs (headache, musculoskeletal pain, pain in extremity, chest pain, upper respiratory tract infection and cough). Of the 7 events, 6 were considered mild and one was considered moderate and 2 events (both headache) were considered related to study treatment. No deaths or other serious adverse events (SAEs) were reported.

No data are provided for period 1 in the study report submitted by the applicant.

There were no remarkable findings in vital signs (heart rate and blood pressure) at this in-clinic visit while patients are under treatment with Ventavis 20.

When asked to compare the convenience of the 20 mcg/mL iloprost inhalation solution to the 10 mcg/mL, all patients responded that the 20 mcg/mL was better. Additionally, the majority of patients (12 patients; 63.2%) indicated that they felt better while on the 20 mcg/mL compared to the 10 mcg/mL. Seven patients (36.8%) said they felt no change after converting from the 10 mcg/mL to the 20 mcg/mL.

This study has limitation as it was conducted retrospectively on a selected and limited sample of 19 patients. Adverse effects were recorded at the in-clinic visit by the interview for any emergent AEs and SAEs occurring over the last 28 days prior to study entry (period 2). Therefore, the collection of adverse effects may be biased by the fact that it is based on patients' memory. As adverse effects during period 1 were not collected, no comparison can be made between period 2 (Ventavis 20 µg/ml) and period 1(Ventavis 10 µg/ml).

Post marketing data in US:

Using the specific US system for data collection the company has provided a comparison of post marketing pharmacovigilance data with Ventavis 20 and Ventavis 10 in USA for the 3 year period from 01 September 2009 (date of launch of Ventavis 20 in USA) trough 31 Oct 2012.

The updated retrieval from the Global Pharmacovigilance Safety Database resulted in a total of 2106 single cases with Ventavis 20 µg/mL during a 3-year period which included a total of 5495 AEs (one case may contain more than one reported AE). For Ventavis 10 µg/mL a total of 2373 US single cases were received for the same period which included a total of 6383 AEs (one case may contain more than one reported AE). In addition, there are 60 cases (with 359 reported AEs) where both concentrations were reported in one single case.

Adverse drug reactions with Ventavis 20 were similar in profile with those already known with Ventavis 10 including cough, dyspnea, headache, dizziness, diarrhea, nausea, flushing and pain in jaw.

Reported rate of bronchospasms, syncope and hypotension were 0.018, 0.063, 0.098 with Ventavis 10 respectively and 0.002, 0.023, and 0.016 with Ventavis 20 respectively.

Serious adverse event / deaths / other significant events

Deaths

A total of 522 fatal case reports with Ventavis 10 µg/mL were received and included 628 AEs with fatal outcome. A total of 356 fatal cases with Ventavis 20 µg/mL were received and included 442 AEs with fatal outcome.

A total of 3 fatal cases were reported in cases with both concentrations. The most frequent AEs leading to fatal outcome in cases with Ventavis 10 µg/mL treatment were respiratory failure and pulmonary hypertension/pulmonary arterial hypertension. The same events were the most commonly reported fatal events in patients with Ventavis 20 µg/mL therapy. The absolute numbers as well as the reporting rates of fatal events or reported causes of death under Ventavis 10 µg/mL (0.424) or Ventavis 20 µg/mL therapy (0.122) did not indicate more fatalities under Ventavis 20 µg/mL or towards different causes of death.

In summary, the reporting number of AEs and the respective reporting rates do not indicate more serious AEs or an overall increase in AEs in patients treated with ventavis 20 µg/ml.

Haemorrhages

A total of 121 single cases were identified which included 146 bleeding AEs for Ventavis 10 and a total of 87 single cases were identified which included 102 bleeding AEs for Ventavis 20 i.e. frequencies were 0.099 and 0.028 for Ventavis 10 and Ventavis 20 respectively.

The most frequent bleeding AEs under Ventavis 10 µg/mL were epistaxis (N=52), haemoptysis (N=21), and contusion (N=12). The same bleeding types were the most commonly reported with Ventavis 20 µg/mL therapy; epistaxis (N=34), haemoptysis (N=16), and contusion (N=8). The frequency of total number and the respective reporting rates do not hint towards more frequent or more serious bleeding events under Ventavis 20 µg/mL therapy.

De-challenge/re-challenge

Out of 2144, 20 cases (20/2144, 0.9%) were identified which can be interpreted as positive de-challenge with resolving symptoms after discontinuation of Ventavis 20, a switch back to the Ventavis 10 concentration, and/or a reduction in dose.

In 11/20 cases symptoms improved after Ventavis 20 *discontinuation*; these cases mainly included side effects that are known to be associated with inhaled iloprost: headache (5), vomiting (2), nausea (3), diarrhoea (1), cough (3), bronchospasm (1), palpitation (2), heart rate increase (1), tachycardia (1), dizziness (1), dyspnoea (1), chest pain (1), epistaxis (1), allergy (1), fatigue (2), stress (1), and decreased appetite (1).

In 7/20 case reports symptoms improved after *switching back* to the Ventavis 10 concentration. In one patient dizziness, fatigue, migraines, flushing and vertigo improved after Ventavis 20 was switched to Ventavis 10. In 6 patients improvement of dyspnea (2), wheezing (1), headache (3), nausea (1), and fatigue (1) was reported after switching back to the 10 µg/mL concentration.

From the case information it is not clear whether patients stayed on 5 µg/ml on Ventavis 10 or whether they simultaneously reduced the dose to 2.5 µg.

In 2 further cases it was explicitly described that the *dose was reduced* to 2.5 µg/mL which led to improvements of headache (n=1) and hair loss (n=1).

Positive re-challenge under Ventavis 20 with recurring symptoms of headache, nausea, and fatigue were reported for 2 patients after resuming therapy or increasing inhalation frequencies.

In one case de-challenge results were reported to be negative in a patient who experienced hoarseness under Ventavis therapy.

Drug discontinuation

Next to the above cases with positive de-challenge after drug discontinuation, in about 25 cases patients reportedly discontinued Ventavis therapy due to following AEs (de-challenge results unknown):

AE not further specified, oral disorders, oral pain, headache, agitation, feeling abnormal, flushing, throat irritation, tongue and oral mucosal blistering, glossodynia, PAH worsening, fatigue, chest pain/discomfort, cough, musculoskeletal pain, throat irritation, dyspnea, oedema/fluid retention, blurry vision, nausea, dizziness, and presyncope.

Overall, inhalation time was rarely addressed in the single case reports.

2.6.1. Discussion on clinical safety

Clinical safety results obtained specifically with Ventavis 20 were collected from the postmarketing data following marketing authorization in the USA obtained from 01 Sep 2009 through 31 Oct 2012, from a phase 4 retrospective study in 19 US patients with PAH who converted from the Ventavis 10 to the Ventavis 20 inhalation solution using the I-Neb AAD System (CONVERT study) and from the clinical pharmacology study no. 15762 in 21 healthy adult male subjects conducted in Germany.

Based on the 3-year review of US postmarketing data, the most frequently reported events with Ventavis 20 were the same in nature as compared to Ventavis 10. No new safety concern has been identified with Ventavis 20 µg/mL compared to Ventavis 10 µg/mL. Reporting rates and total number of events for bronchospasm, syncope, hypotension, cough, dizziness, nausea, pain in jaw, dyspnoea, headache, and flushing were similar or lower than with Ventavis 10 µg/mL. The frequency of hypotension, syncope or bronchospasm, where not shown to be higher or more serious with Ventavis 20 as compared to Ventavis 10. Similarly, hemorrhages or the types of bleeding events were comparable between the two concentrations. Causes of death were as expected mainly associated to the underlying progression of PAH and other conditions. The data do not indicate more fatalities under Ventavis 20 µg/mL or towards different causes of death compared to Ventavis 10 µg/mL. As based on spontaneous reporting system, this review cannot be considered as proper controlled data, but it is based on a homogeneous setting i.e. all from the US coding, and it helps to provide a safety comparison between Ventavis 10 and Ventavis 20 in real life practice. It is noticed that according to the applicant, more than 70% of the patients were treated with Ventavis 20 suggesting a good tolerance as compared to Ventavis 10 in clinical practice.

Cases of challenge and dechallenge after the switch from 10 µg/ml to the 20 µg/mL concentration and/or improved after switching back to Ventavis 10 were mainly vasodilating nature or the inhalative route of administration related to the shorter inhalation time with Ventavis 20 and then more rapid delivery of iloprost. As well it can be the interpretation of the higher rate of flushing cases in the single dose study 15762 conducted in healthy volunteers. The higher Cmax observed with Ventavis 20 as compared to Ventavis 10 in the PK study 15762 would suggest possible higher acute systemic exposure that may subsequently translate in more acute undesirable events relating to systemic vasodilatation.

The safety data from USA (3-year post marketing and CONVERT phase 4 study) were issued from patients using I-Neb system equipped with power disk 6. In Europe only the I-Neb system equipped with power disk 10 will be used. In response to Day 180 list of question, the applicant has provided clarifications on the impact of the power of the control disk of I-Neb system i.e. 6 versus 10. Power disk level (6 versus 10) had no impact on particles size distribution with Ventavis 20 µg/ml reflecting similar pulmonary deposition when using power disk 6 or 10. The drug delivery rate measured *in vitro*

was slightly faster in average with power level 10 disk as compared to power disk 6 (i.e.: 1.30 µg/min versus 1.62 µg/min, respectively with Ventavis 20 µg/ml) but there was a widely overlapping range between power disk 10 and power disk 6 (dose delivery time ranges: 139-247 seconds versus 156-338 seconds, respectively) allowing to consider that safety post marketing experience in USA remains contributory despite a slightly shorter time of inhalation is possible with I-Neb AAD system for some patients in Europe (power disk 10) as compared to USA (power disk 6).

Ventavis 20 is intended for patients who are maintained at the 5 µg dose and who have repeatedly experienced extended treatment times which could result in incomplete dosing, those patients will remain with a slow breathing pattern, even if transitioning to the 20 mcg/mL concentration using the I-Neb-AAD System will decrease treatment times. This would contribute to individually minimising the higher Cmax observed in the European PK study (15762 (A59983) conducted with I-neb equipped with power disk 10) that would lead to acute adverse reactions when switching. Moreover, Section 4.2 of the SmPC adequately mentions that supervision by the treating physician is necessary if a switch is made from Ventavis 10 µg/ml to Ventavis 20 µg/ml in order to control the acute tolerance.

From the safety database all the adverse reactions reported in clinical trials and post-marketing have been included in the Summary of Product Characteristics.

2.6.2. Conclusions on the clinical safety

The safety of Ventavis 20 is considered acceptable in those patients maintained at the 5 mcg dose with Ventavis 10 and who have repeatedly experienced extended treatment times which could result in incomplete dosing, and provided the switch from Ventavis 10 to Ventavis 20 is made under medical supervision in order to control the acute tolerance is acceptable.

2.7. Pharmacovigilance

Detailed description of the pharmacovigilance system

The CHMP considered that the Pharmacovigilance system as described by the applicant fulfils the legislative requirements.

2.8. Risk Management Plan

The CHMP received the following PRAC Advice on the latest submitted Risk Management Plan:

PRAC Advice

The PRAC, having assessed the latest version of the RMP submitted by the MAH on 9 March 2014 as response to the LoQ, endorses the updates without further changes.

This advice is based on the following content of the Risk Management Plan:

- **Safety concerns**

Table 1: Summary of safety concerns	
Important identified risks	Hypotension Syncope Local Irritations Bleeding events Thrombocytopenia Tachycardia Medication error
Important potential risks	None
Missing information	Use in pediatric population Use in pregnant or lactating women Use in elderly patients Use in patients with severe hepatic impairment Use in patients with renal impairment

Pharmacovigilance plans

5.1 Table of on-going and planned additional PhV studies / activities in the Pharmacovigilance Plan

Not applicable.

5.2 Table of completed studies / activities from the Pharmacovigilance Plan

Study/activity type, title and category (1-3)	Objectives	Safety concerns addressed	Status (Completed)	Date for submission of final study reports
Study 308120 (PASS): Open-label, uncontrolled, prospective long-term observation of Ventavis inhalation therapy in the treatment of patients with primary pulmonary hypertension up to 4 years	To assess the clinical effects, safety and tolerability, and survival during long-term Ventavis inhalation therapy over at least 2 years and up to 4 years in a usual care setting	No particular safety concern was addressed. General tolerability and safety was observed.	Completed. Final study report submitted	Final study report submitted November 2012

- **Risk minimisation measures**

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
Hypotension (identified risk)	Text in SmPC **4.2 Posology and method of administration:** …In case of poor tolerability of the 5.0 microgram dose, the dose should be reduced to 2.5 micrograms **4.4 Warnings and Precautions:** Blood pressure should be checked while initiating Ventavis. In patients with low systemic blood pressure and in patients with postural hypotension or receiving drugs known to reduce blood pressure levels, care should be taken to avoid further hypotension. Ventavis should not be initiated in patients with systolic blood pressure less than 85 mmHg. Physicians should be alert to the presence of concomitant conditions or drugs that might increase the risk of hypotension and syncope (see section 4.5). **4.5 Interaction with other medicinal products and other forms of interaction** Iloprost may increase the effects of vasodilatators and antihypertensive agents and then favour the risk of hypotension (see section 4.4). Caution is	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	recommended in case of co-administration of Ventavis with other antihypertensive or vasodilatating agents as dose adjustment might be required. **4.7 Effects on ability to drive and use machines** Care should be exercised during initiation of therapy until any effects on the individual have been determined. In patients experiencing hypotensive symptoms such as dizziness, the ability to drive or operate machines may be seriously affected. **4.8 Undesirable effects:** Summary of safety profile: The most frequently observed adverse reactions (20 %) in clinical trials include vasodilatation (including hypotension), headache and cough. The most serious adverse reactions were hypotension, bleeding events, and bronchospasm. Listed as ADR: hypotension (common), vasodilation (very common). Hypotension marked with asterisks in SmPC to indicate that life-threatening and/or	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	fatal cases have been reported. **4.9 Overdose** Symptoms: No case of overdose has been reported. In the case of an overdose hypotensive/vasovagal reaction might be anticipated as well as headache, flushing, nausea, vomiting, and diarrhoea. **5.3 Preclinical safety data** Systemic toxicity: As expected for a prostacyclin, iloprost produced haemodynamic effects (vasodilatation, reddening of skin, hypotension, inhibition of platelet function, respiratory distress) and general signs of intoxication such as apathy, gait disturbances, and postural changes. Continuous IV/SC infusion of iloprost up to 26 weeks in rodents and non-rodents did not cause any organ toxicity at dose levels which exceeded the human therapeutic systemic exposure between 14 and 47 times (based on plasma levels). Only expected pharmacological effects like hypotension, reddening of skin, dyspnoea, increased	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	intestinal motility were observed.	
Syncope (identified risk)	Text in SmPC **4.2 Posology and method of administration:** In case of poor tolerability of the 5.0 microgram dose, the dose should be reduced to 2.5 micrograms **4.4 Warnings and Precautions:** Blood pressure should be checked while initiating Ventavis. In patients with low systemic blood pressure and in patients with postural hypotension or receiving drugs known to reduce blood pressure levels, care should be taken to avoid further hypotension. Ventavis should not be initiated in patients with systolic blood pressure less than 85 mmHg. Physicians should be alert to the presence of concomitant conditions or drugs that might increase the risk of hypotension and syncope (see section 4.5). The pulmonary vasodilatory effect of inhaled iloprost is of short duration (one to two hours). Syncope is a common symptom of the disease itself and can also occur under therapy. Patients who experience syncope in association with pulmonary	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	hypertension should avoid any exceptional straining, for example during physical exertion. Before physical exertion it might be useful to inhale. The increased occurrence of syncopes can reflect therapeutic gaps, insufficient effectiveness and/or deterioration of the disease. The need to adapt and/or change the therapy should be considered (see section 4.8). **4.8 Undesirable effects:** Listed as ADR: Syncope (common). Description of selected adverse reactions: Syncope is a common symptom of the disease itself, but can also occur under therapy. The increased occurrence of syncopes can be related to the deterioration of the disease or insufficient effectiveness of the product (see section 4.4). **4.9 Overdose** Symptoms: No case of overdose has been reported. In the case of an overdose hypotensive/vasovagal reaction might be anticipated as well as headache, flushing, nausea, vomiting, and	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	diarrhoea.	
Local Irritations (identified risk)	Text in SmPC **4.4 Warnings and Precautions:** Ventavis inhalation might entail the risk of inducing bronchospasm, especially in patients with bronchial hyperactivity (see section 4.8 Undesirable effects). Moreover, the benefit of Ventavis has not been established in patients with concomitant Chronic Obstructive Pulmonary Disease (COPD) and severe asthma. Patients with concomitant acute pulmonary infections, COPD and severe asthma should be carefully monitored. Ventavis nebuliser solution should not come into contact with skin and eyes; oral ingestion of Ventavis solution should be avoided. During nebulisation sessions a facial mask must be avoided and only a mouthpiece should be used. **4.8 Undesirable effects:** Listed as ADRs: Common: Pharyngolaryngeal pain, Throat irritation, Mouth and tongue irritation including pain Frequency not known: Bronchospasm/Wheezing,	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Dysgeusia Bronchospasm marked with asterisks in SmPC to indicate that life-threatening and/or fatal cases have been reported.	
Bleeding events (identified risk)	Text in SmPC **4.3 Contraindications** Conditions where the effects of Ventavis on platelets might increase the risk of haemorrhage (e.g. active peptic ulcers, trauma, intracranial haemorrhage). **4.5 Interaction with other medicinal products and other forms of interaction** Since iloprost inhibits platelet function its use with anticoagulants (such as heparin, coumarin-type anticoagulants) or other inhibitors of platelet aggregation (such as acetylsalicylic acid, non-steroidal anti-inflammatory medicinal products, ticlopidine, clopidogrel, glycoprotein IIb/IIIa antagonists: abciximab, eptifibatide and tirofiban) may increase the risk of bleeding. A careful monitoring of the patients taking anticoagulants or other inhibitors of platelet aggregation according to common medical practice is	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	recommended. Intravenous infusion of iloprost has no effect either on the pharmacokinetics of multiple oral doses of digoxin or on the pharmacokinetics of co-administered tissue plasminogen activator (t-PA) in patients. Although, clinical studies have not been conducted, *in vitro* studies investigating the inhibitory potential of iloprost on the activity of cytochrome P450 enzymes revealed that no relevant inhibition of drug metabolism via these enzymes by iloprost have to be expected. **4.8 Undesirable effects:** Summary of the safety profile: The most serious adverse reactions were hypotension, bleeding events, and bronchospasm. Listed as ADRs: Very common: bleeding events Further information on bleeding events in 4.8.: Bleeding events (mostly epistaxis and haemoptysis) were very common as expected in this patient population with a high proportion of patients taking	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	anticoagulant co-medication. Fatal cases included cerebral and intracranial haemorrhage.	
Thrombocytopenia (identified risk)	Text in SmPC **4.8 Undesirable effects:** Listed as ADRs: Frequency not known: thrombocytopenia	Not applicable
Tachycardia (identified risk)	Text in SmPC **4.3 Contraindications** -Severe arrhythmias; **4.8 Undesirable effects:** Tachycardia is not yet listed as ADR in SmPC. The company's Global Labeling Committee approved in January 2013 a CCDS update to add tachycardia as ADR.	Not applicable
Medication error (identified risk)	1. Label on Ventavis ampoules indicates that it is a solution for inhalation 2. Different color coded rings on glas ampoule to differentiate Ventvais 10 from Ventvais 20 µg/mL 3. Different color coding of I-Neb control disc and medication chamber to differentiate material to be used with respective Ventavis concentrations (10 versus 20 µg/mL) 4. Text in SmPC: 4.2.1 Method of	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	administration Ventavis 10 microgram / mL: The ready-to-use Ventavis 10 microgram / mL nebulizer solution is administered with a suitable inhalation device (nebulizer) as recommended in the section 'Instructions for use/handling'. Ventavis 20 microgram / mL: The ready-to-use Ventavis 20 microgram / mL nebulizer solution is to be inhaled using the pulmonary drug delivery device I-Neb AAD System. For more detailed explanation see the section 'Instructions for use/handling'. 4.2.2 Dosage regimen Ventavis 20 µg/ml: Patients who are maintained at the 5 microgram dose and who have repeatedly experienced extended treatment times which could result in incomplete inhalation may be considered to switch to the 20 microgram / mL. The dose per inhalation session should be administered 6 to 9 times per day according to individual need and tolerability. Supervision by the treating physician is necessary if a switch is made from	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Ventavis 10 microgram / mL to Ventavis 20 microgram / mL (see section 'instructions for use / handling). 4.4 Special warnings and precautions for use Ventavis nebulizer solution should not come into contact with skin and eyes; oral ingestion of Ventavis solution should be avoided. During nebulization sessions a facial mask must be avoided and only a mouthpiece should be used. 4.9 Overdose 4.9.1 Symptoms No case of overdose has been reported. In the event of an overdose hypotensive reaction might be anticipated as well as headache, flushing, nausea, vomiting, and diarrhea. An increase of blood pressure, bradycardia or tachycardia and limb or back pain might be possible. 6.6.1 Use with nebulizers Ventavis 10 microgram / mL: In general suitable nebulizers to be used for the inhalation therapy with Ventavis 10 microgram / mL nebulizer solution are registered according to the regional medical device regulations and work with compressed air, ultrasound or vibrating	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	mesh technology. Nebulizers suitable for inhalation of iloprost Ventavis 10 microgram / mL fulfill the following requirements: The nebulizing devices deliver 2.5 microgram or 5 microgram iloprost at the mouthpiece in a time period of approximately 4 to 10 minutes. The Mass Median Aerodynamic Diameter (MMAD) of the aerosol is between 1 and 5 micrometer. The following nebulizers have been tested suitable for the application of Ventavis 10 microgram / mL: - HaloLite AAD (Philips Respironics) - Prodose AAD (Philips Respironics) - Venta-Neb (Nebu-Tec) - I-Neb AAD (Philips Respironics.) If switching to a different type of nebulizer supervision by the treating physician is necessary. Ventavis 20 microgram / mL: The Ventavis 20 microgram / mL nebulizer solution is to be inhaled using the	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	pulmonary drug delivery device I-Neb AAD System. The nebulizing device delivers 5 microgram iloprost at the mouthpiece. The Mass Median Aerodynamic Diameter (MMAD) of the aerosol is between 1 and 5 micrometers. Ventavis 10 microgram /mL and Ventavis 20 microgram / mL: To minimize accidental exposure, it is recommended to use Ventavis with nebulizers with a filter or inhalation-triggered systems, and to keep the room well ventilated. User intructions for the I-Neb AAD system: When using the I-Neb AAD system the following instructions need to be followed. The dose delivered by the I-Neb AAD system is controlled by the medication chamber in combination with a control disc. For each medication chamber there is a corresponding color coded control disc. Ventavis 10 microgram / mL:	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	For the 2.5-microgram dose the medication chamber with the red latch is used together with the red control disc. For the 5-microgram dose the medication chamber with the purple colored latch is used together with the purple control disc. For each inhalation session with the I-Neb AAD, the content of one 1-ml ampoule of Ventavis 10 microgram / mL nebulizer solution, showing two colored rings (white-yellow), will be transferred into the appropriate nebuliser medication chamber immediately before use. Ventavis 20 microgram / mL: For the 5-microgram dose the medication chamber with the gold colored latch is used together with the gold control disc. For each inhalation session with the I-Neb AAD, the content of one 1-mL ampoule of Ventavis 20 microgram /mL nebulizer solution, showing two colored rings (yellow-red), will be transferred into the	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	medication chamber immediately before use.	
Use in pediatric population (missing information)	Text in SmPC **4.2 Posology and method of administration** Paediatric population No specific paediatric control studies have been conducted with Ventavis. **5.1 Pharmacodynamic properties** Efficacy in adult patients with pulmonary hypertension: No study has been performed with Ventavis in children with pulmonary hypertension.	Not applicable
Use in pregnant or lactating women (missing information)	Text in SmPC **4.4 Special warnings and precautions for use** **Exposure to Ventavis** Newborns, infants, and pregnant women should not be subjected to Ventavis in the room air. **4.6 Fertility, pregnancy and lactation** Pregnancy Animal studies have shown reproductive effects (see section 5.3). There is a limited amount of data from the use of iloprost in pregnant women. Taking	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	into account the potential maternal benefit, the use of Ventavis during pregnancy may be considered in those women who choose to continue their pregnancy, despite the known risks of pulmonary hypertension during pregnancy. Breast-feeding It is not known whether iloprost/metabolites are excreted in human breast milk. Very low levels of iloprost into milk were observed in rats (see section 5.3). A potential risk to the breast-feeding child cannot be excluded and it is preferable to avoid breast-feeding during Ventavis therapy. Fertility Animal studies have not shown harmful effect of iloprost on fertility. **5.3 Preclinical safety data** Reproduction toxicology In embryo- and foetotoxicity studies in rats continuous intravenous administration of iloprost led to anomalies of single phalanges of the forepaws in a few foetuses/pups without dose dependence.	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	These alterations are not considered as teratogenic effects, but are most likely related to iloprost induced growth retardation in late organogenesis due to haemodynamic alterations in the foetoplacental unit. No disturbance of postnatal development and reproductive performance was seen in the offspring that were raised, indicating that the observed retardation in rats was compensated during the postnatal development. In comparable embryotoxicity studies in rabbits and monkeys no such digit anomalies or other gross-structural anomalies were observed even after considerably higher dose levels which exceeded the human dose multiple times. In rats, passage of low levels of iloprost and/or metabolites into the milk was observed (less than 1% of iloprost dose given intravenously). No disturbance of post-natal development and reproductive performance was seen in animals exposed during lactation.	
Use in elderly patients (missing information)	Text in SmPC **5.2 Pharmacokinetic properties** Age and gender	No additional risk minimization activities planned.

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	Gender is not of clinical relevance to the pharmacokinetics of iloprost. No pharmacokinetic data are available in elderly patients.	
Use in patients with severe hepatic impairment (missing information)	Text in SmPC **4.2 Posology and method of administration** *Patients with hepatic impairment* Iloprost elimination is reduced in patients with hepatic dysfunction (see section 5.2). To avoid undesired accumulation over the day, special caution has to be exercised with these patients during initial dose titration. Initially, doses of 2.5 microgram should be administered using Ventavis 10 microgram/mL with dosing intervals of 3-4 hours (corresponds to administration of max. 6 times per day). Thereafter, dosing intervals may be shortened cautiously based on individual tolerability. If a further increase in the dose up to 5 microgram is indicated, again dosing intervals of 3-4 hours should be chosen initially and shortened according to	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	individual tolerability. An accumulation of iloprost following treatment over several days is not likely due to the overnight break in administration of the medicinal product. **4.4 Special warnings and precautions for use** *Renal or hepatic impairment* Data with intravenously administered iloprost indicated that the elimination is reduced in patients with hepatic dysfunction and in patients with renal failure requiring dialysis (see section 5.2). A cautious initial dose titration using dosing intervals of 3-4 hours is recommended (see section 4.2). **5.2 Pharmacokinetic properties** Characteristics in patients *Hepatic dysfunction* Because iloprost is extensively metabolised by the liver, the plasma levels of the active substance are influenced by changes in hepatic function. In an intravenous study, results were obtained involving 8 patients suffering from liver cirrhosis. The mean	

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	clearance of iloprost is estimated to be 10 mL/minute/kg.	
Use in patients with renal impairment (missing information)	**4.2 Posology and method of administration** *Patients with renal impairment* There is no need for dose adaptation in patients with a creatinine clearance >30 mL/min (as determined from serum creatinine using the Cockroft and Gault formula). Patients with a creatinine clearance of ≤30 mL/min were not investigated in the clinical trials. Data with intravenously administered iloprost indicated that the elimination is reduced in patients with renal failure requiring dialysis. Therefore, the same dosing recommendations as in patients with hepatic impairment (see above) are to be applied. 4.4 Special warnings and precautions for use *Renal or hepatic impairment* Data with intravenously administered iloprost indicated that the elimination is reduced in patients with hepatic dysfunction and in patients with renal failure requiring dialysis (see section 5.2). A cautious	Not applicable

Safety concern	Routine risk minimisation measures	Additional risk minimisation measures
	initial dose titration using dosing intervals of 3-4 hours is recommended (see section 4.2). **5.2 Pharmacokinetic properties** Characteristics in patients *Renal dysfunction* 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 that observed in patients with renal failure not undergoing intermittent dialysis treatment (mean CL = 18 ± 2 mL/minute/kg).	

The CHMP endorsed this advice without changes.

2.9. Paediatric studies

N/A

2.10. User consultation

The results of the user consultation with target patient groups on the package leaflet submitted by the applicant show that the package leaflet meets the criteria for readability as set out in the *Guideline on the readability of the label and package leaflet of medicinal products for human use.*

3. Benefit-Risk Balance

Benefits

Beneficial effects

Reduced time of inhalation has been shown when using the double concentration of iloprost solution 20 µg/ml in ampoule of 1 ml with I-Neb system for 5 µg at mouth piece as compared to Ventavis 10 µg/ml solution.

Hence, it provides those patients who have repeatedly experienced extended treatment times with Ventavis 10 µg/ml (and which could result in incomplete inhalation), with a more convenient medication expected to shorten their inhalation times with the aim to improve dose completion.

No efficacy study has been conducted but this is considered acceptable, as *in vitro* and PK data are strongly in favour of similar lung deposition and efficacy on pulmonary vasculature as compared to Ventavis 10.

Uncertainty in the knowledge about the beneficial effects.

Available studies do not allow to formally concluding that compliance to treatment is indeed improved when using Ventavis 20 µg/ml. However, from a pragmatic point of view, it is noticed that since Ventavis 20 is marketed in US, 70% of patients are treated with Ventavis 20.

Data only refers to I-Neb AAD system. No data are available with the other nebuliser systems currently mentioned as suitable for Ventavis 10 µg/ml i.e.: Prodose, Venta-Neb. Therefore, only I-Neb is recommended in the SmPC. This is acceptable as I-Neb is the most frequently nebulizer system used.

Risks

Relating to the double concentration of the solution and subsequent shorter inhalation time, the delivery rate of iloprost is slightly increased leading to possible increase of acute adverse effects relating to the vasodilatory effect of iloprost. Though no cluster is identified based on the 3-year US Pharmacovigilance database, cases challenge and dechallenge after the switch from 10 µg/ml to the 20 µg/mL concentration and/or improved after switching back to Ventavis 10 were reported through post marketing reports in US. Moreover, flushing was reported more frequently with Ventavis 20 than with Ventavis 10 in the small study single dose study conducted in Europe in 21 healthy subjects.

Benefit-risk balance

Importance of favourable and unfavourable effects

Despite differences observed *in vitro* and in study 15762 between Ventavis 20 as compared to the currently approved Ventavis 10 a positive benefit/risk balance is maintained .

For a maintenance dose of 5 µg, the estimated inhalation time is 6.5 minutes. However, in practice some patients need an extended inhalation time, frequently exceeding 15 minutes, to inhale the 5 µg dose using Ventavis 10 and this may raise compliance issues due to failing completed doses.

With the aim to shorten inhalation time, Ventavis 20 offers to deliver a 5 µg single dose to patients who have repeatedly experienced extended inhalation times. In those patients, the shortened inhalation duration resembles the one administered in clinical trials with Ventavis 10. Data on individual patient inhalation duration and compliance can be recorded and stored in their individual I-Neb AAD System. Physicians are therefore able to select those patients with compliance issues and evaluate their responses through monitoring of well-being and inhalation duration.

Compared to the 10 µg/mL iloprost nebuliser solution, Ventavis 20 requires half the volume to be nebulized allowing about half the amount of nebulisation time to receive the same 5 µg at the mouthpiece. Therefore, the amount of drug substance in the medication chamber of the device will not change and the total dose delivered at mouthpiece will remain unchanged.

The manufacturer of I-Neb AAD system, Philips Respironics, is using a colour coding for the dedicated setting for Ventavis allowing differentiation of Ventavis doses. The colour code “red” (i.e. colour of the latch of the medication chamber and the control disk that activate the system) is used for a 2.5 µg dose with Ventavis 10, purple for a 5 µg dose with Ventavis 10 and golden for a 5 µg dose with Ventavis 20.

Experience has been gained for more than 3 years in US since the marketing of Ventavis 20 µg/ml and it is used by a high rate of patients is US. The clinical experience to date confirms that this concentration may be a useful alternative for patients maintained at 5 µg but experiencing prolonged inhalation time with Ventavis 10 µg/ml

Discussion on the benefit-risk balance

The overall B/R of Ventavis 20 µg/ml is positive for the treatment of primary pulmonary hypertension in those patients maintained at the 5 mcg dose with Ventavis 10 µg/ml and who have repeatedly experienced extended treatment times which could result in incomplete dosing and provided the switch

from Ventavis 10 to Ventavis 20 is made under medical supervision in order to control the acute tolerance as stated in the SmPC.

4. Recommendations

Similarity with authorised orphan medicinal products

The CHMP by consensus is of the opinion that Ventavis is not similar to Revatio, Volibris, Opsumit, Adempas within the meaning of Article 3 of Commission Regulation (EC) No. 847/200. See appendix 1.

Outcome

Based on the CHMP review of data on quality, safety and efficacy, the CHMP considers by consensus that the risk-benefit balance of Ventavis, 20 microgram / ml nebuliser solution in the treatment of patients with primary pulmonary hypertension, classified as NYHA functional class III, to improve exercise capacity and symptoms is favourable and therefore recommends the granting of the marketing authorisation subject to the following conditions:

Conditions or restrictions regarding supply and use

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2)..

Conditions and requirements of the Marketing Authorisation

- **Periodic Safety Update Reports**

The marketing authorisation holder shall submit periodic safety update reports for this product in accordance with the requirements set out in the list of Union reference dates (EURD list)) provided for under Article 107c(7) of Directive 2001/83/EC and published on the European medicines web-portal.

Conditions or restrictions with regard to the safe and effective use of the medicinal product

- **Risk Management Plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the Marketing Authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

If the dates for submission of a PSUR and the update of a RMP coincide, they can be submitted at the same time.

Conditions or restrictions with regard to the safe and effective use of the medicinal product to be implemented by the Member States.

Not applicable.