15 March 2012
EMA/CHMP/11888/2012
Committee for Medicinal Products for Human Use (CHMP)

Assessment report

Ventavis

iloprost

Procedure No.: EMEA/H/C/000474/II/0038/G

Note

Variation assessment report as adopted by the CHMP with all information of a commercially confidential nature deleted.

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1. Background information on the procedure

1.1. Requested Type II Group of variations

Pursuant to Article 7.2.(b) of Commission Regulation (EC) No 1234/2008, Bayer Pharma AG submitted to the European Medicines Agency on 3 November 2011 an application for a group of variations.

This application concerns the following medicinal product:

Medicinal product:	International non-proprietary name:	Presentations:
Ventavis	iloprost	See Annex A

The following variations were requested in the group:

Variation(s) requested		**Type**
C.I.3.z	Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Other variation	II
C.I.4	Variations related to significant modifications of the Summary of Product Characteristics due in particular to new quality, pre-clinical, clinical or pharmacovigilance data	II
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The MAH proposed the update of sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.2 and 5.3 of the SmPC to:

- update the effect of vasodilatators and antihypertensive agents further to the assessment of FU2 026.2 (section 4.5).
- amend the posology section and update the information on pharmacokinetic properties (sections 4.2, 4.4 and 5.2);
- update the information on pregnancy as requested in the 7th Annual Reassessment (S-036) and 9th PSUR assessment and to review the information on lactation (section 4.6);
- delete pregnancy and lactation contraindications (section 4.3) further to the assessments of the 9th PSUR and FU2 029.1;
- update the safety information in line with the SmPC guideline and results of a further reassessment of preclinical and clinical data, and post-marketing events (sections 4.8 and 5.3).

The Package Leaflet (PL) was proposed to be updated in accordance.

Additionally, the MAH also proposed wording in section 6.6 of the SmPC and section 3 of the PL regarding the recommendations of use and hygiene during nebulisation treatment with Ventavis which was requested as part of the outcome of the 9th PSUR.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

Furthermore, the MAH proposed this opportunity to bring the PI in line with the latest QRD template version 8.0.

The requested group of variations proposed amendments to the SmPC, Annex II, labelling and Package Leaflet.

Rapporteur: Pierre Demolis

1.2. Steps taken for the assessment

Submission date:	3 November 2011
Start of procedure:	20 November 2011
Rapporteur's preliminary assessment report circulated on:	23 December 2011
Rapporteur's updated assessment report circulated on:	13 January 2012
Request for supplementary information and extension of timetable adopted by the CHMP on:	19 January 2012
MAH's responses submitted to the CHMP on:	13 February 2012
Rapporteur's preliminary assessment report on the MAH's responses circulated on:	29 February 2012
CHMP opinion:	15 March 2012

2. Scientific discussion

2.1. Introduction

The active substance contained in Ventavis 10 µg/ml nebuliser solution is iloprost (as iloprost trometamol). Iloprost is a synthetic prostacyclin analogue. 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.

In this submission the Marketing Authorisation Holder (MAH) proposed a group of variations related to safety, motivated partly by previous assessments, by alignment with the SmPC guideline and by adaptation to the revised Company Reference Safety Information. The MAH also proposed to update the product information in line with QRD template version 8.0, leading to an extensive revision of the product information. The PL was updated accordingly.

The documentation provided by the MAH in support of this variation consisted of a non-clinical overview, a clinical overview and published references. The MAH did not provide any clinical study reports to support the application.

2.2. Non-clinical aspects

Replacement of the lactation contraindication by warning statements.

Low incidences of digit growth retardations (without clear dose dependency) in preclinical reproduction toxicity and peri/postnatal studies in rats, together with a lack of human data during pregnancy and breast-feeding led to an absolute contraindication during pregnancy and lactation in the Company Core Data Sheet (CCDS) at time of marketing authorisation in 2003. In this variation the MAH put forward arguments to lift the lactation contraindication.

The excretion of iloprost in milk has only been studied in rats. In rats, iloprost and/or metabolites were observed to be excreted in milk to a very low extent (less than 1% of iloprost given intravenously). It is unknown whether iloprost and/or its metabolites are transferred or not into mothers milk in humans. No studies have been conducted to analyse iloprost exposure in breast milk and its consequence for the suckling child. The MAH has not identified any article on iloprost exposure via breastfeeding, nor have they identified any cases of iloprost exposure during lactation in their safety data base.

Since the time of marketing authorisation no clinical data have been reported to justify an absolute contraindication. On the other hand, the total lack of any reported or published information from clinical practice in women who would have breast fed during Ventavis treatment can also reflect the full acceptance of PAH women not to breastfeed their baby when being treated with Ventavis in accordance with the contraindication in force. In view of this, the lactation contraindication is not considered to be an essential point for physicians in clinical practice or for the mother and the CHMP agreed it could be removed.

No human clinical data are available; therefore, as a risk to the suckling child cannot be formally excluded especially relating to the strong vasodilatory effect of iloprost and potentially poor tolerance in neonates, a warning to avoid breastfeeding during treatment with Ventavis is warranted. This conclusion was agreed by the CHMP and reflected in the SmPC section 4.6 and 5.3.

Inclusion of further details on non clinical results

Section 5.3 of the SmPC was updated to further clarify the wording regarding reproductive toxicology, and aligned with section 4.6. No new non-clinical studies have been performed since the marketing authorisation. The following changes were accepted by the CHMP:

5.3 Preclinical safety data

[…]

Reproduction toxicology

[…]

"These alterations are not considered as ~~true~~ 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 ~~extremely~~ 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."***

2.3. Clinical Safety aspects

Dosing interval in patients with hepatic impairment

In the current SmPC, sections 4.2 and 4.4 include information on the dosing interval in patients with hepatic impairment and renal impairment stating that the dosing interval for these special populations should be of "at least 3 hours". This information is based on the available clinical data and is summarised below:

In a clinical study the pharmacokinetics of iloprost in seven patients with renal insufficiency but not requiring dialysis and eight patients with renal insufficiency requiring dialysis after single intravenous infusion of 1 ng/kg/min for 60 min were investigated.

Patients depending on dialysis had a decreased total clearance of iloprost by a factor of about 3 (5.2 ± 2.2 mL/min/kg vs. 17.6 ± 5.2 mL/min/kg in patients with renal insufficiency not depending on dialysis). The total clearance in patients with renal insufficiency not depending on dialysis was similar to healthy subjects. In patients depending on dialysis, plasma levels at the end of infusion were about 3.5 fold higher compared to those in patients not depending on dialysis (193 vs. 51 pg/mL).

In another clinical study the pharmacokinetics of iloprost in eight patients with hepatic dysfunction (cirrhosis) after single intravenous (IV) infusion of 1 ng/kg/min for 60 min were investigated.

Patients with hepatic dysfunction had a decreased total clearance of iloprost by a factor of about 2 (10 ± 5 mL/min/kg vs. 21 ± 3 mL/min/kg in healthy subjects). Steady state plasma levels were about double compared to those in healthy subjects (93 vs. 46 pg/mL). Mean terminal half-live was prolonged (28 ± 24 min) compared to 20 ± 7 min in healthy subjects. Furthermore, a considerable higher variability was noticed in patients with hepatic impairment.

Patients without hepatic or renal impairment should inhale 6 to 9 times per day (no more than once every 2 hours) during waking hours, according to individual need and tolerability.

Due to the reduced clearance and the resulting longer half-life of iloprost, for patients with hepatic and renal impairment a cautious initial dose titration is recommended. An initially longer dosing interval of 3-4 hours should be chosen, i.e. these patients should inhale a maximum of 6 times per day. Shorter initial dosing intervals might lead to undesired accumulation over the day.

However, longer intervals than 4 hours might lead to reduced therapeutic efficacy."

Based on the above, the MAH amended the information provided on the dosing to change the term "at least 3 hours" to "3-4 hours". The corresponding warning statement in section 4.4 of the SmPC has been changed accordingly. This change was considered acceptable by the CHMP.

Size of the medication chamber in the I-Neb AAD System instructions

The MAH proposed that there is no need to specify the volume of the medication chamber in the product information as the colour-coded medication chamber and the control disc are considered enough to minimize any dosing mistake. This proposal was considered acceptable by the CHMP, and the changes were reflected in section 4.2 of the SmPC and in the PL.

Deletion of the pregnancy contraindication.

During the assessment of the 9th PSUR, which covered the period from 16 September 2009 to 15 September 2010, the MAH was asked to provide a proper risk-benefit assessment concerning use of iloprost during pregnancy and justify whether an absolute contraindication during pregnancy was needed any longer.

In the corresponding response (FU2 029.1) the MAH proposed to remove the pregnancy contraindication, which was accepted by the CHMP in September 2011. This has been implemented in

this variation. Below is a summary of the discussion which lead to the decision to remove the pregnancy contraindication:

“In reproductive toxicity studies in rats, continuous IV administration of iloprost led to anomalies of single phalanges of forepaws in a few foetus/pups without a clear dose dependency. As these alterations were also observed following iloprost administration after organogenesis, they are not considered as teratogenic effects and most likely resulted from the haemodynamic alterations in the foetoplacental unit induced by iloprost. A species specific effect is probable as no embryotoxicity and teratogenicity were observed in rabbits and monkeys.

Based on the limited clinical data on exposure during pregnancy presented by the MAH, several points can be raised:

Among the 42 cases, patients were usually exposed after 22 weeks of gestation:

- for inhaled iloprost, the median time point regarding start of iloprost exposure was at week 26th of gestation and the median treatment duration was 8.5 weeks.

- for IV iloprost, 5 women were shortly exposed in the first weeks of pregnancy. In one case, a woman was treated with IV iloprost starting 5 days prior and throughout delivery.

Among the 37 known outcomes of pregnancy (33 with inhaled and 4 with IV exposure), the following was observed:

- 3 elective terminations

- 1 spontaneous abortion at week 10

- 1 foetal death at 26 weeks of gestation (Eisenmenger Syndrome)

- 4 stillbirths with delivery between 24 and 26 weeks of gestation (Eisenmenger Syndrome)

- 28 live births, all but 2 being premature birth, including severe prematurity in 5 cases.

Obstetric complications related to maternal disease were mostly observed in patients with Eisenmenger syndrome. No adverse effects directly attributable to iloprost treatment were reported. Of note, no maternal death occurred during pregnancy but 2 women died 17 days and 4 weeks after delivery.

Regarding potential teratogenicity, no digital anomalies were observed among the newborns. One congenital anomaly was observed (patent ductus arteriosus and mitral valve prolapse requiring surgery at 12 months) in a premature newborn exposed before delivery to inhaled iloprost and IV alprostadil from a mother with Eisenmenger Syndrome. Detailed examination of the cases evidenced that only 11 women were possibly exposed during the first trimester of pregnancy (6 with inhaled iloprost and 5 with IV iloprost) but the exact period of exposure was lacking in most cases. Accordingly, only 4 women were possibly exposed during skeletal embryogenesis. Outcome of pregnancy in these 11 cases was known in 7 with 4 normal babies and 3 elective abortions (outcome unknown in 4).Consequently, among these clinical data, no specific adverse effect of iloprost has been observed in the mother or in the newborns.

Pulmonary hypertension is a life-threatening disease and physiologic haemodynamic changes during pregnancy pose an additional circulatory burden leading to strong potential of deterioration of the haemodynamic status. As a consequence of the increased mortality associated to pregnancy in patients with PAH (30-50% mortality), the consensus views from the Study Group of the Royal College of Obstetricians and Gynaecologists and the current Guidelines for Management of Pulmonary hypertension strongly recommend that women with pulmonary hypertension should be informed of the high risk of pregnancy and birth control is recommended as well as termination of pregnancy in case a

PAH woman would become pregnant. But, as outlined in the clinical guidance, those women with PAH who voluntary choose to continue pregnancy should be treated with disease-targeted therapies and pulmonary arterial vasodilator therapy during pregnancy can improve the chances of maternal survival. Published data reported pregnancies with beneficial outcome with iloprost (as well as with epoprostenol). Thus, in this critical context, the recommendation relating to Ventavis with respect to pregnancy should consider the benefit of the treatment and there is no rational any more for a contraindication during pregnancy. It can be agreed that iloprost could be considered as PAH target treatment during pregnancy."

Update of information on the effect of vasodilatators and antihypertensive agents

In FU2 026.2 the MAH presented the final study report for the double-blind phase of the VISION trial. The objective of this study was to assess the safety and efficacy of iloprost in patients with pulmonary arterial hypertension receiving oral sildenafil. The study was prematurely closed with only 67 patients enrolled instead of 180 initially planned (i.e. 37 % of the planned population). No new safety concerns arose from this study. In relation to the safety assessment of this study, it was concluded that the issue on the effects of concomitant use of Ventavis with oral sildenafil especially on exercise capacity and functional status (and potential dose adjustment) had not been solved and were not properly documented in the product information. Therefore the CHMP asked the MAH to complete the first sentence in section 4.5. of the Ventavis SmPC with the following message:

4.5 Interaction with other medicinal products and other forms of interaction

Iloprost may increase the effect of vasodilators and antihypertensive agents. Caution is recommended in case of co-administration with other treatments for pulmonary hypertension as dose adjustment might be required.

The MAH proposed a slightly different wording to better reflect the medical practice and convey that a dose reduction may be applicable either for Ventavis, or the other antihypertensive or vasodilating agents administered. Given the life-threatening nature of PAH a dose reduction of iloprost as PAH treatment may not always be the first choice, since the treatment with an antihypertensive agent may not at all contribute to the treatment effect on PAH. Thus, depending on the medical circumstances the treating physician will need to decide for which of the administered drugs the dose should be adjusted. The proposal of the MAH was accepted by the CHMP. The final wording is as follow:

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 recommended in case of co-administration of Ventavis with other antihypertensive or vasodilatating agents as dose adjustment might be required."

Update of summary of safety profile, inclusion of information on most serious (life-threatening and fatal) ADRs, update of MedDRA terms.

The MAH updated section 4.8 of the SmPC as per the current SmPC guideline. The MAH also presented a general review of all case reports received since the Marketing Authorisation in 2003. This review showed that fatal outcomes had been reported for each of the following adverse drug reactions (ADRs):

Fatal outcomes of adverse drug reactions	Case numbers
Bronchospasm	1 case
Bleeding events	1 case of subdural haematoma 3 cases of cerebral haemorrhage 1 case of intracerebral haemorrhage

	2 cases of intracranial bleed 1 case of gastrointestinal bleeding 1 case of intracerebral haemorrhage 1 case of haemorrhagic shock 1 case of haemoptysis

Adverse drug reactions with reports of medically reasonable life-threatening situations were reported for the following adverse drug reactions:

Life-threatening adverse drug reactions	Case numbers
Hypotension	1 case

As a result of this review the MAH proposed to list all ADRs with severe medical conditions/outcomes (i.e., "life-threatening" and "fatal") in section 4.8 of the SmPC 'Undesirable effects' as most serious ADRs. This was accepted by the CHMP.

Inclusion of thrombocytopenia as a new ADR.

An article referring to a possible iloprost-induced thrombocytopenia was published [Taegtmeyer AB et al, 2010] and triggered a cumulative safety analysis of this topic. This signal investigation including a review of postmarketing- and pre/clinical trial data as well as a review of literature was performed by the MAH to evaluate a possible association between inhaled iloprost and the development of drug-induced thrombocytopenia.

It is well known that a decrease in platelet count has multiple factors and can be induced by a broad variety of drugs and medical conditions. Thus, the PAH population may be prone to develop thrombocytopenia due to multiple comedications and underlying medical conditions. In addition, severely elevated right atrial pressure in PAH was associated with thrombocytopenia, predisposing this patient population to experience reduced platelet counts. However, as many drugs may trigger a reduction in platelet count this signal investigation was initiated due to a single case report with possible iloprost induced thrombocytopenia derived from literature.

To date iloprost (Prostaglandin I2) was not considered to induce thrombocytopenia, whereas other prostaglandins indicated in PAH are reported to be associated with thrombocytopenia. Epoprostenol, intravenous treprostenil and alprostatil have established side effects of thrombocytopenia. The underlying pathomechanism is not yet clearly understood, but include discussions of immunogenic origins (autoantibody formation), specific effects on bone marrow (suppressed megakaryocytopoiesis), and direct effects on platelets. In this context a possible class of prostaglandin-induced thrombocytopenia cannot be excluded.

Clinical and preclinical study data with inhaled iloprost did not indicate an iloprost triggered decrease in platelet count; however clinical studies were rather small scale trials regarding patient numbers and treatment duration due to the orphan indication status with a low overall incidence of PAH. In literature no further clinical data was identified pertaining to iloprost induced reduction in platelet count. To the contrary iloprost was published to be used intravenously to treat a possible prostaglandin deficiency in Thrombotic Thrombocytopenic Purpura (TTP) and to treat and prevent thrombocytopenia secondary to heparin medication or during cardio-pulmonary bypass surgery due to its ability to reduce platelet activity.

However, the MAH did receive case reports of thrombocytopenia with a temporal relationship to start of iloprost medication which may be suggestive for a contributory role of iloprost. In addition, a positive de-challenge was reported in the sense of an increase in platelet count after discontinuation of

iloprost medication although in some cases other comedications were also discontinued. One case report states a positive re-challenge with a decrease in platelet count after re-start of iloprost therapy followed by an increase in number of platelets after stopping its medication. In this incident a contributory role of iloprost cannot be excluded.

As thrombocytopenia was observed with other prostaglandins which may indicate a possible class effect and the existence of isolated single cases could suggest a contributory role of iloprost to decrease the platelet count, the MAH added thrombocytopenia as an ADR to the SmPC.

No events of thrombocytopenia have been reported during randomization phases of inhaled iloprost clinical trials; therefore thrombocytopenia will be assigned to the frequency category "unknown".

Update of information on bleeding events, mouth and tongue irritations.

As Ventavis has anti-aggregatory features, a contributory role in the increased risk of bleeding particularly when given concomitantly with anticoagulant agents and/or platelet inhibitors cannot be excluded. The current explanatory footnote on bleeding events in the ADR table in section 4.8 refers only to the one larger pivotal AIR study. It was considered important to refer in this footnote to the frequency category and overall study population of both the phase II and III trials, and to include the information that the studied patients consisted of a high proportion of anticoagulated patients together with a cross-reference to section 4.5 'Interaction with other medicinal products and other forms of interaction'.

Mouth-, tongue irritations and dysgeusia are currently considered local ADRs with the use of Ventavis. During the postmarketing experience, the cumulative review resulted in 60 case reports of inhaled iloprost linked to these complaints. Some of these case reports included symptoms of pain sensations. Tongue pain was described in 5 cases, sore/burning tongue in 9 cases, and oral pain in 8 cases. In view of this, additional information to the ADR "mouth and tongue irritation" has been added in the ADR table in section 4.8 to indicate that these symptoms may include sensations of pain.

Inclusion of information on cytochrome P-450 metabolism

Section 5.2 "Pharmacokinetic properties" subsection "Metabolism" of the SmPC, currently includes the following information on the metabolism of iloprost by cytochrome P450 enzymes.

5.2 Pharmacokinetic properties

[…]

Metabolism

No studies performed following inhalation.

Iloprost is extensively metabolised principally via ß-oxidation of the carboxyl side chain. No unchanged substance is eliminated. The main metabolite is tetranor-iloprost, which is found in the urine in free and conjugated form in 4 diastereoisomers. Tetranor-iloprost is pharmacologically inactive as shown in animal experiments. Results of *in vitro* studies reveal that CYP 450-dependent metabolism plays only a minor role in the biotransformation of iloprost. Further *in vitro* studies suggest that metabolism of iloprost in the lungs is similar after intravenous administration or inhalation.

In order to increase the clearness and readability of the above text, the MAH clarified that these studies where performed following IV administration, deleted imprecise wording about metabolism of Iloprost via B-oxidation of the carboxyl side chain (deletion of "principally") and deleted information not relevant for the prescribing physician (deletion of "in 4 diastereoisomers"). This proposal was considered acceptable by the CHMP and implemented in the SmPC.

Inclusion of information on the use of nebulisers

A cumulative evaluation regarding respiratory tract infection and the use of Ventavis was included in the 9th PSUR. This analysis concluded that there is no indication that Ventavis serves as a trigger for patients to develop a drug-induced respiratory tract infection.

However, during the assessment of this PSUR, the MAH was asked to revise the package leaflet in order to improve the recommendations of use and hygiene during nebulisation treatment with Ventavis.

It is known that home nebulizers are widely used among patients with chronic pulmonary diseases. In the inpatient setting, bacterial contamination of nebulizers has been associated with nosocomial pneumonia and isolated publications report that reservoir nebulizers are exceedingly vulnerable to bacterial contamination by gram negative organisms and produce aerosols containing bacteria which may play a causal role in bacterial colonization of the respiratory tract and nosocomial pneumonia. In this context, the MAH agreed to add the following statement in the PL on handling instructions for the nebulizers used with Ventavis to accentuate the need to properly follow the hygiene and cleaning instruction of the applied nebulizer.

"How to use Ventavis:

For each inhalation session you should use a new ampoule of Ventavis. Just before you start to inhale, break open the glass ampoule and transfer the complete content into the nebuliser medication chamber.

Any Ventavis solution remaining in the nebuliser that you do not use in one inhalation session has to be thrown away.

In addition, follow any instructions about hygiene and cleaning of the nebuliser that come with the nebuliser."

The MAH aligned the information in section 6.6 of the SmPC with the information in the package leaflet.

2.4. Changes to the Product Information

The MAH proposed the update of sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.2 and 5.3 of the SmPC to which the CHMP agreed.

Changes were also made to the PI to bring it in line with the current QRD template and SmPC guideline, which were reviewed and accepted by the CHMP.

In addition, the list of local representatives in the PL has been revised to amend contact details for the representative of Cyprus.

3. Overall conclusion and impact on the benefit/risk balance

This variation proposed changes in the SmPC and package leaflet of Ventavis for adaptation of the text to the revised Company Reference Safety Information. Annex II and the labelling have also been modified due to the QRD template update. These changes do not change the benefit/risk balance for Ventavis which remains favourable.

4. Recommendations

Based on the review of the submitted data, the CHMP considers the following group of variations acceptable and therefore recommends the variations to the terms of the Marketing Authorisation, concerning the following changes:

Variations accepted		**Type**
C.I.3.z	Implementation of change(s) requested following the assessment of an USR, class labelling, a PSUR, RMP, FUM/SO, data submitted under A 45/46, or amendments to reflect a Core SPC - Other variation	II
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Update of sections 4.2, 4.3, 4.4, 4.5, 4.6, 4.8, 5.2 and 5.3 of the SmPC to:

- update the effect of vasodilatators and antihypertensive agents further to the assessment of FU2 026.2 (section 4.5).
- amend the posology section and update the information on pharmacokinetic properties (sections 4.2, 4.4 and 5.2);
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- delete pregnancy and lactation contraindications (section 4.3) further to the assessments of the 9th PSUR and FU2 029.1;
- update the safety information in line with the SmPC guideline and results of a further reassessment of preclinical and clinical data, and post-marketing events (sections 4.8 and 5.3).

The Package Leaflet was proposed to be updated in accordance.

Additionally, the MAH also proposed wording in section 6.6 of the SmPC and section 3 of the PL regarding the recommendations of use and hygiene during nebulisation treatment with Ventavis which was requested as part of the outcome of the 9th PSUR.

In addition, the MAH took the opportunity to update the list of local representatives in the Package Leaflet.

Furthermore, the PI is being brought in line with the latest QRD template version 8.0.

The requested group of variations proposed amendments to the SmPC, Annex II, Labelling and Package Leaflet.