EU RISK MANAGEMENT PLAN (RMP)

Ventavis (Solution for Inhalation)

BAY No. Q6256
(Iloprost aerosol nebulizer solution)

No. 9.0

Date of Report:
28 AUG 2025

Confidential

EU Risk Management Plan for Ventavis (Iloprost aerosol)

RMP version to be assessed as part of this application:

RMP Version number: 9.0

Data lock point for this RMP: 30 JUN 2025

Date of final sign-off: 28 AUG 2025

Rationale for submitting an updated RMP:

- An update of version 8.0 to version 9.0 is based on the recommendation in procedure No. EMEA/H/C/PSUSA/00001724/202309 to remove lower respiratory tract infections from the list of safety concerns and remove the use of iloprost specific targeted follow-up questionnaire to collect additional information for reports of LRTI from RMP.

Summary of significant changes in this RMP:

- Transfer to new integrated template of RMP as per Good Pharmacovigilance Practice (GVP) Module V Revision 2 (Rev.2) (2018)
- Removed lower respiratory tract infections (LRTIs) from the list of safety concerns and removed the use of iloprost specific targeted follow-up questionnaire for LRTIs and Follow-up questionnaire User Guidance for LRTIs. Applicable changes were performed to
    - Part I Table Part I.1–Product(s) overview updated.
    - Part II: Module SI: Epidemiology data updated
    - Part II: Module SII: No significant changes
    - Part II: Module SIII: Study details updated
    - Part II: Module SIV: No significant changes
    - Part II: Module SV: Post-authorisation exposure data included as of DLP 30 JUN 2025
    - Part II: Module SVI: No significant changes
    - Part II: Module SVII: Important potential risk has been removed as per the PRAC assessment report
    - Part II: Module SVIII: Important potential risk has been removed as per the PRAC assessment report
    - Part III: Removed Follow up Questionnaires for LRTIs.
    - Part IV: No changes
    - Part V: Only routine pharmacovigilance activities and risk minimisation measures are currently in place for iloprost trometamol.
    - Part VI: The important potential risk of LRTIs has been removed from the summary of safety concerns.
    - Part VII: Updated to align with the RMP updates.

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Other RMP versions under evaluation: Not applicable/None

Details of the currently approved RMP:

Version number: 8.0

CHMP positive opinion: 05 OCT 2020

EU commission approval: 29 OCT 2020

Approved with procedure: EMEA/H/C/000474/II/0066

Date of approval (opinion date): 06 AUG 2020

QPPV signature:

EU QPPV name	Dr. Jutta Pospisil
Contact person for this RMP	[redacted]
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Electronic QPPV signature is attached at the end of the document.

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List of abbreviations

%	Percent
µg	Microgram
<	Less than
>	Greater than
≥	Greater than or equal to
AAD	Adaptive Aerosol Delivery
AE	Adverse Event
AIR	Aerosolized Randomized Iloprost Study
Annex.	Annexure
APAH	Associated Pulmonary Arterial Hypertension
APAH-CTD	Associated Pulmonary Arterial Hypertension-Connective Tissue Disease
ATC	Anatomical Therapeutic Chemical Classification System
BMI	Body Mass Index
CHMP	Committee for Medicinal Products for Human Use
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CSR	Clinical Study Report
CTEPH	Chronic Thromboembolic Pulmonary Hypertension
dL	Deciliter
DLP	Data Lock Point
Dr.	Doctor
eCTD	electronic-Common Technical Document
EEA	European Economic Area

EMA	European Medicines Agency
EMEA	European Medicines Evaluation Agency
EPAR	European Public Assessment Report
ERA	Endothelin Receptor Antagonist
ERS	European Respiratory Society
ESC	European Society of Cardiology
EU	European Union
F	Female
FPAH	Familial Pulmonary Arterial Hypertension
GOT	Glutamic Oxaloacetic Transaminase
GPT	Glutamic Pyruvic Transaminase
GVP	Good Pharmacovigilance Practices
HMA	Heads of Medicines Agencies
HPAH	Heritable Pulmonary Arterial Hypertension
Inc	Incorporated
I-Neb	Iloprost Nebulizer
INN	International Non-proprietary Name
IPAH	Idiopathic Pulmonary Arterial Hypertension
iv	Intravenous
LRTI	Lower Respiratory Tract Infection
m	Meter
M	Male
MAH	Marketing Authorisation Holder
Max	Maximum

mg	Milligram
Min	Minimum
mL	Millilitre
mmHg	Millimetre of Mercury
mPAP	Mean Pulmonary Arterial Pressure
MSSO	Maintenance and Support Services Organization
No./N/n	Number
NYHA	New York Heart Association
p	Probability
PAH	Pulmonary Arterial Hypertension
PASS	Post-Authorisation Safety Study
PBRER	Periodic Benefit-Risk Evaluation Report
PDE-5I	Phosphodiestaras-5 Inhibitor
PE	Pulmonary Embolism
PGI2	Prostacyclin
pH	Potential for Hydrogen
PH/PHT	Pulmonary Hypertension
PH-CTD	Pulmonary Hypertension-Connective Tissue Disease
PH-LD	Pulmonary Hypertension-Lung Disease
PH-LVD	Pulmonary Hypertension-Left Ventricular Disease
PV	Pharmacovigilance
PK	Pharmacokinetic
PL	Product Leaflet
PPH	Primary Pulmonary Hypertension

PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
PSUSA	Periodic Safety Update Report Single Assessment
PT	Preferred Term
PPA	Pulmonary Artery Pressure
QPPV	Qualified Person Responsible for Pharmacovigilance
Ref.	Reference
Rev.2	Revision 2
REVEAL	Registry to Evaluate Early and Long-term Pulmonary Arterial Hypertension Disease Management
RMP	Risk Management Plan
RR	Research Report
SD	Standard Deviation
sGC	Soluble Guanylate Cyclase
SmPC	Summary of Product Characteristics
SMQ	Standardised MedDRA Query
SPH	Secondary Pulmonary Hypertension
US	United States
Venta-Neb	Ventavis Nebulizer
vs.	Versus

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Part I: - Product(s) overview

Part I: Product(s) overview

Table Part I.1 – Product(s) overview

Active substance(s) (INN or common name)	Iloprost trometamol
Pharmacotherapeutic group(s) (ATC Code)	B01AC11
Marketing Authorisation <Holder> <Applicant>	Bayer AG
Medicinal products to which this RMP refers	Nebuliser solution, 10 µg/mL Nebuliser solution, 20 µg/mL
Invented name(s) in the European Economic Area (EEA)	Ventavis
Marketing authorisation procedure	Centralized Procedure EU/1/03/255/001-014
Brief description of the product	Chemical class Iloprost, the active substance of Ventavis is a synthetic prostacyclin (PG I_2) analogue
	Summary of mode of action The following pharmacological effects have been observed *in vitro*: • Inhibition of platelet aggregation, platelet adhesion, and release reaction; • Dilatation of arterioles and venules; • Increase of capillary density and reduction of increased vascular permeability caused by mediators such as serotonin or histamine in the microcirculation. • Stimulation of endogenous fibrinolytic potential. The pharmacological effects after inhalation of Ventavis are: Direct vasodilatation of the pulmonary arterial bed with consecutive significant improvement of pulmonary artery pressure, pulmonary vascular resistance, and cardiac output as well as mixed venous oxygen saturation
	Important information about its composition: Iloprost trometamol Ethanol 96% Sodium chloride Hydrochloric acid (for pH adjustment) Water for injections
Hyperlink to the Product Information	EMEA/H/C/000474/N/0074, eCTD seq 0101
Indication(s) in the EEA	Current: Treatment of adult patients with primary pulmonary hypertension, classified as NYHA functional Class III, to improve exercise capacity and symptoms.

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Part I: Product(s) Overview

Table Part I.1 – Product(s) overview

	Proposed: Not applicable
Dosage in the EEA	Current: Solution for inhalation • Ventavis 10 µg/mL: 2.5 µg/5 µg at the mouthpiece, 6 - 9 times per day • Ventavis 20 µg/mL: 5 µg at the mouthpiece, 6-9 times per day
	Proposed: Not applicable
Pharmaceutical form(s) and strengths	Current: Nebulizer solution, 10 µg/mL Nebulizer solution, 20 µg/mL
	Proposed: Not applicable
Is/will the product be subject to additional monitoring in the EU?	No

Part II: Safety specification

Part II: Module SI-Epidemiology of the indication(s) and target population(s)

Epidemiology of the disease

- Incidence and prevalence
- Demographics of the target population–age, sex, race/ethnic origin.
- Risk factors for the disease
- Main treatment options
- Mortality and morbidity (natural history)

SI.1 Indications

Indication: Pulmonary hypertension

Ventavis is used in the treatment of moderate or severe stages of idiopathic pulmonary arterial hypertension (IPAH) and heritable pulmonary arterial hypertension (HPAH), Pulmonary arterial hypertension (PAH) associated with connective tissue disease, drug- or toxin-induced pulmonary arterial hypertension, and chronic thromboembolic pulmonary hypertension where surgery is not possible.

In the EU, Ventavis has the approved indication for the treatment of patients with primary pulmonary hypertension, classified as NYHA functional Class III, to improve exercise capacity and symptoms.

Pulmonary hypertension (PH) is a rare disease that is further sub-divided into five classes (Simonneau *et al.* 2009 (1)):

- Pulmonary arterial hypertension (PAH),
- Pulmonary hypertension due to left heart disease (PH-Left Ventricular Disease [PH-LVD]),
- Pulmonary hypertension due to lung disease and/or hypoxia (PH-LD)
- Pulmonary hypertension due to chronic thrombo-embolic disease (CTEPH).
- Pulmonary hypertension with unclear and/or multifactorial mechanisms

In a survey performed in an echocardiography laboratory amongst 483 PH patients, the large majority presented with left heart disease PH-LVD (79%) and 10% presented with PH-LD (Gabbay *et al.* 2007 (2)). In 7% it was not possible to define a diagnosis.

Pulmonary arterial hypertension and CTEPH cases were very rare in this survey (4.2% and 0.6%, respectively).

Pulmonary arterial hypertension is further divided into five sub-forms (Galie *et al.* 2009 (3)):

- Idiopathic (IPAH)
- Heritable
- Drug and toxins induced
- Associated PAH (APAH, secondary PAH)
- Persistent pulmonary hypertension of the newborn

Associated PAH is further divided into six classes, of which connective tissue disease associated PAH (APAH-CTD) is the most prominent form.

Ventavis has three indications amongst the different PAH forms:

Idiopathic PAH, drug associated PAH, and PAH secondary to connective tissue disease.

Incidence:

Pulmonary arterial hypertension incidence in cases per million adult populations were reported as 2.4 in France (Humbert *et al.* 2006 (4)); 7.6 in Scotland (Peacock *et al.* 2007 (5)); 3.5 in Switzerland (Tueller *et al.* 2008 (6)) The incidence of IPAH/HPAH and APAH in Sweden was reported as being 5 and 3 cases per million inhabitants and year, respectively (7). In South Korea, the incidence of PAH was estimated at 1.9 per million inhabitants and year (Chung *et al.* 2015 (8)).

Prevalence

Pulmonary arterial hypertension prevalence per million adult populations were reported to be 15 in France (Humbert *et al.* 2006 (4)); 26 in Scotland (Peacock *et al.* 2007 (5)); 15 in Switzerland (Tueller *et al.* 2008 (6)).

By extrapolation this would correspond to 3,600–6,200 cases each for Europe and the United States (US).

The Global Burden of Diseases study for PAH 1990-2021 reported that the global age-standardized prevalence of PAH has remained stable from 2.30 (1.87-2.82) per 100,000 population in 1990 to 2.28 (1.85-2.80) in 2021. Higher in females than in males (2·81 [2·29 - 3·46] *vs.* 1·75 [1·42–2·13] in 1990 and 2·75 [2·24–3·39] *vs.* 1·78 [1·44–2·17] in 2021, respectively) (9).

Prevalence of Ventavis PAH indications:

In the French study, 64% of the registered PAH cases corresponded to the three Ventavis indications with IPAH (39%), PH with connective tissue disease (PHCTD, 15%), and drug induced PAH (10%).

According to the US REVEAL PAH registry (Badesch *et al.* 2010 (10)), about 80% of PAH cases correspond to the three Ventavis PAH indications with IPAH (50%), PH-CTD (25%), and drug induced PAH (5%).

Therefore, 2,300–5,000 PAH cases are potentially indicated for Ventavis each in Europe and the US.

The prevalence of IPAH in Japan was reported as 7.5 per million (Satoh 2008 (11)). Assuming that IPAH accounts for 40%-50% of all PAH cases in Europe and the US, the Japanese PAH prevalence can be estimated to be similar to the European prevalence with around 15 per million populations. The prevalence of IPAH/HPAH and APAH in Sweden was reported to be 25 and 24 per million inhabitants, respectively (7).

Mortality in target indication: PAH mortality

Idiopathic PAH, familial and drug induced PH mortality

- Humbert *et al.* 2010 (12): Three year mortality is 42% in France (Data from 354 cases registered in 2002/2003).
- Kawut *et al.* 2003 (13): Three year mortality is 30% in the US (Data from 33 cases registered between 1997-2001).
- Jing *et al*. 2007 (14): Three year mortality is 39% in China (Data from 72 cases registered between 1999 and 2004).
- Rådegran *et al* 2016 (7): One-, 3- and 5-year mortality is 15%, 29% and 41%, respectively, in Sweden (Data from incident 457 cases registered between 2008 and 2014).

The Global Burden of Disease for PAH 1990-2021 analyses reported that the global age-standardized mortality attributed to PAH has remained slightly decreased from 0.35 (0.29 - 0.42) per 100,000 population in 1990 to 0.27 (0.23-0.32) in 2021. Similar in males and females from 1990-2021.(9).

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Part II: Module SI - Epidemiology of the indication(s) and target population(s)

Figure 1: Age-standardised mortality attributed to PAH by sex and region in 2021; error bars show 95% uncertainty intervals

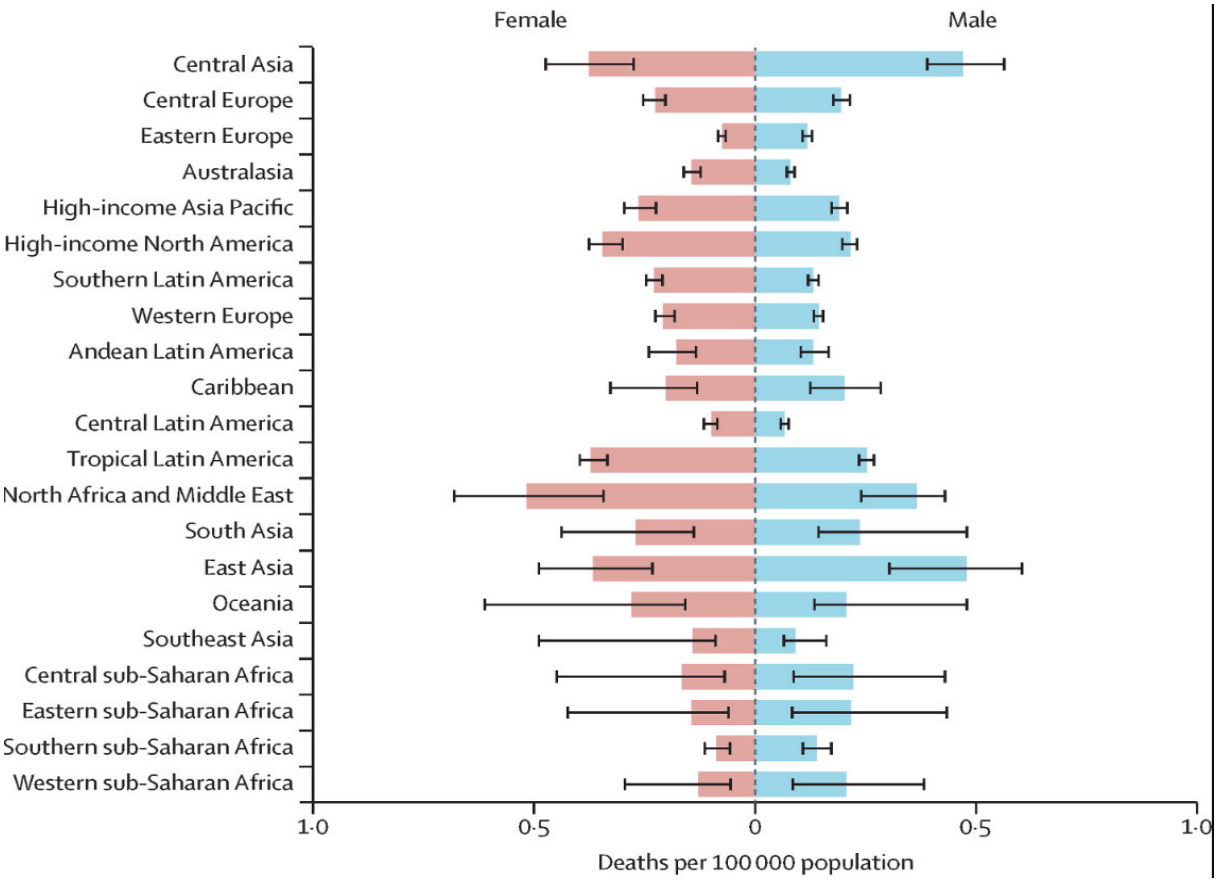

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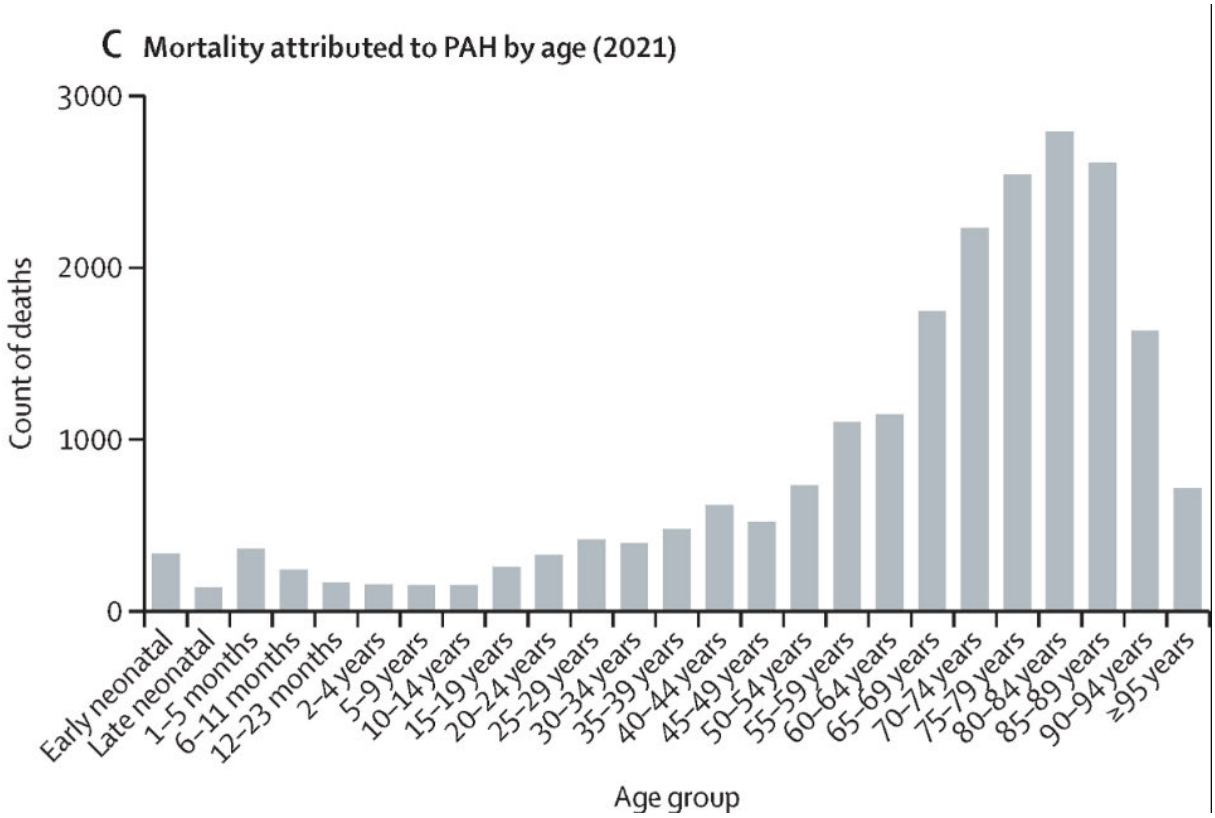
Figure 2-Total global deaths from PAH by age group in 2021



PH-CTD mortality

Kawut *et al.* 2003 (13): Three year mortality is > 80% in the US (Data from 22 PH-CTD cases registered between 1997-2001).

Demographic profile of target population PAH

Studies on PAH found more women affected than men (with female/male ratios of 2.3 and 1.9 and 1.4, respectively for Peacock *et al.* 2007 (5), Humbert *et al.* 2010 (12), and Tueller *et al.* 2008 (6)). The US registry for PAH patients found a female to male ratio of approximately 4 (Badesch *et al.* 2010 (10)). The Chinese registry found a female to male ratio of 2.4 (Jing *et al.* 2007 (14)).

Mean age of PAH patients recorded in the European studies was around 50 ± 15 years indicating that, PAH is a disease of all adult ages. In the US and Chinese patient registries age was 36 ± 1215 years. Where reported, the age distribution was similar in men and women.

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Figure 3-Age-standardised prevalence of PAH by sex and region in 2021; error bars show 95% uncertainty interval

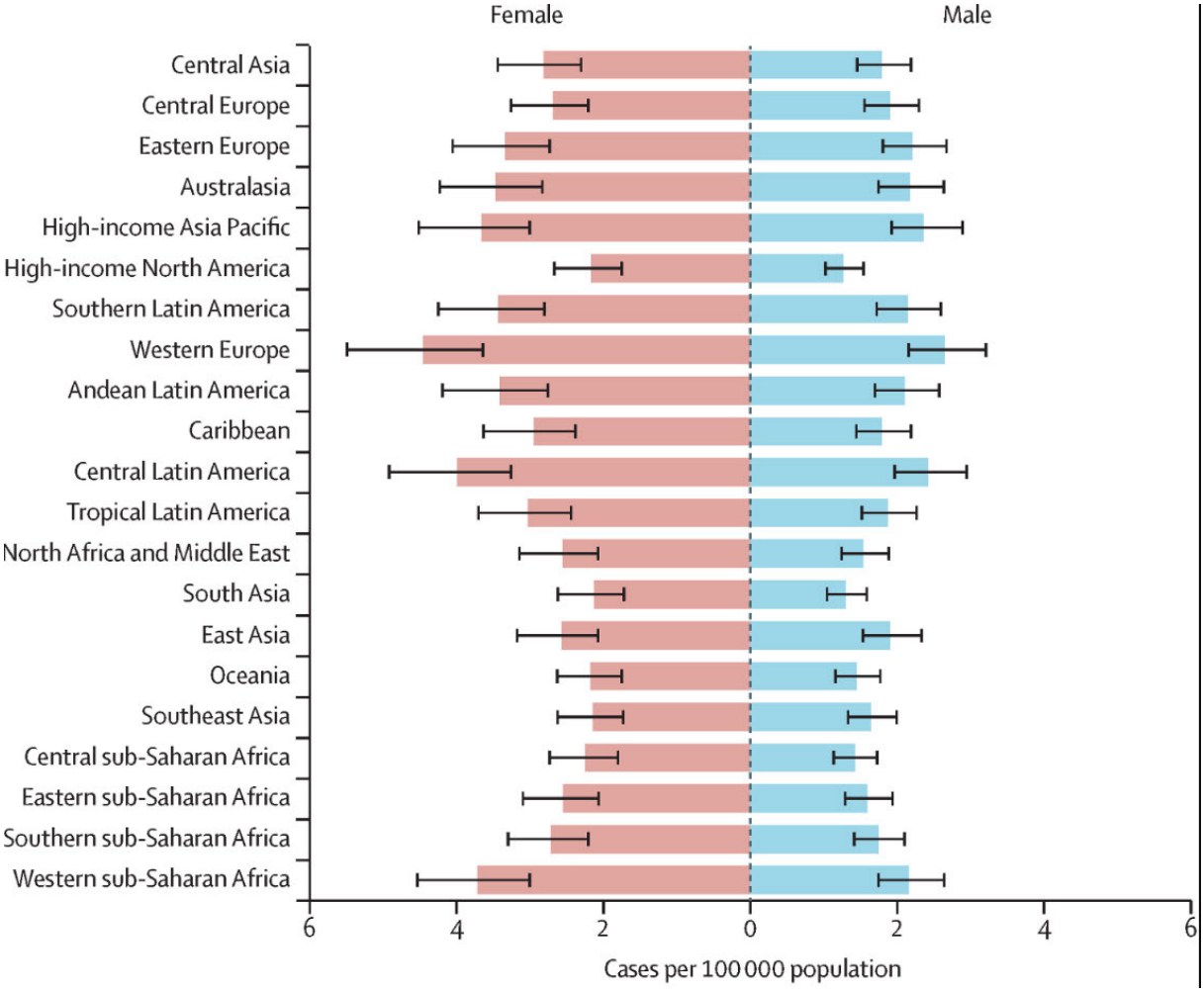

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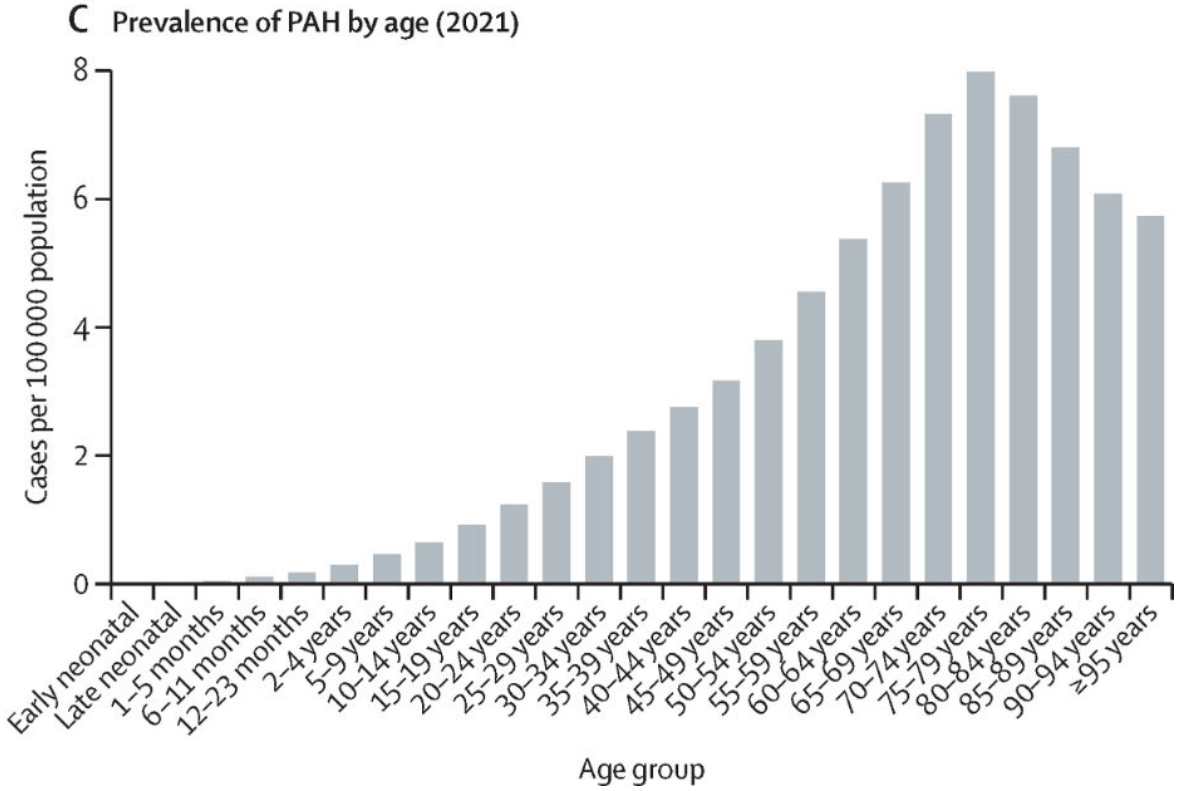
Figure 4-Global age-specific prevalence of PAH in 2021



Risk factors for the disease

Recognized risk factors for PAH include connective tissue diseases, Human immunodeficiency virus infection, portal hypertension, congenital heart disease, Schistosomiasis, chronic haemolytic anaemia-, and intake of several drugs known to induce PAH (e.g., Aminorex, Fenfluramine; Ref.: European Society of Cardiology guidelines [ESC] guidelines, Galie *et al.* 2009 (3)).

Treatment of moderate or severe chronic thromboembolic pulmonary hypertension (CTEPH), where surgery is not possible.

Incidence:

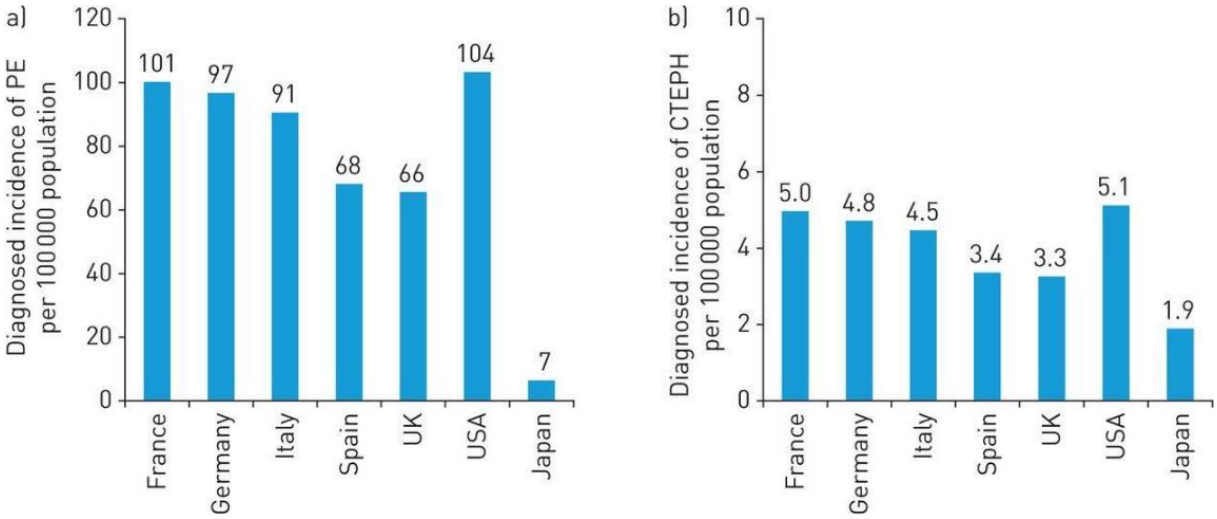
The cumulative incidence of CTEPH in the years following an acute pulmonary embolism (PE) was reported as 0.8%–5.1% in four publications from Italy and Sweden (Ribeiro 1999 (15), Pengo *et al.* 2004 (16), Becattini *et al.* 2006 (17), Miniati *et al.* 2006 (18)). The ESC (Galie *et al.* 2009 (3)) assume a cumulative incidence of 0.5%–2% in PE cases.

Incidence of CTEPH in data from a registry in Spain was 0.9 cases/per million per year (Perez-Ruiz *et al.* 2012 (19)).

Incidence of CTEPH in data from a registry in Spain was 0.9 cases/per million per year (Perez-Ruiz *et al*. 2012 (19)). In Sweden, CTEPH incidence was reported to be 2 per million inhabitants and year (Rådegran *et al*. (7)).

Gall *et al* 2017, conducted a literature review reported crude incidence rates of PE and CTEPH from Europe, USA, and Japan based on studies up to 2014.(20).

Figure 5-Annual diagnosed incidence of pulmonary embolism (PE), and annual full incidence of chronic thromboembolic pulmonary hypertension (CTEPH) per 100,000 population in Europe, the USA and Japan (crude rates for the year 2015)



Further this study, projected the full incidence and diagnosed incidence of CTEPH will increase from 32,636, and 5,334 in 2015 to 37,009 and 10,205 in 2025 in Europe, USA, and Japan.(20).

Prevalence of target indication:

Prevalence of CTEPH based on data from Spain was 3.2 cases per million adults (PerezRuiz *et al*. 2012 (19)).

A literature review by Gall *et al* 2017 reported proportion of patients in the region of Europe and USA who developed CTEPH following an episode of PE ranged from 0.1% to 9.1%, with a calculated weighted average of 4%. The estimate calculated for Japan was higher, with 10% of patients (20).

CTEPH mortality

- Riedel *et al*. 1982 (21): Three-year mortality was 50%85%, depending on the mean pulmonary artery pressure at diagnosis.
- Lewzuk *et al*. 2001 (22): Three-year mortality was 60% for patients with mean pulmonary artery pressure (PPA) > 30 mmHg.
- Perez-Ruiz *et al*. 2012 (19): One-, three-, and five-year survival were 87%, 75%, and 65%, respectively.

- Rådegran *et al.* 2016 (7): One-year, 3-year, and 5-year survival for patients with versus without pulmonary endarterectomy was 96%, 89%, and 86%, versus 91%, 75%, and 69%, respectively.

Demographic profile of CTEPH

Based on the data from the registry in Spain, mean age was 61 years and 40% of the patients were males. Similar findings were reported from the swiss registry with a proportion of males being 45% and an age distribution of 16% younger than 50 years of age and 84% older than 50 years (Tueller *et al*. 2008 (6)). Data from an international CTEPH registry reported a mean age of 63 years and a proportion of 50% males (Pepke-Zaba *et al*. 2011 (23)). The national Swedish Pulmonary Arterial Hypertension Register (SPAHR) reported a median age of 70 years among CTEPH patients, with the proportion of females being 50% (Rådegran *et al* 2016 (7)).

Risk factors for the disease

Conditions associated with an increased risk of CTEPH include previous splenectomy, the presence of a ventriculo-atrial shunt for the treatment of hydrocephalus, myeloproliferative disorders, and chronic inflammatory bowel diseases (Ref.: ESC guidelines, Galie *et al*. 2009 (3)).

In the EU CTEPH is not an approved indication for Ventavis.

Purpose of medicinal product

Ventavis is indicated for the treatment of moderate or severe stages of idiopathic pulmonary arterial hypertension (IPAH) and heritable pulmonary arterial hypertension (HPAH), Pulmonary arterial hypertension (PAH) associated with connective tissue disease, drug- or toxin-induced pulmonary arterial hypertension, and chronic thromboembolic pulmonary hypertension, where surgery is not possible. The purpose of the treatment with Ventavis is to improve exercise capacity and symptoms in patients with the mentioned conditions and in general to delay the progression of the disease.

Concomitant medication(s) in the target population

Specific PAH therapies are often administered as a combination treatment, therefore; Ventavis is often administered in combination treatment with Phosphodiestaras5 inhibitors (PDE-5Is) such as sildenafil or tadalafil and with Endothelin Receptor antagonists (ERAs) such as bosentan and ambrisentan and with soluble guanylate cyclase (sGC) such as riociguat or in combination with multiple classes of substances. The recently published 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension recommended that combination therapy may be applied sequentially or initially (24). As Ventavis is not metabolized *via* the Cytochrome P450 system, no drug-drug interactions are expected in combination with other specific PAH therapies.

In addition, supportive therapies are recommended are: Diuretic treatment in PAH patients with signs of right ventricular failure and fluid retention, and oral anticoagulant treatment in patients with IPAH, heritable PAH, and PAH due to use of anorexigens, as well as lifelong

anticoagulation in patients with CTEPH. Digoxin as supportive therapy may be considered in patients with PAH, who develop atrial tachyarrhythmias to slow ventricular rate.

Important co-morbidities found in the target population

Co-morbidities in PAH

(data from REVEAL registry–Badesch 2010 (10))

Idiopathic PAH:

Amongst 1,114 patients with IPAH, the following comorbidities were most common (>10%):

Hypertension (42%), obesity (Body Mass Index [BMI] > 30) (38%), sleep apnoea (27%), clinical depression (25%), obstructive airways disease (23%), hypothyroidism (20%), diabetes (14%), history of ischemic cardiovascular events (10%).

Associated PAH–Connective Tissue Disease (APAH-CTD)

Amongst 617 patients with APAH-CTD, the following comorbidities were most common (>10%): connective tissue disease (100%), hypertension (46%), obesity (BMI > 30) (25%), sleep apnoea (14%), clinical depression (26%), obstructive airways disease (23%), hypothyroidism (29%), history of ischemic cardiovascular events (10%).

Drug induced PAH

Amongst 132 patients with PAH-drug induced, the following comorbidities were most common (>10%): hypertension (41%), obesity (BMI > 30) (55%), sleep apnoea (29%), clinical depression (35%), obstructive airways disease (19%), hypothyroidism (22%), diabetes (13%).

Co-morbidities in CTEPH

The disease is associated with a history of acute pulmonary embolism.

Associated medical conditions in the data from the international CTEPH registry were (reported in > 10% of the patients): thrombophilic disorder in 31.9%, previous major surgery in 21.,7%, varicose veins in 20.8%, obesity in 17.6%, chronic venous insufficiency in 15.5%, prolonged hospitalization in 16%, history of cancer in 12.7%, coronary disease and/or myocardial infarction in 11.8% (Pepke-Zaba *et al*. 2011 (23)).

Part II: Module SII-Non-clinical part of the safety specification

Table Part II SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Systemic toxicity (single and repeat-dose) severe symptoms of intoxication (apathy, gait disturbances, postural changes) and lethality in iv single dose studies at dosages two orders of magnitude above human therapeutic doses • no off-target organ toxicity observed • exaggerated pharmacological effects like hypotension, vasodilation, reddening of skin, inhibition of platelet function, dyspnoea, and increased intestinal motility	• no acute toxicity expected due to safety margins to therapeutic dose. • exaggerated pharmacodynamics effects also to be expected in humans at higher dose levels.
Nephrotoxicity • no findings	• None
Hepatotoxicity • no findings	• None
Fertility • no effects on male and female fertility in rats with iv administration.	• no effects on fertility expected in humans.
Developmental toxicity • materno- and fetotoxic at high doses • no clear teratogenic effects observed in rats and rabbits • digit anomalies seen in rats in a few foetuses/pups after continuous iv administration without dose-dependency; assumed to be reversible • no such effects seen in rabbits and in monkeys	• unknown
Genotoxicity • no mutagenic potential observed in *in vitro* and *in vivo* studies.	• None
Carcinogenicity • no tumorigenic potential observed in tumorigenicity studies in mice and rats with oral administration of iloproste clathrate.	• no tumorigenic effects expected in humans even after chronic administration
General safety pharmacology • no additional relevant findings at therapeutic dose levels	• exaggerated pharmacodynamics effects also to be expected in humans at higher dose levels

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Part II: Module SII – Non-clinical part of the safety specification

Table Part II SII-1: Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Mechanisms for drug-drug interactions • no relevant non-clinical findings	• None
Transfer into mother's milk and through the placenta • extremely low levels of iloprost and/or metabolites are transferred into mother's milk in rats (less than 1% of dose administered intravenously) • in rats, minor amounts of iloprost and/or metabolites) are transferred through the placenta after iv administration	• unknown • placenta transfer might also be expected in humans
Sensitizing potential • no effects in guinea pigs	• None

iv: Intravenous; %: Percent

The human safety profile of iloprost is well characterised due to its long and safe use in humans, and no additional non-clinical studies are therefore planned.

Conclusions on non-clinical data

There are no missing non-clinical data due to the established human safety profile.
In developmental toxicity studies digit anomalies were seen in rats in a few foetuses/pups after continuous intravenous administration without dose-dependency; assumed to be reversible and related to hypoperfusion of the fetoplacental unit (no clear teratogenicity). No such findings were seen in rabbit or monkeys under iloprost exposure. During the post-marketing era increasing cases of beneficial outcome of iloprost exposure during pregnancy became available and no digit anomalies in the newborns were detected, which would suggest a safety concern of iloprost during pregnancy. The absolute contraindication was removed from the Summary of Product Characteristics (SmPC) and Ventavis may be administered during pregnancy based on a benefit-risk evaluation.

Part II: Module SIII - Clinical trial exposure

Brief overview of development

Primary pulmonary hypertension today referred to as Idiopathic and Heritable Pulmonary Arterial Hypertension (IPAH; HPAH) is a serious, life-threatening disease. Ventavis is an established treatment for PAH. The inhalable form has the advantage of selective deposition in the lungs to help reduce systemic pharmacological effects.

Iloprost, the active substance of Ventavis, is a synthetic prostacyclin analogue. The following pharmacological effects have been observed *in vitro*: inhibition of platelet aggregation, platelet adhesion and release reaction, dilatation of arterioles and venules, increase of capillary density, and reduction of increased vascular permeability caused by mediators such as serotonin or histamine in the microcirculation stimulation of endogenous fibrinolytic potential. The pharmacological effects after inhalation of Ventavis are direct vasodilatation of the pulmonary arterial bed occurs with consecutive significant improvement of pulmonary artery pressure, pulmonary vascular resistance, and cardiac output as well as mixed venous oxygen saturation. The haemodynamics observed suggest an acute response with preferential effect of inhaled treatment on the pulmonary vessels. The pulmonary vasodilatory effect of each single inhalation levels off within one to two hours.

The following clinical studies proving efficacy and leading to EMA approval and market authorisation were performed with Ventavis 10:

- An open-label, multicentre, Phase II clinical trial to investigate long-term safety of inhaled iloprost *vs*. standard therapy in 63 patients over two years (protocol ME98008, Research Report [RR] A02237). The study included a three month, two-arm, randomized, controlled phase. Olschewski *et al.*, 2010 (25).
- A device comparison study (protocol ME98051, RR AX15) assessed the hemodynamics as well as pharmacokinetics after administration of single doses of inhaled iloprost using three different inhalation devices in a cross-over design. The study also demonstrated comparability of the inhalation device used in the Phase II study (Ilo-Neb by Nebu-Tec) and the HaloLite device used in the Phase III study. Olschewski *et al.*, 2003 (26).
- One placebo-controlled, double-blind, randomized multicentre Phase III study in 203 patients (protocol ME97218/300180, RR A02997) to investigate the efficacy, safety, and tolerability of inhaled iloprost therapy over 12 weeks added to common background therapy. Olschewski *et al*, 2002 (27).
- A long-term follow-up surveillance study (protocol ME303045) performed after the end of the Phase III study in some countries. Safety data served as supportive in terms of long-term use of inhaled iloprost after the end of the Phase III study (Not published).

The first marketing authorisation for Ventavis 10 µg/mL was granted in the EU on 16 SEP 2003, and the first launch was in 2003 in France and Ireland.

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Ventavis 10 is authorised to be marketed in 73 countries and is marketed in 60 countries as of data lock point (DLP) 30 JUN 2025.

Ventavis is indicated for the treatment of moderate or severe stages of idiopathic pulmonary arterial hypertension (IPAH) and heritable pulmonary arterial hypertension (HPAH), Pulmonary arterial hypertension (PAH) associated with connective tissue disease, drug- or toxin-induced pulmonary arterial hypertension, and chronic thromboembolic pulmonary hypertension where surgery is not possible.

The approved product is dispensed in glass ampoules containing 10 µg/mL iloprost. Patients self-administer the product six to nine times daily using the approved pulmonary drug delivery devices including: HaloLite, Prodose, Venta-Neb or I-Neb, although HaloLite and Prodose are no longer commercially available. HaloLite, Prodose, and Venta-Neb are used with 2 mL ampoules of Ventavis. The I-neb AAD (Adaptive Aerosol Delivery) System, the portable nebulizer of Philips-Respironics, Inc. is used with 1 mL ampoules. The nebulizers deliver the approved dose of either 2.5 or 5 µg iloprost at mouthpiece per inhalation session. The inhalation time ranges from four to 10 minutes per inhalation session for the 2.5 or 5 µg dose (six to nine times per day).

Post-marketing clinical experience, however; indicated that patients may experience prolonged inhalation times which are accompanied with an increasing number of incomplete inhalation sessions and a reduced compliance. Thus, a higher concentration of Ventavis with 20 µg iloprost/mL (10 µg/0.5 mL) was developed for patients on the 5 µg dose with prolonged inhalation times to reduce the inhalation time by maintaining the approved 5 µg/mL dose at the mouthpiece.

Ventavis 20 µg/mL nebuliser solution is used with the I-neb nebulisation device together with a medication chamber designed to deliver the approved 5 µg dose. This would give patients who are maintained on the 5 µg dose, especially those for whom compliance is affected due to extended inhalation duration using the 10 µg/mL concentration, the option of shortening their drug delivery time, and therefore, aiming to achieve the targeted drug exposure in due inhalation time. The proposed higher concentration of the iloprost solution does not affect the functional characteristics of the device (I-neb AAD System) or its components. Compared to the 10 µg/mL solution Ventavis 20 µg/mL solution will require half the volume to be nebulized in about half the amount of time in order to receive the same 5 µg at the mouthpiece.

In 2012, Bayer AG completed a pharmacokinetic (PK) study comparing Ventavis 10 *vs.* 20 µg/mL.

The first marketing authorisation for Ventavis 20 was granted in the US on 07 AUG 2009, and the marketing authorisation in the EU was granted on 18 JUL 2014. The first launch was in SEP 2009 in the US. Ventavis 20 is authorised to be marketed in 38 countries and is marketed in 14 countries as of 31 AUG 2019. Actelion Pharmaceuticals Inc. is the NDAholder for Ventavis in the US.

Ventavis 20 is indicated for PAH patients, who are maintained at the 5 µg dose and who have repeatedly experienced extended treatment times, which could result in incomplete inhalation.

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To provide patients with an option of a reduced inhalation time, it was decided to develop a new nebulizing device for the inhalation of Ventavis. The Phase I/IIa study (16483) was designed to investigate the possibility of using an alternative device (the FOXnebulizer, brand name Breelibwhich allows a more rapid administration, within approximately three minutes, potentially enhancing acceptance by patients and thus improving treatment compliance. The study compared the acute tolerability and the PK of iloprost as administered by the two nebulizing inhalers (Bayer study 16483, Study Report No. PH-38603).

The currently widely used I-Neb adapts iloprost aerosol release to the patient's breathing pattern. In contrast, the newly developed Breelib nebulizer (below simply referred to as Breelib) controls the patient's inhaled volume and flow rate and guides the patient to a steady inhalation.

Clinical Trial exposure

Pulmonary arterial hypertension is a rare disease that affects a small percent of the population (orphan indication); thus, the conduction of a large-scale clinical trial programs is impeded.

The main pivotal study focused on patients with primary or secondary pulmonary hypertension presenting with NYHA functional Class III or IV at study enrolment with a mean pulmonary artery pressure (mPAP) at time of enrolment of ≥ 30 mmHg at rest. Patients with secondary pulmonary hypertension were only included, if the underlying cause was one of the following:

Chronic thromboembolic pulmonary hypertension which was not anatomically operable, connective tissue disease with isolated PHT or interstitial pulmonary disease drug-associated PHT (e.g., due to fenfluramine)

The following relevant prospective clinical studies during the pre-authorisation phase were conducted in the scope of the Bayer AG development program:

- **Study 98008:** An open-label, multicentre, Phase II clinical trial to investigate long-term safety of inhaled iloprost *vs*. standard therapy in 63 patients (protocol ME98008, RR A00794). The study included a three-month, two-arm, randomized, controlled phase followed by a two-year open-label long-term safety phase.
- **Study 97218:** The main pivotal placebo-controlled, double-blind, randomized multicentre Phase III study in 203 patients (protocol ME97218/300180, RR A02237) investigated the efficacy, safety, and tolerability of inhaled iloprost therapy over 12 weeks added to common background therapy.
- **Study 303045:** A long-term follow-up surveillance study (protocol ME303045, RR A31289) performed after the end of the Phase III study in 71 eligible patients in some countries up to 265 weeks until approval/re-imbursement in the respective country.

For the development of Ventavis in Japan a Phase I (Study 15266) and Phase III (Study 15503) were conducted.

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For Ventavis 20 µg/mL formulation one Phase I study to compare pharmacokinetic parameters following the administration of 5 µg iloprost by inhalation of two Ventavis solutions (10 µg/mL vs. 20 µg/mL) using the I-Neb nebulizer was completed.

Study 16483: A Phase I/IIa, multicentre, open-label, randomized cross-over study to compare the acute tolerability and pharmacokinetics of iloprost inhalation using the I-neb nebulizer (used with Ventavis 10) and the FOX nebulizer (used with Ventavis 20 for dose of 5 µg, with Ventavis 10 for the dose of 2.5 µg) in patients with PAH.

For the post-marketing- non-interventional PASS study, please refer to the **Epidemiological study exposure** section.

A summary of relevant Bayer AG/Co-Therix sponsored studies with inhaled iloprost during the clinical study program (pre-authorisation phase), and during the post-marketing- *era* are shown in Table Part II SIII-1.

Studies performed by Actelion Pharmaceuticals Inc. are not addressed in this RMP.

Table Part II SIII-1: Overview clinical studies in the pre-and post-authorisation phase

Study No.	Total No. of patients	Duration of treatment	Median dose and dose range
PRE-AUTHORISATION			
ME98051/AX15 (completed) (device comparison study)	13	One day	Inhaled dose of 5 µg per inhalation one inhalation with each device
ME98008/A02237 (Phase II study) (completed)	63 (40 PPH, 23 SPH)	Up to 19 months	Nominal daily dose filled into the nebulization chamber of 100 µg (range 50 to 200 µg) divided into six inhalations per day (range three to 12)
ME97218/300180/A02297 (Phase III [AIR] study) (completed)	203 (108 PPH, 95 SPH)	12 weeks	Inhaled daily dose of 30 µg (range 15 to 45 µg) divided into six inhalations per day (range five to nine)
ME303045 Long-term surveillance study (completed)	71	Up to 265 weeks (until approval or re-imbursement)	Inhaled daily dose of 30 µg (range 15 to 45 µg) divided into six inhalations per day (range six to nine)
7564-100/CSR 7564-100 C200-004 QT study in healthy volunteers (CoTherix) (completed)	160	One day	Inhaled iloprost, 6 x 2.5 µg every two hours or-ascending doses every two hours x six doses (5µg + 7.5 µg + 10 µg + 12.5 µg + 15 µg + 20 µg = 70 µg total exposure)

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Table Part II SIII-1: Overview clinical studies in the pre-and post-authorisation phase

Study No.	Total No. of patients	Duration of treatment	Median dose and dose range
POST-AUTHORISATION			
Phase I, 352120 (15266) (completed)	23 (12 Japanese, 11 Caucasian), of these six placebo and17 verum	Two inhalations	Two single doses of 2.5 µg and 5.0 µg BAYQ006256 (at the mouthpiece of the nebulizer) were inhaled to the subjects randomized to BAYQ006256 arm
Phase III, 15503 (completed)	27 subjects	Main Treatment Phase: 12 weeks Extension Phase: 40 weeks (If requested, until the first marketing approval)	Initial dose: 2.5 µg BAYQ006256 per inhalation session Dose will be increased to 5.0 µg according to the individual tolerability. Inhalation session (approximately four to 10 minutes) is to be conducted six to nine times per day with dosing intervals of at least two hours.
Phase I, 15762 (completed)	20 healthy male subjects (18 valid subjects)	Two inhalations	Comparison of pharmacokinetic (PK) parameters following administration of 5 µg iloprost by inhalation of two Ventavis solutions (10 µg/mL *vs*. 20 µg/mL) using the I-Neb nebulizer.
Phase I/IIa, 16483 (completed)	24 subjects with PAH	Two weeks	Comparison of acute tolerability and pharmacokinetics of iloprost inhalation using the I-neb nebulizer (used with Ventavis 10) and the FOX nebulizer (used with Ventavis 20 for dose of 5 µg, with Ventavis 10 for the dose of 2.5 µg)

µg: Microgram; AIR: Aerosolized Randomized Iloprost Study; CSR: Clinical Study Report; PAH: Pulmonary Hypertension; PK: Pharmacokinetic; PPH: Primary Pulmonary Hypertension; SPH: Secondary Pulmonary Hypertension.

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Table Part II SIII-2: Estimated cumulative subject exposure up to 15 SEP 2015 of Bayer sponsored- studies (including ongoing studies)

Trial (Status)	Design/phase	Number of subjects/patients		
		Iloprost	Placebo	Comparator
ME98051 (completed)	Open label, randomized, crossover/Phase I	13		
7564-100/C200-004 (completed)	Placebo- and positive-controlled/Phase I	80	40	40
ME98008 (completed)	Open-label, multicentre, randomized, parallel-group, comparative/Phase II			
	Week 12 (n = 63)	30	33[a]	
	Long-term (n = 52)	52[b]		
ME97218 (AIR) (completed)	Double-blind, randomized, parallel-group, comparative/Phase III	101	102	
ME303045 (completed)	Open-label extension follow-up of study ME97218/AIR	71[c]		
352120 (15266) (completed)	Single-centre, randomised, single-blind, placebo-controlled, dose-escalation study/Phase I	17	6	
15762 (completed)	Randomized, open-label, single centre, crossover study with two periods, two treatments and two sequences; wash-out between treatments: at least 24 hours/Phase I	20[d](18)	-	-
15503 (completed)	Non-randomized, open label, single-arm, and multi-centre study/Phase III	27	-	-

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Table Part II SIII-2: Estimated cumulative subject exposure up to 15 SEP 2015 of Bayer sponsored- studies (including ongoing studies)

Trial (Status)	Design/phase	Number of subjects/patients		
		Iloprost	Placebo	Comparator
16483 (completed)	Multi-center, open-label, randomized cross-over study to compare the acute tolerability and pharmacokinetics of iloprost inhalation using the I-neb nebulizer and the FOX nebulizer in patients with PAH	24	-	-

[a] Conventional therapy
[b] Includes 22 subjects from the iloprost group and 30 from the conventional therapy group à a total of 60 subjects have received iloprost in trial ME98008
[c] Includes 40 subjects from the iloprost group and 31 from the placebo group from study ME97218 (AIR), a total of 132 subjects have received iloprost in trials ME97218 and ME303045
[d] Minimum number of subjects with valid PK profiles Treatment and 20 Subject is participated in study
AIR: Aerosolized Randomized Iloprost Study, PAH: Pulmonary Arterial Hypertension,
PASS: Post-Authorisation Safety Study, n: number

Main clinical trial exposure of relevant pre-authorisation studies is shown below. Pooled exposure data is displayed for studies 98008, 97218, and 303045. The post-authorisation safety study is displayed separately in the **Epidemiological study exposure** section.

Pooled exposure data studies 98008, 97218 and 303045 (safety analysis sets):

Patient Demographics:

A total of 192 patients were exposed to Ventavis, 61 were male and 131 were female. The age ranged from 20 to 78 years (mean age was 50.5 years). 87% of the patients were <65 years of age. As the majority of patients were below the age of 65 years, the use of Ventavis in the elderly population is considered missing information.

About 56.3% had primary pulmonary hypertension and 43.8% had secondary pulmonary hypertension.

Table Part II SIII-3: Demographics (safety analysis set)

Pool: A02237, A02997, A31289 (98008, 97218, 303045): Ventavis only	Ventavis N = 192 (100%)
Sex	
M	61 (31.8%)
F	131 (68.2%)
Race	
WHITE	189 (98.4%)
BLACK OR AFRICAN AMERICAN	3 (1.6%)
Ethnicity	
NOT REPORTED	192 (100.0%)

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Table Part II SIII-3: Demographics (safety analysis set)

Pool: A02237, A02997, A31289 (98008, 97218, 303045): Ventavis only	**Ventavis N = 192 (100%)**
Age (YEARS)	
n	192
Mean	50.5
SD	13.0
Min	20
Median	54.0
Max	78
Age Range 1	
<65 YEARS	167 (87.0%)
≥65-< 75 YEARS	24 (12.5%)
≥75 YEARS	1 (0.5%)
Diagnosis Group 1	
PRIMARY PULMONARY HYPERTENSION (PPH)	108 (56.3%)
SECONDARY PULMONARY HYPERTENSION (SPH)	84 (43.8%)

%: Percent; M: Male, F: Female, N/n: Number, SPH: Secondary Pulmonary Hypertension, SD: Standard Deviation, Min: Minimum, Max: Maximum.

Extent of exposure

The data below displays specifics on those patients that were actually exposed to Ventavis therapy.

More than 100 patients were exposed to Ventavis therapy for six months.

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Table Part II SIII-4: Duration of exposure (safety analysis set)

Pool: A02237, A02997, A31289 (98008, 97218, 303045): Ventavis only		
Duration of Exposure (at least)	**Persons**	**Person Time [years]**
Missing	3	
1 day	189	248.556
1 month	183	248.323
2 months	175	247.305
3 months	131	237.06
6 months	104	229.04
12 months	85	215.904
18 months	70	197.936
24 months	39	141.99
36 months	25	111.466
48 months	18	87.773
Total person time		**248.556**

Note: For calculation a month equals 30.4375 days and a year equals 365.25 days.
The following subjects have missing duration of exposure: 98008-000248, 98008-000249, 98008-000602

The majority of patients who were exposed to Ventavis were less than 65 years of age.

Fifty-nine were male and 130 were female.

Table Part II SIII-5: Exposure by age and gender (safety analysis set)

Pool: A02237, A02997, A31289 (98008, 97218, 303045): Ventavis only				
Age Range 1	**Persons**		**Persons Time [years]**	
	M	**F**	**M**	**F**
<65 YEARS	52	112	82.5	125.142
≥65-< 75 YEARS	7	17	11.211	27.918
≥75 YEARS	0	1	0	1.785
TOTAL	59	130	93.711	154.845

M: Male, F: Female
Note: For calculation a month equals 30.4375 days and a year equals 365.25 days.
Subjects with missing duration of exposure are not displayed.

The majority of exposed patients were of Caucasian origin.

Table Part II SIII-6: Exposure by race and ethnicity (safety analysis set)

Pool: A02237, A02997, A31289 (98008, 97218, 303045): Ventavis only			
Race	**Ethnicity**	**Persons**	**Person Time [years]**
WHITE	NOT REPORTED	186	243.461
BLACK OR AFRICAN AMERICAN	NOT REPORTED	3	5.095

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Table Part II SIII-6: Exposure by race and ethnicity (safety analysis set)

Pool: A02237, A02997, A31289 (98008, 97218, 303045): Ventavis only			
Race	**Ethnicity**	**Persons**	**Person Time [years]**
TOTAL		**189**	**248.556**

M: Male, F: Female
Note: For calculation a month equals 30.4375 days and a year equals 365.25 days.
Subjects with missing duration of exposure are not displayed.

Special populations

Patients with renal and hepatic impairment were considered as special populations. Fourteen patients with renal and 64 patients with hepatic impairment were treated with Ventavis.

Due to limited exposure data of Ventavis in patients with renal and severe hepatic impairment, these populations are considered missing information for the use of Ventavis.

Table Part II SIII-7: Exposure in special populations (safety analysis set)

Pool: A02237, A02997, A31289 (98008, 97218, 303045): Ventavis only		
Special Population	**Persons**	**Person Time [years]**
Renal Impairment	14	12.663
Hepatic Impairment	64	71.852

Note: For calculation a month equals 30.4375 days and a year equals 365.25 days.
Note: Subjects with missing duration of exposure are not displayed.
Note: Renal impairment was identified by MSSO SMQs “Chronic kidney disease” or “Acute renal failure.”
Note: Hepatic impairment was identified by MSSO SMQ “Hepatic disorders.”

Epidemiological study exposure

In the EU one PASS study 308120 (post approval commitment) was recently completed. This was an open-label, uncontrolled, multicentre, international, post-marketing surveillance study in patients with primary pulmonary hypertension inhaling Ventavis with a follow-up duration of up to four years. Primary objective was to observe clinical effects, safety and tolerability, and survival during long-term Ventavis inhalation therapy over at least two years and up to four years. Subjects with PPH (i.e., IPAH or FPAH), classified as NYHA functional Class III, where the treating physician had already chosen Ventavis as a suitable long-term treatment, were enrolled.

Demographics:

The table below displays the demographics of patients suitable for safety analysis (N = 102). Not all patients of the safety analysis set were treated with iloprost (99 out of 102 patients of the safety analysis set were treated, see sections below).

Out of 102 patients, 36 were male and 66 were female. Age ranged from 22 to 86 years (mean 59.8 years of age). The majority of patients were below 65 years of age (52%).

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Table Part II SIII-8: Demographics (safety analysis set)

Study: A59320 (308120)	Ventavis N = 102 (100%)
Sex	
M	36 (35.3%)
F	66 (64.7%)
Race	
WHITE	100 (98.0%)
BLACK OR AFRICAN AMERICAN	1 (1.0%)
OTHER	1 (1.0%)
Ethnicity	
HISPANIC OR LATINO	1 (1.0%)
NOT REPORTED	101 (99.0%)
Age (YEARS)	
n	102
Mean	59.8
SD	15.2
Min	22
Median	63.5
Max	86
Age Group 1	
<65 YEARS	53 (52.0%)
≥65-< 75 YEARS	35 (34.3%)
≥75 YEARS	14 (13.7%)
Diagnosis Group 1	
PRIMARY PULMONARY HYPERTENSION (PPH)	102 (100.0%)

%: Percent, M: Male, F: Female, N/n: Number, PPH: Primary Pulmonary Hypertension, SD: Standard Deviation, Min: Minimum, Max: Maximum.

Extent of exposure

The tables below display the data for patients that were actually exposed to Ventavis.

Seventy-five patients were exposed to Ventavis up to six months. 18 patients were treated for 36-months, four patients reached a treatment duration of 48 months.

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Table Part II SIII-9: Duration of exposure (safety analysis set)

Study: A59320 (308120)		
Duration of Exposure (at least)	**Persons**	**Person Time [years]**
Missing	3	-
1 day	99	170.56
1 month	90	170.168
2 months	84	169.435
3 months	78	168.227
6 months	74	166.954
12 months	60	156.071
18 months	53	147.578
24 months	42	126.453
36 months	18	64.496
48 months	4	17.38
Total person time (years)	**-**	**170.56**

Note: For calculation a month equals 30.4375 days and a year equals 365.25 days.
The following subjects have missing duration of exposure: 308120-208001, 308120-212003, 308120-304002

A total of 99 patients were actually exposed to Ventavis treatment. Of these, 36 were male, 63 were female. The majority was below 65 years of age.

Table Part II SIII-10: Exposure by age and gender (safety analysis set)

Study: A59320 (308120)	**Persons**		**Person Time [years]**	
Age Range 1	**M**	**F**	**M**	**F**
<65 YEARS	14	36	30.815	44.679
≥65-< 75 YEARS	14	21	28.142	44.884
≥75 YEARS	8	6	15.206	6.834
TOTAL	**36**	**63**	**74.163**	**96.397**

M: Male, F: Female
Note: For calculation a month equals 30.4375 days and a year equals 365.25 days.
Subjects with missing duration of exposure are not displayed.

The majority of patients were of Caucasian origin.

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Table Part II SIII-11: Exposure by race and ethnicity (safety analysis set)

Study: A59320 (308120)			
Race	**Ethnicity**	**Persons**	**Person Time [years]**
WHITE	NOT REPORTED	97	170,437
BLACK OR AFRICAN AMERICAN	NOT REPORTED	1	0.099
OTHER	HISPANIC OR LATINO	1	0.025
TOTAL		**99**	**170.56**

M: male, F: female
Note: For calculation a month equals 30.4375 days and a year equals 365.25 days.
Subjects with missing duration of exposure are not displayed.

A total of 27 patients treated with inhaled iloprost had renal impairment, and 16 patients had hepatic impairment. Both are considered missing information with the use of Ventavis as available data is limited.

Table Part II SIII-12: Exposure in special populations (safety analysis set)

Study: A59320 (308120)		
Special Population	**Persons**	**Person Time [years]**
Renal Impairment	27	35,754
Hepatic Impairment	16	27,608

Note: For calculation a month equals 30.4375 days and a year equals 365,25 days.
Note: Subjects with missing duration of exposure are not displayed.
Note: Renal impairment was identified by MSSO SMQs “Chronic kidney disease” or “Acute renal failure”.
Note: Hepatic impairment was identified by MSSO SMQ “Hepatic disorders”.

Part II: Module SIV - Populations not studied in clinical trials

SIV.1. Exclusion criteria in pivotal clinical studies within the development program

The following exclusion criteria are listed as contraindication in the SmPC based on the clinical studies summarized below and post-marketing experience.

- Hypersensitivity to the active substance or to any of the excipients;
- Conditions where the effects of Ventavis on platelets might increase the risk of haemorrhage (e.g., active peptic ulcers, trauma, intracranial haemorrhage);
- Severe coronary heart disease or unstable angina;
- Myocardial infarction within the last six months;
- Decompensated cardiac failure if not under close medical supervision;
- Severe arrhythmias;
- Cerebrovascular events (e.g., transient ischaemic attack, stroke) within the last three months;
- Pulmonary hypertension due to venous occlusive disease;
- Congenital or acquired valvular defects with clinically relevant myocardial function disorders not related to pulmonary hypertension.

Main categories of exclusion criteria in the clinical trial program are summarized as "Warnings and precautions" in Section 4.4. of the SmPC as the following can be monitored, the dose adjusted, or the treatment stopped:

- Hepatic and renal impairment
- Respiratory diseases such as asthma or Chronic Obstructive Pulmonary Disease [COPD]
- Patients with low blood pressure.

Former clinical exclusion criteria are also included in Section 4.5. "Interaction with other medicinal products and other forms of interaction" of the SmPC.

- Interaction with anti-hypertensives (risk of hypotension) or anticoagulants (risk of bleeding) can be monitored, the dose adjusted, or treatment be stopped.

Conditions associated with increased bleeding risk should be also closely monitored.

Pregnant and lactating women were excluded from the clinical trial program. The absolute contraindication for Ventavis during pregnancy and lactation was removed; however, the data from the use of iloprost in pregnant women is limited during the post-marketing experience. Taking 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.

Regarding breastfeeding it is not known whether iloprost/metabolites are excreted in human breast milk. The absolute contraindication was lifted, however; a potential risk to the breastfeeding child cannot be excluded, and it is preferable to avoid breast-feeding during Ventavis therapy.

Both the use of Ventavis during pregnancy and lactation are considered missing information.

SIV.2. Limitations to detect adverse reactions in clinical trials development programmes

Limitations of the human safety database

Overall, limitations of the database are the limited sample size of the clinical studies performed in an orphan and life-threatening disease. For ethical reasons, the life-threatening nature of the disease does not allow for a longer placebo-controlled phase, and the rarity does not allow larger patient numbers to be included. Therefore, with regard to suspected long-term adverse reactions (e.g., malignancies) it is unlikely that exposure data is of sufficient duration and latency. The limited size of the clinical trial safety database in this orphan indication limits the power to detect uncommon adverse reactions in a controlled study set up.

SIV.3. Limitations in respect to populations typically under-represented in clinical trial development programmes

SIV.3.1. Children

Children were not investigated in controlled clinical studies.

The experience in children and adolescents (patients below 18 years of age) is limited. Ventavis is not recommended for use in this population.

SIV.3.2. Elderly

No pharmacokinetic data are available in elderly patients.

There is no need for a laboratory screening prior to the use of Ventavis.

In the largest pivotal AIR study patients at the age between 1870 years were included ME97218/300180/A02297); therefore, only limited experience exists of effects in elderly patients from clinical trials.

No specific safety concerns arose from post-marketing case reports in the elderly population.

SIV.3.3. Pregnant or breast-feeding women

No pregnancy occurred during the clinical trial program.

Pulmonary hypertension is a life-threatening disease and physiologic hemodynamic changes during pregnancy pose an additional circulatory burden with exacerbating potential. Therefore, pregnancy in women with PAH is related with a high mortality due to pregnancy associated hemodynamic changes.

As the risk for the women remains high, the consensus views from the Study Group of the Royal College of Obstetricians and Gynaecologists recommend that, patients should be advised of the very high-risk pregnancy represents (30%-50% mortality) and be given clear advice about contraception. It is stated that pulmonary arterial vasodilator therapy during pregnancy may improve the chances of maternal survival. However, safe treatment options during pregnancy are limited in light of the frequent need of combination therapy.

In this context Ventavis might pose a useful treatment option due to its pulmonary selectivity *via* the inhalative application route and only short-lasting systemic exposure. To date, 51 women were exposed to either inhaled or intravenous iloprost during their pregnancy. In the cases reviewed different triggers initiated inhaled iloprost therapy, i.e., the preventive use in case of symptomatic pregnancy in medical history, deterioration of PAH during pregnancy, treatment of pregnancy-induced PH, and replacement of potentially harmful other PAH treatment. Inhaled iloprost has been used successfully to manage these pregnant women with PAH although reporting bias in the sense of publishing clinical experience with mainly beneficial outcome cannot be excluded. However, the overall number of pregnancy reports with iloprost treatment can be regarded as rather high on the basis of the rare incidence of the disease.

So far, there were three maternal deaths postpartum and no maternal death during the pregnancy. This is regarded as beneficial outcome considering the poor maternal prognosis during pregnancy. More importantly no digit anomalies, which were seen in rare incidences in preclinical reproduction toxicity studies with intravenous iloprost, were detected in any human newborn who's mother was exposed to inhaled iloprost during pregnancy. Moreover, explicit recovery of intrauterine growth retardation was reported under iloprost therapy.

Overall, from the review of post-marketing case reports on pregnant women who administered iloprost no variation in benefit or risk from overall target population could be observed.

SIV.3.4. Patients with hepatic impairment

In patients with liver cirrhosis the clearance of iloprost is reduced by a factor of 2 to 4 after intravenous infusion of iloprost (Hildebrandt *et al*. 1990 (28)). To avoid undesired accumulation over the day, special caution should be exercised with these patients during initial dose titration. Initially, doses of 2.5 µg should be administered with dosing intervals of at least 3-4 hours (corresponds to administration of max. six times per day). Thereafter, dosing intervals may be shortened cautiously based on individual tolerability. If a further increase in the dose up to 5.0 µg is indicated, again dosing intervals of at least 3-4 hours should be chosen initially and shortened according to individual tolerability. A further undesired accumulation of the medicinal product following treatment over several days is not likely due to the overnight break in administration of the medicinal product.

Patients with severe hepatic failure (Glutamic Oxaloacetic Transaminase [GOT] and/or Glutamic Pyruvic Transaminase [GPT] ≥ 3-fold of normal value or bilirubin ≥ 3 mg/dL) were excluded from larger pivotal clinical trials.

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SIV.3.5. Patients with renal impairment

In patients with chronic renal failure requiring dialysis, the clearance of iloprost is reduced by a factor of 2 to 4 after intravenous infusion of iloprost. (Hildebrandt *et al*. 1990 (28)). Patients with a creatinine clearance of ≤ 30 mL/min were not investigated in the clinical trials with Ventavis.

To avoid undesired accumulation over the day, special caution should be exercised with these patients during initial dose titration. Initially, doses of 2.5 µg should be administered with dosing intervals of at least three hours (corresponds to administration of max. six times per day). Thereafter, dosing intervals may be shortened cautiously based on individual tolerability. If a further increase in the dose up to 5.0 µg is indicated, again dosing intervals of at least three hours should be chosen initially and shortened according to individual tolerability. A further undesired accumulation of the medicinal product following treatment over several days is not likely due to the overnight break in administration of the medicinal product.

SIV.3.6. Patients with other relevant co-morbidity

The major comorbidities in PAH patients are related to the cardiovascular system. Patients with cardiovascular comorbidities were included in the clinical trial program.

SIV.3.7. Patients with a disease severity different from the inclusion criteria in the clinical trial population

Inhaled iloprost was studied in a controlled clinical trial setting in patients with PAH in NYHA functional Class III and IV. Patients with terminal right heart failure were not enrolled.

An uncontrolled, open, multicentre post-marketing study in PAH patients with end stage right heart failure was performed by Olschewski *et al*. 2000 (29)). Nineteen patients with progressive right-heart failure despite receiving maximum conventional therapy received inhaled iloprost, six to 12 times daily. During the first three months of therapy, New York Heart Association functional class improved in eight patients and was unchanged in seven patients. Four patients died, three of right-heart failure, and one of sepsis. Hemodynamic variables were improved at three months, and the distance walked in six minutes improved by 148 m (95% Confidence Interval [CI]: 4.5 to 282 m; p = 0.048). The authors concluded that, inhaled iloprost may offer a therapeutic option for improvement of haemodynamics and physical function in patients with life-threatening pulmonary hypertension and progressive right-heart failure that is refractory to conventional therapy.

Immuno-compromised including transplant patients were not included into clinical studies.

SIV.3.8. Sub-populations carrying known and relevant polymorphisms

Not applicable

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SIV.3.9. Patients of different racial and/or ethnic origin

Clinical trials participants came from various racial/ethnical backgrounds; the majority of study participants were of Caucasian origin. No specific safety concern was identified for a particular ethnical background.

Differences in the frequency or types of gene variants for drug metabolizing enzymes for iloprost are not known.

Part II: Module SV - Post-authorisation experience

SV.1 Post-authorisation exposure

The data lock point in this section is 30 JUN 2025.

SV.1.1 Method used to calculate exposure

Worldwide cumulative patient exposure to the marketed product was estimated based on the number of ampoules that were sold or distributed (see Table Part II SV-1).

Assuming six to nine (mean: 7.5) ampoules per patient per day as recommended in the SmPC, and patients are treated on average for six months.

SV.1.2 Exposure

A total of 76,822 patients (Ventavis 10 µg/mL: 64,096; Ventavis 20 µg/mL: 12,726) can be assumed have been treated since the first approval of Ventavis in SEP 2003, until 30 JUN 2025.

Table Part II SV-1: Cumulative sales figures and patient exposure (patient-years and treated patients)/Period: start of marketing in SEP 2003 to 30 JUN 2025

Formulations	Number of ampoules	Patient-years[a]	Treated Patients[b]
Iloprost 10 µg/mL Ampoules	87,730,844	32,048	64,096
Iloprost 20 µg/mL Ampoules (launched since SEP 2009)	17,419,433	6,363	12,726
Total	**105,150,277**	**38,411**	**76,822**

[a] Patient-years = number of ampoules/(365 [days] × 7.5 [number of ampoules per day])
[b] Treated patients = number of ampoules/(365 [days] × 7.5 [number of ampoules per day]) × 2
µg: Microgram; mL: Milliliter.

Part II: Module SVI - Additional EU requirements for the safety specification

Not applicable

SVI.1 Potential for misuse for illegal purposes

There is no potential for misuse for illegal purposes with the Ventavis products.

Part II: Module SVII - Identified and potential risks

SVII.1 Identification of safety concerns in the initial RMP submission

Not applicable. According to the EMA guidance on the format of the RMP in the EU GVP Module V, Rev. 2, effective since 31 MAR 2017, Section 1 of Module SVII is expected to be submitted only for initial marketing authorisation applications.

SVII.2 New safety concerns and reclassification with a submission of an updated RMP

In the PRAC Periodic Safety Update Report (PSUR) assessment report (procedure no. EMEA/H/C/PSUSA/00001724/202309), the Rapporteur recommended that the MAH should remove lower respiratory tract infections from the list of safety concerns from RMP. This recommendation is based on the unchanged characterization of this risk over several PSUR periods and the systematic reviews of post-marketing data in PSURs, which are unlikely to identify further new relevant data that would significantly alter the characterization of this risk.

Justification for the removal of safety concerns

Table Part II SVII-1: Justification for the removal of safety concerns

Safety concern	Justification
Important identified risks None	
Important potential risk Lower respiratory tract infections	• The unchanged characterization of this risk over several PSUR periods and the systematic reviews of post-marketing data in PSURs, which are unlikely to identify further new relevant data that would significantly alter the characterization of this risk.
Missing information None	

SVII.3 Details of important identified risks, important potential risks, and missing information

No important identified, potential risks and missing information are classified for Ventavis.

Part II: Module SVIII - Summary of the safety concerns

Table Part II SVIII-1: Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

Part III: Pharmacovigilance plan (including post-authorisation safety studies)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities conducted include the collection, follow-up, evaluation, and expedited reporting (per country regulations) of individual case reports; ongoing monitoring and signal detection activities; preparation of PSURs/PBRERs; and initiation of label changes as required. All procedures are described in applicable Standard Operating Procedures.

III.1.1 Specific adverse reaction follow-up questionnaires for safety concerns

Not applicable.

III.1.2 Other forms of routine pharmacovigilance activities for safety concerns

No other routine pharmacovigilance activities are conducted, and all the safety concerns were removed from the RMP.

III.2 Additional pharmacovigilance activities

Currently no additional pharmacovigilance activities are conducted for any of the risks.

There is one Post-Authorisation Safety Study (PASS) (Study 308120) completed from the pharmacovigilance plan which is provided in Annex 2.

III.3 Summary table of additional pharmacovigilance activities

Not applicable

Part IV: Plans for post-authorisation efficacy studies

Not applicable. No imposed post-authorisation efficacy studies are planned or ongoing.

Part V: Risk minimisation measures (including evaluation of the effectiveness of risk minimisation activities)

Risk minimisation plan

The safety information in the proposed product information is aligned to the reference medicinal product. No additional risk minimisation activities are proposed.

V.1 Routine risk minimisation measures

There are no safety concerns which are considered as important identified risks, important potential risks, and missing information for Ventavis.

V.2 Additional risk minimisation measures

The safety concern associated with Ventavis is appropriately managed by routine risk minimisation measures to be acceptable for a positive benefit-risk balance. Thus, no additional risk minimisation measures are deemed necessary.

V.3 Summary of risk minimisation measures

The safety concern associated with Ventavis is appropriately managed by routine risk minimisation measures to be acceptable for a positive benefit-risk balance. Thus, no additional risk minimisation measures are deemed necessary.

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Part VI: Summary of the risk management plan

Part VI: Summary of the risk management plan

This is a summary of the Risk Management Plan (RMP) for Ventavis.

Ventavis Summary of Product Characteristics (SmPC) and its Package Leaflet give essential information to healthcare professionals and patients on how Ventavis should be used.

Important new concerns or changes to the current ones will be included in updates of Ventavis RMP.

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Part VI: Summary of the risk management plan

I. The medicine and what it is used for

Ventavis is authorised for the treatment of patients with primary pulmonary hypertension, classified as NYHA functional Class III, to improve exercise capacity and symptoms (see SmPC for the full indication). It contains iloprost trometamol as the active substance and it is given by inhalation as Ventavis 10 µg/mL: 2.5 µg/5 µg at the mouthpiece, 6-9 times per day and Ventavis 20 µg/mL: 5 µg at the mouthpiece, 6-9 times per day.

II. Risks associated with the medicine and activities to minimise or further characterise the risks

The risks of Ventavis, together with measures to minimise such risks are outlined below.

Measures to minimise the risks identified for medicinal products can be:

- Specific information, such as warnings, precautions, and advice on correct use, in the Package Leaflet and SmPC addressed to patients and healthcare professionals.
- Important advice on the medicine's packaging.
- The authorised pack size the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

Together, these measures constitute *routine risk minimisation* measures.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PBRER/PSUR, so that immediate action can be taken as necessary. These measures constitute *routine pharmacovigilance activities*.

If important information that may affect the safe use of Ventavis is not yet available, it is listed under "missing information" below.

II.A List of important risks and missing information

Iloprost trometamol has been marketed for nearly 22 years; all the risks mentioned as per previous RMPs are fully characterised and appropriately managed through routine risk minimisations and there are no outstanding ongoing additional pharmacovigilance activities; In the PRAC Periodic Safety Update Report (PSUR) assessment report (procedure no. EMEA/H/C/PSUSA/00001724/202309), the Rapporteur recommended that the MAH should remove lower respiratory tract infections from the list of safety concerns from RMP. This recommendation is based on the unchanged characterization of this risk over several PSUR periods and the systematic reviews of post-marketing data in PSURs, which are unlikely to identify further new relevant data that would significantly alter the characterization of this risk. Therefore, there are no safety concerns which are considered as important identified risks, important potential risks and missing information for Ventavis.

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Part VI: Summary of the risk management plan

Table Part VI-1: Summary of safety concerns

Important identified risks	None
Important potential risks	None
Missing information	None

II.B Summary of important risks

No important risks and no missing information are included in the RMP for Ventavis

II.C Post-authorisation development plan

In the EU, one post authorisation study 308120 (post-approval commitment) was completed. This was an open-label, uncontrolled, multicentre, international, post-marketing surveillance study in patients with primary pulmonary hypertension inhaling Ventavis with a follow up duration of up to four years. The primary objective was to observe clinical effects, safety and tolerability, and survival during long-term Ventavis inhalation therapy over at least two years and up to four years. One-hundred and four subjects with PPH (i.e., IPAH [idiopathic pulmonary arterial hypertension] or FPAH [familial pulmonary arterial hypertension]), classified as NYHA functional Class III (patients with marked limitation of activity: they are only comfortable at rest), where the treating physician had already chosen Ventavis as a suitable long-term treatment, were enrolled.

Table Part VI-2: Completed studies

Category 1-Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation (key to benefit risk)				
Study/activity type, title	**Objectives**	**Safety concerns addressed**	**Status**	**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 four years	To assess the clinical effects, safety and tolerability, and survival during long-term Ventavis inhalation therapy over at least two years and up to four 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 NOV 2012

PASS: Post-Authorisation Safety Study

To date, no further post-authorisation studies are planned.

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II.C.1 Studies which are conditions of the marketing authorisation

Study 308120 was a specific obligation and is a condition of the marketing authorisation.

II.C.2 Other studies in post-authorisation development plan

Not applicable

Part VII: Annexes

Table of Contents

Annex 4 - Specific adverse drug reaction follow-up forms

Not applicable

Annex 6 - Details of proposed additional risk minimisation activities (if applicable)

The safety information in the proposed product information is aligned to the reference medicinal product. No additional risk minimisation activities are proposed.

Annex 7 - Other supporting data (including referenced material)

Annex 7.1 – Literature references

Annex 7.1 - Literature references

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