Module 1.8.2

European Union Risk Management Plan (EU-RMP) for VOLIBRIS (ambrisentan)

RMP version to be assessed as part of this application	
RMP Version number	9.0
Data lock point for this RMP	14 June 2019
Date of final sign off	

Rationale for submitting an updated RMP

In line with a commitment made to the European Medicines Agency (EMA) as agreed in the Paediatric Investigation Plan (PIP) for ambrisentan, GSK was requested to conduct a randomized, open label study comparing safety and efficacy parameters for a high and a low dose of ambrisentan (adjusted for body weight) for the treatment of pulmonary arterial hypertension in paediatric patients aged 8 years up to 18 years (AMB112529). This study has been completed and GSK is submitting a line extension for the 2.5 mg tablet grouped with a Type II variation for the paediatric indication from 8 years to less than 18 years of age. The RMP is being updated and is filed as part of this submission. GSK is additionally conducting an ongoing open label, long term extension study for treatment of PAH in paediatric patients aged 8 up to 18 years who have participated in AMB112529 and in whom continued treatment with ambrisentan is desired. A formal interim analysis of the data from this study as of 23 August 2019 has been conducted to accompany the planned line extension.

Summary of significant changes in this RMP:

PART	MODULE	Changes made in EU-RMP version 9.0
Part II	SI	Addition of epidemiological data relating to the paediatric population.
Part II	SIII	Update to clinical trial exposure data up to 14 June 2019.
Part II	SV	Update to post-authorisation experience data up to 14 June 2019

Other RMP versions under evaluation

Not applicable

RMP Version number	Submitted on	Procedure number
N/A	N/A	N/A

Details of the currently approved RMP		
Version number	Approved with procedure	Date of approval (opinion date)
8.1	EMEA/H/C/000839/II/55	15 February 2019

QPPV Name	Dr. Jens-Ulrich Stegmann, MD Vice President, Head of Vaccines Clinical Safety & Pharmacovigilance and EU QPPV GlaxoSmithKline Biologicals, Avenue Fleming 20, B-1300, Wavre Belgium
QPPV Signature	QPPV signature will be included with finalized approved version submitted to EMA in the closing sequence

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PART I: PRODUCT(S) OVERVIEW

Table 1 Product Overview

Active substance(s) **(INN or common name)**	Ambrisentan
Pharmacotherapeutic group(s) (ATC Code)	Other anti-hypertensives, ATC code: C02KX02
Marketing Authorisation Holder/ Applicant	GlaxoSmithKline (Ireland) Limited 12 Riverwalk, Citywest Business Campus Dublin 24 Ireland
Medicinal products to which this RMP refers	Ambrisentan
Invented name(s) in the European Economic Area (EEA)	VOLIBRIS™ 2.5 mg film-coated tablets VOLIBRIS™ 5 mg film-coated tablets VOLIBRIS™ 10 mg film-coated tablets
Marketing authorisation procedure	Centralised
Brief description of the product	Chemical class Ambrisentan is a non-sulfonamide, propanoic acid-class, endothelin receptor antagonist.
	Summary of mode of action Ambrisentan is an orally active, propanoic acid-class, ET_A selective, endothelin receptor antagonist (ERA). Endothelin plays a significant role in the pathophysiology of PAH and acts through two receptor subtypes: • The ET_A receptor subtype, localized predominantly on vascular smooth muscle cells and cardiac myocytes, activates second messenger

	systems that result in vasoconstriction and smooth muscle cell proliferation. Activation of the ET_B receptor on endothelial cells results in vasodilatation mediated by the production of nitric oxide and prostacyclin.
Reference to the Product Information	Please refer to the Product Information (ANNEX 7)
Indication(s) in the EEA	Current (if applicable): Volibris is indicated for treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, including use in combination treatment. Efficacy has been shown in idiopathic PAH (IPAH) and in PAH associated with connective tissue disease
	Proposed (if applicable): Volibris is indicated for treatment of PAH in adolescents and children (aged 8 to less than 18 years) of WHO Functional Class (FC) II to III including use in combination treatment. Efficacy has been shown in IPAH, familial, corrected congenital and in PAH associated with connective tissue disease.
Dosage in the EEA	Current (if applicable): <u>Adults</u> <u>Ambrisentan monotherapy</u> Volibris is to be taken orally to begin at a dose of 5 mg once daily and may be increased to 10 mg daily depending upon clinical response and tolerability. <u>Ambrisentan in combination with tadalafil</u>

<table>
<tr><td></td><td>When used in combination with tadalafil, Volibris should be titrated to 10 mg once daily.</td></tr>
<tr><td></td><td>Proposed (if applicable):

Paediatric patients aged 8 to less than 18 years:

Ambrisentan monotherapy or in combination with other PAH therapies

Volibris is to be taken orally based on the dose regimen described below:

<table>
<tr><th>Body weight (kg)</th><th>Initial once daily dose (mg)</th><th>Subsequent once daily dose titration (mg)[a]</th></tr>
<tr><td>≥50
≥35 to <50
≥20 to <35</td><td>5
5
2.5</td><td>10
7.5
5</td></tr>
<tr><td colspan="3">a =dependent on clinical response and tolerability</td></tr>
</table>
</td></tr>
<tr><td>Pharmaceutical form(s) and strengths</td><td>Current (if applicable):

5 mg and 10 mg film-coated tablets</td></tr>
<tr><td></td><td>Proposed (if applicable):

2.5 mg film-coated tablets</td></tr>
<tr><td>Is/will the product be subject to additional monitoring in the EU?</td><td>No</td></tr>
</table>

Abbreviations

6MWD	Six (6)-Minute Walking Distance
ADME	Absorption, distribution, metabolism and excretion
ADR	Adverse drug reaction
AE	Adverse Event
AESI	Adverse Event of Special Interest

AIH	Autoimmune hepatitis
ALT	Alanine aminotransferase
ASPIRE	Assessing the Spectrum of Pulmonary hypertension Identified at a Referral centre
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the curve
BCRP	Breast cancer resistance protein
BNP	Brain natriuretic peptide
BSEP	Bile salt export pump
CCB	Calcium channel blocker
CCDS	Company Core Data Sheet
CHF	Congestive heart failure
CHMP	Committee for Medical Products for Human Use
C_{max}	Peak concentration
COPD	Chronic obstructive pulmonary disease
CTD	Connective tissue disease
CTEPH	Chronic thromboembolic pulmonary hypertension
CYP	Cytochrome
DILI	Drug-induced liver injury
ECG	Electrocardiogram
EEA	European Economic Area
EMA	European Medicines Agency
ERA	Endothelin receptor antagonist
ET-1	Endothelin-1
EU SmPC	European Summary of Product Characteristics
FAV	Final assessment visit
FEV_1	Forced expiratory volume in the first second from a maximum inspiration
FSH	Follicle stimulating hormone
g/dL	grams per decilitre
GSK	GlaxoSmithKline
HIV	Human immunodeficiency virus
HLT	High Level Term
hPAH	Heritable pulmonary arterial hypertension
ILD	Interstitial lung disease
INR	International normalized ratio
iPAH	Idiopathic pulmonary arterial hypertension
IPF	Idiopathic pulmonary fibrosis
LEAP	Letairis Education and Access Program
LFT	Liver function tests
LH	Luteinising hormone
LHD	Left heart disease
Ltd	Limited
MAA	Marketing Authorisation Application

MAH	Marketing authorisation holder
MedDRA	Medical Dictionary for Regulatory Activities
mg	milligram
mg/dL	milligrams per decilitre
mITT	modified Intention to Treat
mL/min	millilitre per minute
mmHg	millimetres of mercury
MRP2	Multi-drug resistance protein isoform-2
NTCP	Sodium-taurocholate co-transporter
OATP	Organic anion export pump
OR	Odds ratio
PAH	Pulmonary arterial hypertension
PAWP	Pulmonary artery wedge pressure
PCC	Potential clinical concern
PDE-5	Phosphodiesterase 5 inhibitors
PH	Pulmonary hypertension
PIL	Patient Information Leaflet
PSUR	Periodic Safety Update Report
PT	Prothrombin time
PV	Pharmacovigilance
PVOD	Pulmonary veno-occlusive disease
QT	electrocardiographic QT interval from onset of Q wave to end of T wave
QTcIb	QTc calculated using by individualized baseline data
RCT	Randomised Clinical Trial
RMP	Risk Management Plan
SAE	Serious adverse event
SHBG	Sex hormone binding globulin
SLE	Systemic lupus erythematosus
SmPC	Summary of Product Characteristics
SSc	Systemic Sclerosis
TEAE	Treatment emergent adverse event
TLC	Total lung capacity
ULN	Upper limit of normal
US	United States
VOLT	Volibris Tracking
WCBP	Woman of child-bearing potential
WHO	World Health Organization

Trademark Information

Trademarks of the GlaxoSmithKline group of companies
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Trademarks not owned by the GlaxoSmithKline group of companies
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Thelin
Letairis
SAS

PART II: SAFETY SPECIFICATION

PART II: MODULE SI - EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Pulmonary hypertension (PH) is a vasculopathy of the pulmonary arteries, currently defined via right heart catheterization of a mean pulmonary artery pressure of 25 mm Hg or more (Hoeper, 2013). The term pulmonary arterial hypertension (PAH) describes a group of PH patients characterized haemodynamically by the presence of pre-capillary PH, defined by a pulmonary artery wedge pressure (PAWP) ≤15 mmHg and a PVR >3 Wood units (WU) in the absence of other causes of precapillary PH such as PH due to lung diseases, chronic thromboembolic pulmonary hypertension (CTEPH) or other rare diseases (Hoeper, 2013). Patients with PAH develop progressive narrowing of the pulmonary arteries from an imbalance of vasoactive mediators. This leads to an increased right ventricular afterload, right heart failure, and premature death (Kiely, 2013). Recent advances in imaging have enabled more detailed patient assessment, but PAH continues to be a life shortening condition, and there is often a delay of around two years from onset of symptoms to diagnosis (Badesch, 2007). According to the 2015 ESC/ERS Guidelines for the diagnosis and treatment of PH, a screening method for PH/PAH should be applied to asymptomatic individuals who belong to groups in which PH/PAH is highly prevalent, using non-invasive tools such as pulmonary function tests (PFTs), circulating biomarkers and echocardiography (Galie, ERS/ESC 2015). Mean age at diagnosis is >50 years, and the disease is more common among women than men. Most patients present with moderate-to-severe disease and prognosis is poor (Berger, 2012).

SI.1 Indication – Adult Pulmonary Arterial Hypertension

SI.1.1 Incidence & Prevalence

The epidemiology of PAH is poorly understood, though it has been described in several registries (Galie ERS/ESC, 2015). In Europe, PAH prevalence and incidence have been estimated to be in the range of 15–60 subjects per million population, and 5–10 cases per million per year, respectively (Peacock, 2007). In registries, around half of PAH patients have idiopathic (iPAH), heritable (hPAH) or drug-induced PAH. The remaining half have associated PAH conditions (APAH), the leading cause of which is connective tissue disease (CTD), mainly systemic sclerosis (SSc) (Humbert, 2006).

SI.1.2 Demographics of the population in the PAH indication and risk factors for the disease

PAH patients in a UK registry from 2001 to 2009 were 70% female, 12% nonwhite, and the majority were over the age of 50 (Ling, 2012). Similar findings were observed in the Assessing the Spectrum of Pulmonary hypertension Identified at a Referral centre (ASPIRE) registry (Hurdman, 2012) and summaries across registry data (McGoon, 2013). In the US, females account for 56.3% and 69.1% of diagnosed PAH cases aged <65 and 65+, respectively (Kirson, 2011). Kirson (Kirson, 2011) interrogating claims databases in the US found that PAH and CTEPH were both more prevalent in women and rise with age. The age-related increase in CTEPH was larger.

Half of all PAH cases referred to pulmonary vascular centres have no identifiable risk factor. Pulmonary hypertension is more common in severe respiratory and cardiac disease, occurring in 18-50% of patients assessed for transplantation or lung volume reduction surgery, and in 7-83% of those with diastolic heart failure (Thabut, 2005; Lam, 2009; Damy, 2010; Arcasoy, 2003). Recent reviews indicate that PAH is more frequent in certain patient groups such as those with connective tissue disease (CTD) (12 cases per million) or with systemic sclerosis (9%), portal hypertension (2-6%), congenital heart disease (5-10%), and HIV (0.5%) (Avouac, 2010; Hadengue, 1991; Castro, 1996, Colle, 2003, Gatzoulis, 2009; Sitbon, 2008, Yang, 2013). PAH is inherited in fewer than 10% of cases (McLaughlin, 2009), however genetic mutations are now under active investigation for contribution to the development of PAH (Ma, 2013).

SI.1.3 The main existing treatment options

The treatment strategy for PAH can be divided into three main steps; pharmacological, general (non-pharmacological and supportive) and transplantation (Galie ERS/ESC, 2015).

Pharmacotherapies:

The overall treatment goal in patients with PAH is achieving a low risk status, which is usually associated with good exercise capacity, good quality of life, good RV function and a low mortality risk, which includes the management of underlying risk factors, such as pregnancy avoidance, early treatment of respiratory infection, and immunizations against pneumococcal disease and influenza (Galie ERS/ESC, 2015). Several classes of medicinal agents have been developed for the treatment of PAH and may be used as monotherapy followed by stepwise combination therapy or using initial or combination therapies, depending on the risk class of the patient. Patients should be regularly assessed, and treatment escalated depending on the risk status of the patient (Galie ERS/ESC, 2015). Other medications are used to treat associated symptoms (Seferian, 2013).

Specific PAH treatments include:

Calcium channel blockers: High doses of calcium channel blocker (e.g., diltiazem or nifedipine) are indicated for PAH patients with a positive response to vasoreactivity testing at right heart catheterisation (Rich, 1992; Sitbon, 2005). However, fewer than 5% of patients exhibit vasoreactivity on RHC.

Prostanoid pathway: Epoprostenol (iv) was the first PAH specific drug shown to be efficacious in a small randomised clinical trial (RCT), demonstrating improvements in exercise capacity, haemodynamics, and survival (Barst, 1996). Development of other prostanoids has led to treatments with improved stability and/or half life and new routes of administration: including epoprostenol (iv), iloprost (iv, inhaled), treprostinil (iv, sc, inhaled, oral-US only). Another oral synthetic prostanoid analogue (selexipag) has also been approved in the multiple territories (Sitbon, 2015).

Endothelin receptor antagonists (ERAs): Endothelin is a potent vasoconstrictor of vascular smooth muscle. Bosentan, ambrisentan and macitentan are all ERAs approved for the treatment of PAH, with the latter two also indicated for use in combination therapy, and efficacy and safety demonstrated in large well conducted RCTs (Rubin, 2002; Galiè, 2008a; Humbert, 2007; Pulido, 2013, Galie, 2015).

Phophodiesterase-5 inhibitors: Two oral phophodiesterase-5 inhibitors (sildenafil and tadalafil) have market approval for treating PAH. These compounds inhibit the breakdown of nitric-oxide activated cGMP, leading to vasodilation, and have been shown to improve exercise and functional capacity in PAH patients in large well-conducted RCTs (Galiè, 2005; Galiè, 2009).

Guanylate cyclase (sGC)/Nitric Oxide/GMP pathway: Riociguat is a stimulator of soluble guanylate cyclase (sGC) and represents a class of drug that restores the Nitric Oxide-sGC-cGMP pathway, by independently stimulating the production of cGMP, with subsequent vasodilation. Riociguat was approved in the EU as well as other countries for the treatment of both PAH and CTEPH based on two RCT (Ghofrani, 2013a; Ghofrani, 2013b).

Other Medications Used for Treatment of Associated Symptoms:

For PAH other associated medications can include diuretics for the associated symptoms of oedema, anticoagulants, oxygen when needed for anoxia, and digoxin when needed for heart failure (Mann, 2012).

Supportive and non-pharmacological measures:

Supportive and non-pharmacological measures outlined in the 2015 European ESC/ERS Guidelines are listed in the Table 2 below. The measures include physical activity and supervised rehabilitation, breathing exercises, pregnancy avoidance and birth control, post-menopausal hormonal therapy, elective surgery, infection prevention, psychosocial support, adherence to treatments, genetic counselling and travel advice. In addition, supportive therapy (oral anticoagulants, diuretics, O_2, digoxin), referral to expert centres and acute vasoreactivity testing for the indication of chronic CCB therapy are recommended. (Galie ERS/ESC, 2015).

Table 2 Recommendations for general measures (Galie ERS/ESC, 2015)

Recommendations	Class[a]	Level[b]	Ref.[c]
It is recommended that PAH patients avoid pregnancy	I	C	160, 161
Immunization of PAH patients against influenza and pneumococcal infection is recommended	I	C	
Psychosocial support is recommended in PAH patients	I	C	168

Supervised exercise training should be considered in physically deconditioned PAH patients under medical therapy	**IIa**	**B**	**153-157**
In-flight O_2 administration should be considered for patients in WHO-FC III and IV and those with arterial blood O_2 pressure consistently <8 kPa (60 mmHg)	**IIa**	**C**	
In elective surgery, epidural rather than general anaesthesia should be preferred whenever possible	**IIa**	**C**	
Excessive physical activity that leads to distressing symptoms is not recommended in PAH patients	**III**	**C**	

O_2 = oxygen, PAH = pulmonary arterial hypertension, WHO-FC = World Health Organization functional class.
[a]Class of recommendation
[b]Level of evidence
[c]Reference(s) supporting recommendations

Transplantation
Transplantation should remain an option for patients who fail on medical therapies. Both heart and lung transplantation have been performed for PAH, although the threshold of unrecoverable right ventricle (RV) systolic function and/or left ventricle (LV) diastolic function is unknown. While RV afterload is immediately reduced after double lung transplantation, RV systolic and LV diastolic functions do not improve immediately and haemodynamic instability is a common problem in the early postoperative period. Both single and bilateral procedures have been performed with similar survival. Any complications occurring in the allograft following single lung transportation is associated with severe hypoxemia. The overall 5-year survival rate following transplantation for PAH is 45 to 50% with evidence of a good quality of life (Galiè, 2009).

SI.1.4 Natural history of the indicated condition in the (untreated) population, including mortality and morbidity

The National Institutes of Health Registry from 1981 to 1985 estimated the median survival of patients with iPAH as 2.8 years with 1, 3 and 5-year survival rates of 68%, 48% and 34%, respectively (D'Alonzo, 1991). These data reflected the era prior to the development of targeted medications for PAH. More recently, the 3-yr survival rate was 68% for PAH, 73% for PAH associated with LHD, 44% for PH-lung, 71% for CTEPH and 59% for miscellaneous PH (Hurdman, 2012) as shown in the following figure:

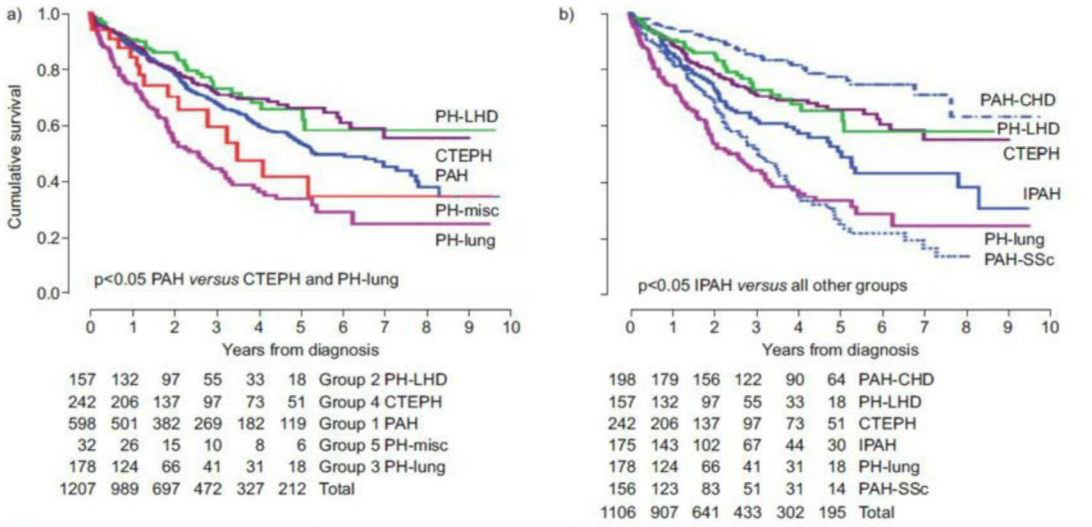

FIGURE 2. Cumulative survival from date of diagnosis a) in pulmonary hypertension (PH) by diagnostic group and b) in the six most common diagnostic subgroups of PH. PH-LHD: PH associated with left heart disease; CTEPH: chronic thromboembolic pulmonary hypertension; PAH: pulmonary arterial hypertension; PH-misc: miscellaneous PH; PH-lung: PH associated with lung disease; PAH-CHD: PAH associated with congenital heart disease; IPAH: idiopathic PAH; PAH-SSc: PAH associated with systemic sclerosis.

Pellino and colleagues evaluated mortality in all patients with iPAH or hPAH diagnosed at the Scottish Pulmonary Vascular Unit between January 1992 and March 2016; 1, 3 and 5-year survival was 82%, 52% and 41% respectively (Pellino, 2018). 5-year survival amongst iPAH was highest in patients aged 18–45 years (88%), whilst survival rates of 63%, 56% and 36% were observed for patients aged 6–64, 65–74 and ≥75 years, respectively in a study which evaluated data from all seven Swedish PAH centres ($p<0.001$). Ischaemic heart disease and kidney dysfunction independently predicted survival. Most individuals in this study started PAH targeted therapy within 3 months of diagnosis (Hjalmarsson, 2018).

An analysis of 1588 newly diagnosed with PAH between 2009 and 2016 from the COMPERA database which includes data from several specialist centres in Europe found that 29% of patients had died within 5 years after the diagnosis of PAH. Patients were stratified according to 2015 European pulmonary hypertension guidelines (based on WHO functional class, 6MWD, brain natriuretic peptide or its N-terminal fragment, right atrial pressure, cardiac index and mixed venous oxygen saturation) into low, intermediate and high-risk groups. The 5-year survival rates in the low, intermediate and high-risk groups were 75.9%, 51.9% and 32.4%, respectively (Hoeper, 2017).

All large published evaluations implicate hemodynamics as an important predictor of survival (McLaughlin, 2009). While a number of individual parameters have been investigated in PAH, few have demonstrated a predictive association with mortality in all, or even the majority of studies (Saggar, 2012). Predictors of a poor prognosis include: advanced functional class, poor exercise capacity as measured by 6-minute walk (6MW) test or cardiopulmonary exercise test, high right atrial (RA) pressure, significant right ventricular (RV) dysfunction, evidence of RV failure, low cardiac index, elevated brain natriuretic peptide (BNP), and underlying diagnosis of scleroderma spectrum of diseases (McLaughlin, 2009). Additional risk determinants for poor survival summarized across existing registry data include also higher risk for patients with increased creatinine

levels, lower diffusing capacity of the lung for carbon monoxide (DLCO), older age, male gender, etiology associated with CTD, increased cardiac index/outcome, and higher pulmonary vascular resistance (McGoon, 2013; Matsubara, 2014).

SI.1.5 Important co-morbidities

PAH Associated Symptoms

PAH symptoms are non-specific and can include dyspnoea (exertional dyspnoea and tachypnoea), unproductive cough, fatigue, dizziness, syncope/near syncope, hepatomegaly, oedema/peripheral oedema, and in some cases, chest pain. These symptoms, even in later stages of disease, can be confused with other cardiac and pulmonary disorders (Rich, 1987; Rich, 2012).

The prevalence of specified comorbidities present at baseline amongst incident iPAH patients in a recent Swedish study were: systemic hypertension 51%, diabetes mellitus 29%, ischaemic stroke 7%, ischaemic heart disease 18%, atrial fibrillation 17%, obesity 21% and kidney dysfunction 51%; differences by age group were observed (Hjalmarsson, 2018). Progression of PAH results in right ventricular failure manifested by progressive hypoxemia, tachycardia, hypotension, and oedema/peripheral oedema (Rich, 2012).

In patients with right ventricular failure, other symptoms observed to be prominent include congestive hepatomegaly and systemic venous distension. Liver function test (LFT) abnormalities have been observed in patients with chronic congestive heart failure (CHF) with higher elevations associated with increasing haemodynamic severity of heart failure, as evidence by increased right arterial pressure, increased pulmonary wedge pressure and decreased cardiac index (Kubo, 1987). While hepatic enzymes are frequently elevated, the occurrence of jaundice appears to be a late finding in heart failure secondary to hepatic congestion and hepatocellular hypoxia associated with central lobular atrophy (Mann, 2012).

Although hepatic congestion due to increased central venous pressure and right-sided heart failure secondary to pulmonary hypertension is not unexpected in PAH patients, specific information regarding the background incidence of transaminase elevations or liver injury in patients with PAH and PAH subpopulations (iPAH, PAH due to CTD, etc.) are not readily available. Hypoxic liver injury due to hepatic ischemia in the presence of underlying hepatic congestion or chronic liver disease has been described in typically elderly individuals with right-sided CHF and low cardiac output and has been characterized by massive transaminase elevations that are reversible, when other causes of liver injury have been excluded. However, hypoxic liver injury may also occur in cases confirmed by liver biopsy with low transaminase levels (Ebert, 2006).

PAH Associated Conditions

Several conditions including CTD, portal hypertension, human immunodeficiency virus (HIV), as well as exposure to drugs and toxins, are associated with PAH. The epidemiology of PAH associated with these conditions in Europe are also limited (Table 3). A recent literature review provided pooled prevalence estimates for PAH (Table 3).

Table 3 Epidemiology of PAH associated conditions

Diagnosis	Prevalence of PAH	Other Characteristics
Systemic sclerosis	See pooled estimate below (Table 4).	Mean Age 66; Male: Female ratio 1:4; Survival 1-year 81%; 2-year 63%, 3-year 56%. (Mukerjee, 2003).
HIV	0.5% (Rich, 2005)	Clinical and haemodynamic features similar to iPAH (McLaughlin, 2004). Male: Female ratio 1.6:1; No known link between stage/severity of HIV and PAH (Seoane, 2001).
Portal hypertension	2-6% (Hadengue, 1991) (Arcangali, 1996)	Histology and presenting symptoms are similar to iPAH; Older; Higher cardiac output and lower systemic and pulmonary vascular resistance than those with iPAH (McLaughlin, 2004).
Congenital heart disease	15-20% (Rich, 2005)	Related to type and size of the defect; Better prognosis than iPAH. Morphological changes indistinguishable from iPAH. Clinical manifestations similar to iPAH but may also experience cyanosis, haemoptysis, blood dyscrasias and paradoxical embolization resulting in cerebrovascular accidents (McLaughlin, 2004)
Appetite suppressants	OR=6.3 (95%CI 3.0-13.2) OR=10.1 (3.4-29.9) if drugs used in past year OR=23.1 (6.9-77.7) if drugs used more than 3 months (Abenhaim, 1996)	

Table 4 Pooled prevalence estimates of PAH by meta-analysis (adapted from Yang, 2013)

Subgroup	Pooled prevalence	95% Confidence interval	Number of studies
iPAH (cases/million)	12	5-22	3
CTD (%)	13	9.18-18.16	17
SS (%)	13	8.96-17.87	12
SLE (%)	3.34	2.10-4.86	2
RA (%)	22.3	16.63-28.48	2

iPAH: idiopathic pulmonary arterial hypertension, CTD: connective tissue disease, SS: systemic sclerosis; SLE: systemic lupus erythematous; RA: rheumatoid arthritis

Connective Tissue Diseases Associated Symptoms

PAH linked with a range of connective tissue diseases comprises approximately 30% of the ambrisentan registration patient population. Clinically, histologically and therapeutically, PAH associated with collagen vascular disease, such as systemic lupus erythematosus (SLE), rheumatoid arthritis, Sjögrens' syndrome and scleroderma, is often indistinguishable from iPAH (Hoeper, 2002). However, when considering the safety profile of therapies such as ERAs used to treat CTD associated PAH, it is important to consider that the CTDs may frequently involve multiple organ systems such as the heart (independent of PAH related right heart failure), kidneys, gastrointestinal, hematologic, neurologic, skin, eyes, and musculoskeletal system. Liver and hepatobiliary involvement may also be a prominent feature for some patients with CTDs.

Although liver involvement associated with CTD is not the most common complication, abnormal LFTs are not uncommon (Youssef, 2002) and autoimmune hepatitis with severe cholestasis and acute liver failure in association with mixed CTD and Sjögren's syndrome have been reported in the literature (Min, 2001). Further, SLE-associated hepatitis is a well recognised entity. Albeit limited, published data suggest that the lifetime prevalence of transaminase abnormalities for patients with SLE may range from 25 to 50%. Another important consideration in patients with CTD- associated PAH and transaminase abnormalities is that hepatic injury associated with therapies for the CTD such as aspirin, salicylates, gold therapy, and methotrexate may represent a significant confounding factor in evaluating the safety profile of PAH therapies (Youssef, 2002).

SI.2 Indication – Paediatric Pulmonary Arterial Hypertension

Historically, the threshold for pulmonary arterial hypertension (PAH) among children has been identical to that in adults (mean pulmonary arterial pressure (mPAP) ≥25 mm Hg) (Ivy, 2016). PAP is similar to systemic pressure in fetal circulation and rapidly falls after birth, achieving levels similar to those of adults by age 2–3 months. Given variability in pulmonary

hemodynamics during post-natal transition, paediatric PAH has been defined as mPAP ≥25 mm Hg after age 3 months. Age of onset for this condition is diverse within the paediatric population and there is a characteristic difference compared to adult PAH in etiology – idiopathic PAH and PAH associated with congenital heart disease and developmental lung disease are more common in paediatric PAH. Paediatric PAH, especially idiopathic PAH, is a progressive condition marked by substantial disability and eventual death. Treatments for paediatric PAH borrow from experience in the adult setting and constitute the same major classes – calcium channel blockers (CCBs), prostanoids, phosphodiesterase-5 inhibitors, and endothelin receptor antagonists (ERAs) (Rosenzweig, 2019).

SI.2.1. Incidence and Prevalence

Paediatric PAH is a rare condition with low incidence and prevalence in Europe. A Dutch study assessing paediatric PAH (mean age 2.2 years overall, 4.3 for idiopathic PAH) for the 1991-2005 period reported annual average incidence rates of 3.0 cases per million per year and 0.7 cases per million per year for overall and idiopathic PAH, respectively (van Loon, 2011). A retrospective study of 64 children (mean age 6.5 years at presentation) at a tertiary referral centre in the United Kingdom reported similar incidence rates to the Dutch study for idiopathic PAH at 0.48 per million per year (Moledina, 2010). A Spanish registry on 225 patients from 2009 to 2012 similarly reported an idiopathic PAH incidence rate of 0.49 cases per million per year. Overall PAH was 4.3 cases per million per year (del Cerro Marín, 2014).

Reported prevalence of idiopathic PAH in the Dutch, English, and Spanish cohorts was 4.4 cases per million, 2.07 cases per million, and 2.9 cases per million, respectively. Prevalence of overall PAH in the Dutch and Spanish cohorts was relatively consistent at 20 and 20.2 cases per million, respectively. In a French cohort with mean age 8.9 years, overall prevalence was 3.7 cases per million (Fraisse, 2010).

Reported incidence and prevalence patterns for European sub-populations are in line with United States estimates but differ from Canadian estimates. A MarketScan based study in the United States reported annual incidences ranging from 1-3 cases per million children years for overall PAH, as well as a prevalence of roughly 20 cases per million for the 12 - <18 age group (Li, 2017). A population-based cohort in Ontario, Canada reported a much higher incidence rate and prevalence at of 31 per million children years and 57.9 per million, respectively (Wijeratne, 2018).

SI.2.2. The main existing treatment options

As in adults, the goal of treatment for paediatric PAH patients is prevention of clinical progression markers such as right ventricular failure, worsening symptoms, syncope, significantly elevated or rising brain natriuretic peptide (BNP) levels, pericardial effusion, and hemodynamic parameters such as mPAP/mean systemic arterial pressure (mSAP) ratio >0.75 (Ivy, 2013). There is a lack of complete agreement on treatment strategy, but the general framework is repeated monitoring accompanied by pharmacological intervention with lung transplantation reserved for the most severe or non-responsive cases. Several factors contribute to the choice of pharmacological agent including severity/course of symptoms as well as acute vasoreactivity. For those positive for acute vasoreactivity testing, calcium channel blockers

(CCB) are most frequent. For those negative for acute vasoreactivity, monotherapy or combination therapy with endothelin receptor antagonists and phosphodiesterase-5 inhibitors are generally administered for lower risk of progression patients while prostanoids are generally administered for higher risk of progression patients. In many cases, background therapy with anticoagulants, diuretics, and oxygen is also administered (Rosenzweig, 2019).

Common pharmacological classes:

Calcium channel blockers (CCB): CCBs are first line pharmacological therapy for acute responders and are often combined with other treatment options such as sildenafil. Proportion of patients administered CCBs range from 7%-12% (Moledina, 2010; Zijlstra, 2014; Fraisse, 2010).

Endothelin Receptor Antagonists (ERAs): ERAs are first line pharmacological treatments among non- acute responders. Bosentan is the most commonly used ERA, followed by Ambrisentan. In notable UK and French (mean age 8.9 years) cohorts of paediatric PAH patients, 48% and 76% of patients were administered Bosentan as monotherapy (Moledina, 2010; Fraisse, 2010). Bosentan has shown favorable safety and efficacy in clinical studies in the paediatric population (Ivy, 2010; Berger, 2016).

Phosphodiesterase-5 inhibitors (PDE-5): Along with ERAs, PDE-5 are first line pharmacological treatments among non-acute responders. PDE-5 administration appears more variable, ranging from 6% and 8% in notable French (mean age 8.9 years) and UK cohorts to 57% in a US cohort (Moledina, 2010; Fraisse, 2010; Barst 2012). PDE-5 has shown favorable efficacy but there are some concerns about safety of sildenafil in the paediatric population, due to an apparent increase in mortality during long-term therapy. Evidence suggests that low-dose sildenafil is likely to be safe for children (Abman 2013).

Prostacyclins: Prostacyclins are both first-and second line pharmacological treatments among non-acute responders, administered orally (Iloprost, treplostinil) or intravenously (epoprostenol, treprostinil) in more high-risk patients. In a US cohort, 42% of patients were administered prostacyclin analogs (Barst 2012). Prostacyclins are often combined with PDE-5 and ERAs in management of progressive PAH. Prostacyclins have shown favorable efficacy and safety in the paediatric population (Ivy, 2008; Tissot 2009).

SI.2.3 Mortality and natural course of condition

Paediatric PAH is a progressive condition and there is substantial continued decline in survival even with treatment. Moledina, 2010. reported survival at 1, 3, and 5 years of 89%, 84%, and 75%, respectively, as well as transplantation-free survival of 89%, 76%, and 57%, respectively. Zijlstra, 2014 and Ploegstra, 2015 (mean age **8** years) reported similar transplantation-free survival proportions of 84%, 71%, and 62% and 76%, 64%, and 56%, respectively, in two Dutch cohorts. Zuk, 2016 reported 1,3,5, and 10-year survival of 83.1%, 77.1%, 70.7%, and 65.2%, respectively for patients treated at a single Polish centre from 2004-2013. Another Dutch cohort with substantial follow-up of nearly 15 years estimated a median survival time of 7.7 years (van Loon, 2011).

SI.2.4 Important co-morbidities

Paediatric PAH is associated with several co-morbidities, including congenital heart disease, portal hypertension, and connective tissues disorders, which in themselves can be causative of the condition. Of these, congenital heart disease is by far the most common co-occurring condition. Other rare co-morbidities include HIV positive status and Down Syndrome. Congenital heart disease is highly common among PAH patients, present in nearly half (van Loon, 2011). Portal hypertension and connective tissue disorders, by comparison, are significantly rarer at 2% and 4% among paediatric PAH patients (Fraisse, 2010). Above estimates by Fraisse et al. in France are slightly higher than United States estimates of 0.4% and 0.5% for portal hypertension and connective tissue disorders, respectively (Ong, 2019).

PART II: MODULE SII - NON-CLINICAL PART OF THE SAFETY SPECIFICATION

A high-level summary of significant non-clinical safety findings is presented in Table 5.

Table 5 Key safety findings from non-clinical studies and relevance to human usage

Key Safety findings (from non-clinical studies)	Relevance to human usage
Toxicity including:	
Key issues identified from acute or repeat-dose toxicity studies Nasal effects	Nasal congestion common ADR generally tolerated by patients, as there were few withdrawals or severe events.
Reproductive/developmental toxicity	
Male fertility: Testicular tubular atrophy without consistent findings related to sperm motility or fertility. A slight (10%) decrease in the percentage of morphologically normal sperms was noted.	Uncertain clinical relevance to human male reproductive hormones or fertility. Data, albeit limited, from clinical studies did not demonstrate clinically relevant effects of ambrisentan on semen or male reproductive hormones.
Developmental toxicity: Teratogenicity is a class effect of ERAs including ambrisentan. There are no preclinical or clinical data with ambrisentan available to assess if ambrisentan is excreted into breast milk.	Teratogenicity findings appear to be pharmacologically mediated and have occurred at clinically relevant exposures that are considered to have clinical relevance to humans.
Genotoxicity	
Clastogenic when tested at high concentrations in mammalian cells in vitro. No evidence for mutagenic or genotoxic effects was seen in bacteria or in two in vivo rodent studies.	The in vitro finding was not considered relevant to humans, since there was no evidence of genotoxicity in animal studies.
Carcinogenicity	
Statistically significant increase in the incidence of mammary gland fibroadenoma, a benign tumor, in male rats treated at the highest dose level (mean dose of 42 mg/kg/day).	Not considered relevant to humans. Since mammary fibroadenoma is a benign tumor which can occur spontaneously in male rats of this strain, this small increase is not considered to signify carcinogenic potential.

General Safety Pharmacology Cardiovascular System: Electrocardiogram (ECG) findings – cardiovascular effects were variable between studies and between species.	AMB-104 definitive QT study: a slight increase in QTcIb interval but was less than threshold of usual clinical concern. Study results support conclusion that therapeutic doses of ambrisentan are not likely to be associated with QT prolongation. ECG abnormalities observed in clinical trials were considered consistent with the underlying disease or assessed as not clinically significant and were relatively similar across treatment groups.
Other toxicity-related information or data Brain-weight decrement in 7 day old juvenile rats given ambrisentan for 8 weeks with no morphologic or neurobehavioral changes occurred after breathing sounds, apnoea and hypoxia were observed, at exposures approximately 1.8 to 7 times human paediatric (age 9 to 15 years) exposures at 10 mg, based on AUC. Juvenile rat mean AUCs were 21.4, 52.5 and 89.25 µg.h/mL on Postnatal Day 7 (Day 1 of dosing) at 4, 10 and 20 mg/kg, which is 1.8, 4.4 and 7.4 times the paediatric exposure of AUC of 12.0 ug.hr/mL associated with a 10 mg dose in published literature [Takatsuki 2013], respectively.	This finding is considered not relevant to human adults or children aged 8 to less than 18 years. The clinical relevance of this finding to the younger paediatric population is not fully understood. Ambrisentan is not indicated for treatment of pulmonary arterial hypertension in patients below 8 years of age.

PART II: MODULE SIII - CLINICAL TRIAL EXPOSURE

The following tables present ambrisentan exposure from clinical trials sponsored by GILEAD and GSK.

Table 6 Estimated Cumulative Duration of Exposure to Ambrisentan in Ambrisentan Clinical Trials (sponsored by Gilead) through 14 June 2019 by Indication

		Double-Blind in Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Indication	Duration of Exposure	N	Person-Years	N	Person Years
Chronic Allograft Injury	≥ 1 Day	0	0	87	2
	> 10 Days	0	0	24	0.8
	> 20 Days	0	0	0	0
	> 30 Days	0	0	0	0
	> 90 Days	0	0	0	0
	> 180 Days	0	0	0	0
	> 365 Days	0	0	0	0
	Total person time	0	0	87	2
Idiopathic Pulmonary Fibrosis	≥ 1 Day	0	0	329	235.6
	> 10 Days	0	0	328	235.6
	> 20 Days	0	0	319	235.2
	> 30 Days	0	0	315	234.9
	> 90 Days	0	0	278	228.3
	> 180 Days	0	0	215	204.5
	> 365 Days	0	0	79	101.5
	Total person time	0	0	329	235.6

		Double-Blind in Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Indication	**Duration of Exposure**	**N**	**Person-Years**	**N**	**Person Years**
Pulmonary Arterial Hypertension	≥ 1 Day	0	0	1171	2503.4
	> 10 Days	0	0	1097	2502
	> 20 Days	0	0	964	2496.1
	> 30 Days	0	0	952	2495.2
	> 90 Days	0	0	916	2489.6
	> 180 Days	0	0	868	2473
	> 365 Days	0	0	749	2381.4
	Total person time	0	0	1171	2503.4
Pulmonary Hypertension	≥ 1 Day			224	412.8
	> 10 Days			219	412.7
	> 20 Days			218	412.7
	> 30 Days			212	412.2
	> 90 Days			198	409.7
	> 180 Days			174	399
	> 365 Days			113	352.9
	Total person time			224	412.8
Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis	≥ 1 Day	0	0	25	9.9
	> 10 Days	0	0	24	9.9
	> 20 Days	0	0	24	9.9
	> 30 Days	0	0	19	9.5
	> 90 Days	0	0	13	8.7

		Double-Blind in Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Indication	Duration of Exposure	N	Person-Years	N	Person Years
	> 180 Days	0	0	11	7.9
	> 365 Days	0	0	0	0
	Total person time	0	0	25	9.9

Note: Studies included are AMB-220, AMB-220E, AMB-222, AMB-320, AMB-321, AMB-320/321, AMB-323, GS-US-300-0111, GS-US-300-0112, GS-US-300-0113, GS-US-300-0116, GS-US-300-0117, GS-US-300-0124, GS-US-300-0128, GS-US-300-0139, GS-US-300-0140, GS-US-231-0101, GS-US-244-0102, GS-US-244-0103.

Note: Subjects receiving ambrisentan and another drug are counted under the ambrisentan group only.

Note: Person Years = sum of days on study drug over all subjects, divided by 365.25. For ongoing subjects, date of last dose is estimated.

Table 6A Estimated Cumulative Duration of Exposure to Ambrisentan in Ambrisentan Clinical Trials (sponsored by GSK) through 14 June 2019 by Indication

		Double-Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Indication	Duration of Exposure	Patient (N)	Patient Years[1]	Patient (N)	Patient Years[1]
CTEPH	≥ 1 Day	17	5.0	19	13.0
	> 10 Days	17	5.0	19	13.0
	> 20 Days	17	5.0	19	13.0

		Double-Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Indication	**Duration of Exposure**	**Patient (N)**	**Patient Years[1]**	**Patient (N)**	**Patient Years[1]**
	> 30 Days	17	5.0	18	12.9
	> 90 Days	15	4.6	17	12.8
	> 180 Days	0	0	13	11.4
	> 365 Days	0	0	6	6.8
	Total	17	5.0	19	13.0
Healthy Volunteers	≥ 1 Day	0	0	113	1.2
	> 10 Days	0	0	0	0
	> 20 Days	0	0	0	0
	> 30 Days	0	0	0	0
	> 90 Days	0	0	0	0
	> 180 Days	0	0	0	0
	> 365 Days	0	0	0	0
	Total	0	0	113	1.2
Pediatric Pulmonary Arterial Hypertension	≥ 1 Day	41	18.1	38	144.6
	> 10 Days	41	18.1	38	144.6
	> 20 Days	40	18.1	38	144.6
	> 30 Days	40	18.1	38	144.6

		Double-Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Indication	**Duration of Exposure**	**Patient (N)**	**Patient Years[1]**	**Patient (N)**	**Patient Years[1]**
	> 90 Days	38	17.7	38	144.6
	> 180 Days	2	1.0	37	144.3
	> 365 Days	0	0	34	141.8
	Total	41	18.1	38	144.6
Pulmonary Arterial Hypertension	≥ 1 Day	0	0	184	128.9
	> 10 Days	0	0	182	128.9
	> 20 Days	0	0	180	128.8
	> 30 Days	0	0	180	128.8
	> 90 Days	0	0	172	127.7
	> 180 Days	0	0	24	59.8
	> 365 Days	0	0	21	57.7
	Total	0	0	184	128.9

[1]Patient years = sum of days on study drug over all patients / 365.2422

Included studies are AMB115812, AMB112529, AMB114588, AMB115811, AMB116457, 201964, AMB107623 and AMB107816.

Table 7 Estimated Cumulative Duration of Exposure to Ambrisentan in Ambrisentan Clinical Trials (sponsored by Gilead) through 14 June 2019 – for all indications

	Double-Blind in Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Duration of Exposure	N	Person Years	N	Person Years
≥ 1 Day	0	0	1836	3163.7
> 10 Days	0	0	1692	3161
> 20 Days	0	0	1525	3153.9
> 30 Days	0	0	1498	3151.9
> 90 Days	0	0	1405	3136.2
> 180 Days	0	0	1268	3084.4
> 365 Days	0	0	941	2835.8
Total	0	0	1836	3163.7

Note: Studies included are AMB-220, AMB-220E, AMB-222, AMB-320, AMB-321, AMB-320/321, AMB-323, GS-US-300-0111, GS-US-300-0112, GS-US-300-0113, GS-US-300-0116, GS-US-300-0117, GS-US-300-0124, GS-US-300-0128, GS-US-300-0139, GS-US-300-0140, GS-US-231-0101, GS-US-244-0102, GS-US-244-0103.

Note: Subjects receiving ambrisentan and another drug are counted under the ambrisentan group only.

Note: Person Years = sum of days on study drug over all subjects, divided by 365.25. For ongoing subjects, date of last dose is estimated.

Table 7A Estimated Cumulative Duration of Exposure to Ambrisentan in Ambrisentan Clinical Trials (GSK sponsored) through 14 June 2019

	Double-Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Duration of Exposure	Patient (N)	Patient Years[1]	Patient (N)	Patient Years[1]
≥ 1 Day	58	23.1	354	287.7
> 10 Days	58	23.1	239	286.5
> 20 Days	57	23.1	237	286.4
> 30 Days	57	23.1	236	286.3
> 90 Days	53	22.3	227	285.1
> 180 Days	2	1.0	74	215.5
> 365 Days	0	0	61	206.3
Total	58	23.2	354	287.7

[1]Patient years = sum of days on study drug over all patients / 365.2422

Included studies are AMB115812, AMB112529, AMB114588, AMB115811, AMB116457, 201964, AMB107623 and AMB107816.

Table 8 Estimated Cumulative Duration of Exposure to Ambrisentan in Ambrisentan Clinical Trials (sponsored by Gilead) through 14 June 2019 by Indication and Dose

		Double-Blind in Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Indication	Dose Level	N	Person-Years	N	Person-Years
	1 mg	0	0	0	0
	2.5 mg	0	0	0	0

		Double-Blind in Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Indication	**Dose Level**	**N**	**Person-Years**	**N**	**Person-Years**
Chronic Allograft Injury	5 mg	0	0	87	2
	10 mg	0	0	0	0
	Total	0	0	87	2
Idiopathic Pulmonary Fibrosis	1 mg	0	0	0	0
	2.5 mg	0	0	0	0
	5 mg	0	0	0	0
	10 mg	0	0	329	235.6
	Total	0	0	329	235.6
Pulmonary Arterial Hypertension	1 mg	0	0	2	0.3
	2.5 mg	0	0	40	70.7
	5 mg	0	0	320	566.2
	10 mg	0	0	809	1866.3
	Total	0	0	1171	2503.4
Pulmonary Hypertension	1 mg	0	0	0	0
	2.5 mg	0	0	0	0
	5 mg	0	0	103	101.5
	10 mg	0	0	121	311.3
	Total	0	0	224	412.8
Pulmonary Hypertension Associated with	1 mg	0	0	0	0
	2.5 mg	0	0	0	0
	5 mg	0	0	0	0

		Double-Blind in Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Indication	Dose Level	N	Person-Years	N	Person-Years
Idiopathic Pulmonary Fibrosis	10 mg	0	0	25	9.9
	Total	0	0	25	9.9

Note: Studies included are AMB-220, AMB-220E, AMB-222, AMB-320, AMB-321, AMB-320/321, AMB-323, GS-US-300-0111, GS-US-300-0112, GS-US-300-0113, GS-US-300-0116, GS-US-300-0117, GS-US-300-0124, GS-US-300-0128, GS-US-300-0139, GS-US-300-0140, GS-US-231-0101, GS-US-244-0102, GS-US-244-0103.

Note: Subjects receiving ambrisentan and another drug are counted under the ambrisentan group only.

Note: Person Years = sum of days on study drug over all subjects, divided by 365.25. For ongoing subjects, date of last dose is estimated.

Note: For studies GS-US-300-0117, GS-US-300-0128, GS-US-231-0101, titration from 5 mg to 10 mg was specified per protocol and patients are counted under the 10 mg dose; for other studies, patients receiving more than one dose level are counted under the maximum dose received.

Table 8A Estimated Cumulative Duration of Exposure to Ambrisentan in Ambrisentan Clinical Trials (GSK sponsored) 14 June 2019 by Indication and Dose

		Double-Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Indication	Dose Level [2]	Patient (N)	Patient Years[1]	Patient (N)	Patient Years[1]
CTEPH	2.5 mg	0	0	0	0
	5 mg	17	5.0	19	9.0
	7.5 mg	0	0	0	0

		Double-Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Indication	**Dose Level [2]**	**Patient (N)**	**Patient Years[1]**	**Patient (N)**	**Patient Years[1]**
	10 mg	0	0	8	4.0
	N/A [4]	0	0	0	0
	Data currently not recorded in eCRF [3]	0	0	0	0
	Total	17	5.0	19	13.0
Healthy Volunteers	2.5 mg	0	0	12	0
	5 mg	0	0	11	0.0
	7.5 mg	0	0	0	0
	10 mg	0	0	101	1.1
	N/A [4]	0	0	0	0
	Data currently not recorded in eCRF [3]	0	0	0	0
	Total	0	0	113	1.2
Pediatric Pulmonary Arterial Hypertension	2.5 mg	0	0	10	21.4
	5 mg	0	0	25	75.7
	7.5 mg	0	0	11	20.2
	10 mg	0	0	12	27.3
	N/A [4]	41	18.1	0	0

		Double-Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Indication	**Dose Level [2]**	**Patient (N)**	**Patient Years[1]**	**Patient (N)**	**Patient Years[1]**
	Data currently not recorded in eCRF [3]	0	0	0	0
	Total	41	18.1	38	144.6
Pulmonary Arterial Hypertension	2.5 mg	0	0	0	0
	5 mg	0	0	184	67.3
	7.5 mg	0	0	0	0
	10 mg	0	0	111	59.7
	N/A [4]	0	0	0	0
	Data currently not recorded in eCRF [3]	0	0	0	0
	Total	0	0	184	127.0

[1]Patient years = sum of days on study drug over all patients / 365.2422

[2]Patients may be counted for more than one dose level

[3]In the absence of data, patients are assumed to be ongoing with study drug from date of entry into the study

[4]N/A as dose level not available since patients are still in DB phase

Included studies are AMB115812, AMB112529, AMB114588, AMB115811, AMB116457, 201964, AMB107623 and AMB107816.

Table 9 Estimated Cumulative Duration of Exposure to Ambrisentan in Ambrisentan Clinical Trials (sponsored by Gilead) through 14 June 2019 by Dose

	Double-Blind in Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Dose Level	**N**	**Person-Years**	**N**	**Person-Years**
1 mg	0	0	2	0.3
2.5 mg	0	0	40	70.7
5 mg	0	0	510	669.6
10 mg	0	0	1284	2423.1
Blinded Study Medication	0	0	0	0
Total	0	0	1836	3163.7

Note: Studies included are AMB-220, AMB-220E, AMB-222, AMB-320, AMB-321, AMB-320/321, AMB-323, GS-US-300-0111, GS-US-300-0112, GS-US-300-0113, GS-US-300-0116, GS-US-300-0117, GS-US-300-0124, GS-US-300-0128, GS-US-300-0139, GS-US-300-0140, GS-US-231-0101, GS-US-244-0102, GS-US-244-0103.

Note: Subjects receiving ambrisentan and another drug are counted under the ambrisentan group only.

Note: Person Years = sum of days on study drug over all subjects, divided by 365.25. For ongoing subjects, date of last dose is estimated.

Note: For Studies GS-US-300-0117, GS-US-300-0128, GS-US-231-0101, titration from 5 mg to 10 mg was specified per protocol and patients are counted under the 10 mg dose; for other studies, patients receiving more than one dose level are counted under the maximum dose received.

Table 9A Estimated Cumulative Duration of Exposure to Ambrisentan in Ambrisentan Clinical Trials (GSK sponsored) through 14 June 2019 by Dose

	Double-Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Dose Level [2]	**Patient (N)**	**Patient Years[1]**	**Patient (N)**	**Patient Years[1]**
2.5 mg	0	0	22	21.4
5 mg	17	5.0	239	152.1
7.5 mg	0	0	11	20.2
10 mg	0	0	232	92
N/A [4]	41	18.1	0	0
Data currently not recorded in eCRF [3]	0	0	0	0
Total	58	23.2	354	285.8

[1]Patient years = sum of days on study drug over all patients / 365.2422

[2]Patients may be counted for more than one dose level

[3]In the absence of data, patients are assumed to be ongoing with study drug from date of entry into the study

[4]N/A as dose level not available since patients are still in DB phase

Included studies are AMB115812, AMB112529, AMB114588, AMB115811, AMB116457, 201964, AMB107623 and AMB107816.

Table 10 Estimated Cumulative Duration of Exposure to Ambrisentan in Ambrisentan Clinical Trials (sponsored by Gilead) through 14 June 2019 by Indication, Age Group and Sex

	Double-Blind in Blind Phase (Exposure to Blinded Treatment)					Open Label/Completed (Exposure to Ambrisentan)			
	Person			Patient-Years		Person		Patient-Years	
Indication	Age Group	M	F	M	F	M	F	M	F
Chronic Allograft Injury	<18 Yrs	0	0	0	0	0	0	0	0
	18 - 64 Yrs	0	0	0	0	87	0	2	0
	65 - 75 Yrs	0	0	0	0	0	0	0	0
	>75 Yrs	0	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0	0
	Total	0	0	0	0	87	0	2	0
Idiopathic Pulmonary Fibrosis	<18 Yrs	0	0	0	0	0	0	0	0
	18 - 64 Yrs	0	0	0	0	103	34	80.9	23
	65 - 75 Yrs	0	0	0	0	120	42	82.6	27.2
	>75 Yrs	0	0	0	0	21	9	14.2	7.6
	Missing	0	0	0	0	0	0	0	0
	Total	0	0	0	0	244	85	177.7	57.9
Pulmonary Arterial Hypertension	<18 Yrs	0	0	0	0	0	1	0	13
	18 - 64 Yrs	0	0	0	0	266	626	378.4	1574.7

	Double-Blind in Blind Phase (Exposure to Blinded Treatment)					Open Label/Completed (Exposure to Ambrisentan)			
	Person			Patient-Years		Person		Patient-Years	
Indication	Age Group	M	F	M	F	M	F	M	F
	65 - 75 Yrs	0	0	0	0	59	200	104.2	395.4
	>75 Yrs	0	0	0	0	5	14	8.6	29
	Missing	0	0	0	0	0	0	0	0
	Total	0	0	0	0	330	841	491.3	2012.1
Pulmonary Hypertension	<18 Yrs	0	0	0	0	0	0	0	0
	18 - 64 Yrs	0	0	0	0	34	118	73.3	202.8
	65 - 75 Yrs	0	0	0	0	25	30	38	64.7
	>75 Yrs	0	0	0	0	9	8	15.4	18.6
	Missing	0	0	0	0	0	0	0	0
	Total	0	0	0	0	68	156	126.7	286.1
Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis	<18 Yrs	0	0	0	0	0	0	0	0
	18 - 64 Yrs	0	0	0	0	9	1	5.1	0.1
	65 - 75 Yrs	0	0	0	0	7	3	2.3	0.7
	>75 Yrs	0	0	0	0	4	1	1.6	0.1
	Missing	0	0	0	0	0	0	0	0
	Total	0	0	0	0	20	5	9	0.9

Note: Studies included are AMB-220, AMB-220E, AMB-222, AMB-320, AMB-321, AMB-320/321, AMB-323, GS-US-300-0111, GS-US-300-0112, GS-US-300-0113, GS-US-300-0116, GS-US-300-0117, GS-US-300-0124, GS-US-300-0128, GS-US-300-0139, GS-US-300-0140, GS-US-231-0101, GS-US-244-0102, GS-US-244-0103.

Note: Subjects receiving ambrisentan and another drug are counted under the ambrisentan group only.

Note: Person Years = sum of days on study drug over all subjects, divided by 365.25. For ongoing subjects, date of last dose is estimated.

Table 10A Estimated Cumulative Duration of Exposure to Ambrisentan in Ambrisentan Clinical Trials (GSK sponsored) through 14 June 2019 by Indication, Age Group, and Sex

		Double-Blind Phase (Exposure to Blinded Treatment)				Open Label/Completed (Exposure to Ambrisentan)			
		Patient [N]		Patient Year[1]		Patient [N]		Patient Year[1]	
Indication	Age Group	M	F	M	F	M	F	M	F
CTEPH	Children (2-11 years)	0	0	0	0	0	0	0	0
	Adolescents (12-17 years)	0	0	0	0	0	0	0	0
	Adults (18-64 years)	5	4	1.5	1.2	6	6	4.6	3.7
	Elderly people (65-74 years)	1	3	0.3	0.9	2	2	1.9	1.8
	Elderly people (75-84 years)	3	1	0.8	0.3	1	2	0.2	0.8
	Missing	0	0	0	0	0	0	0	0
	Total	9	8	2.6	2.4	9	10	6.6	6.4
Healthy Volunteers	Children (2-11 years)	0	0	0	0	0	0	0	0
	Adolescents (12-17 years)	0	0	0	0	0	0	0	0
	Adults (18-64 years)	0	0	0	0	112	1	1.2	0.0
	Elderly people (65-74 years)	0	0	0	0	0	0	0	0
	Elderly people (75-84 years)	0	0	0	0	0	0	0	0

		Double-Blind Phase (Exposure to Blinded Treatment)				Open Label/Completed (Exposure to Ambrisentan)			
		Patient [N]		Patient Year[1]		Patient [N]		Patient Year[1]	
Indication	**Age Group**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
	Missing	0	0	0	0	0	0	0	0
	Total	0	0	0	0	112	1	1.2	0.0
Pediatric Pulmonary Arterial Hypertension	Children (2-11 years)	5	9	2.3	4.0	5	9	27.7	39.3
	Adolescents (12-17 years)	9	18	4.0	7.8	8	16	24.4	53.1
	Adults (18-64 years)	0	0	0	0	0	0	0	0
	Elderly people (65-74 years)	0	0	0	0	0	0	0	0
	Elderly people (75-84 years)	0	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0	0
	Total	14	27	6.4	11.8	13	25	52.2	92.5
Pulmonary Arterial Hypertension	Children (2-11 years)	0	0	0	0	0	0	0	0
	Adolescents (12-17 years)	0	0	0	0	0	0	0	0
	Adults (18-64 years)	0	0	0	0	26	154	18.7	106.7
	Elderly people (65-74 years)	0	0	0	0	0	4	0	3.5
	Elderly people (75-84 years)	0	0	0	0	0	0	0	0

		Double-Blind Phase (Exposure to Blinded Treatment)				Open Label/Completed (Exposure to Ambrisentan)			
		Patient [N]		Patient Year[1]		Patient [N]		Patient Year[1]	
Indication	**Age Group**	**M**	**F**	**M**	**F**	**M**	**F**	**M**	**F**
	Missing	0	0	0	0	0	0	0	0
	Total	0	0	0	0	26	158	18.7	110.2

Table 11 Estimated Cumulative Duration of Exposure to Ambrisentan in Ambrisentan Clinical Trials (sponsored by Gilead) through 14 June 2019 by Product, Age Group and Sex

		Double-Blind in Blind Phase (Exposure to Blinded Treatment)				Open Label/Completed (Exposure to Ambrisentan)			
		Person		Person-Years		Person		Person-Years	
Product	Age Group	M	F	M	F	M	F	M	F
Ambrisentan	<18 Yrs	0	0	0	0	0	1	0	13
	18 - 64 Yrs	0	0	0	0	499	779	539.7	1800.6
	65 - 75 Yrs	0	0	0	0	211	275	227.2	488
	>75 Yrs	0	0	0	0	39	32	39.8	55.3
	Missing	0	0	0	0	0	0	0	0
	Total	0	0	0	0	749	1087	806.7	2357
Cyclosporine	<18 Yrs	0	0	0	0	0	0	0	0
	18 - 64 Yrs	0	0	0	0	2	0	0	0
	65 - 75 Yrs	0	0	0	0	0	0	0	0
	>75 Yrs	0	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0	0
	Total	0	0	0	0	2	0	0	0
Mycophenolate Mofetil	<18 Yrs	0	0	0	0	0	0	0	0
	18 - 64 Yrs	0	0	0	0	2	0	0	0

		Double-Blind in Blind Phase (Exposure to Blinded Treatment)				Open Label/Completed (Exposure to Ambrisentan)			
		Person		Person-Years		Person		Person-Years	
Product	Age Group	M	F	M	F	M	F	M	F
	65 - 75 Yrs	0	0	0	0	0	0	0	0
	>75 Yrs	0	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0	0
	Total	0	0	0	0	2	0	0	0
Ritonavir	<18 Yrs	0	0	0	0	0	0	0	0
	18 - 64 Yrs	0	0	0	0	1	0	0	0
	65 - 75 Yrs	0	0	0	0	0	0	0	0
	>75 Yrs	0	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0	0
	Total	0	0	0	0	1	0	0	0
Placebo	<18 Yrs	0	0	0	0	0	0	0	0
	18 - 64 Yrs	0	0	0	0	42	30	29.7	14.9
	65 - 75 Yrs	0	0	0	0	69	31	45.1	25.1
	>75 Yrs	0	0	0	0	12	5	8.3	4.2
	Missing	0	0	0	0	0	0	0	0
	Total	0	0	0	0	123	66	83.2	44.2
Tadalafil	<18 Yrs	0	0	0	0	0	0	0	0

		Double-Blind in Blind Phase (Exposure to Blinded Treatment)				Open Label/Completed (Exposure to Ambrisentan)			
		Person		Person-Years		Person		Person-Years	
Product	Age Group	M	F	M	F	M	F	M	F
	18 - 64 Yrs	0	0	0	0	17	64	24.7	102.1
	65 - 75 Yrs	0	0	0	0	9	33	10.9	52
	>75 Yrs	0	0	0	0	0	0	0	0
	Missing	0	0	0	0	0	0	0	0
	Total	0	0	0	0	26	97	35.6	154.1

Note: Studies included are AMB-220, AMB-220E, AMB-222, AMB-320, AMB-321, AMB-320/321, AMB-323, GS-US-300-0111, GS-US-300-0112, GS-US-300-0113, GS-US-300-0116, GS-US-300-0117, GS-US-300-0124, GS-US-300-0128, GS-US-300-0139, GS-US-300-0140, GS-US-231-0101, GS-US-244-0102, GS-US-244-0103.

Note: Subjects receiving ambrisentan and another drug are counted under the ambrisentan group only.

Note: Person Years = sum of days on study drug over all subjects, divided by 365.25. For ongoing subjects, date of last dose is estimated.

As GSK did not use additional medicinal products in the GSK sponsored ambrisentan studies, no Table 11A is required.

Table 12 Estimated Cumulative Duration of Exposure to Ambrisentan in Ambrisentan Clinical Trials (sponsored by Gilead) through 14 June 2019 by Age Group and Sex

	Double-Blind in Blind Phase (Exposure to Blinded Treatment)				Open Label/Completed (Exposure to Ambrisentan)			
	Person		Person-Years		Person		Person-Years	
Age Group	M	F	M	F	M	F	M	F
<18 Yrs	0	0	0	0	0	1	0	13
18 - 64 Yrs	0	0	0	0	499	779	539.7	1800.6
65 - 75 Yrs	0	0	0	0	211	275	227.2	488
>75 Yrs	0	0	0	0	39	32	39.8	55.3
Missing	0	0	0	0	0	0	0	0
Total	0	0	0	0	749	1087	806.7	2357

Note: Studies included are AMB-220, AMB-220E, AMB-222, AMB-320, AMB-321, AMB-320/321, AMB-323, GS-US-300-0111, GS-US-300-0112, GS-US-300-0113, GS-US-300-0116, GS-US-300-0117, GS-US-300-0124, GS-US-300-0128, GS-US-300-0139, GS-US-300-0140, GS-US-231-0101, GS-US-244-0102, GS-US-244-0103.

Note: Subjects receiving ambrisentan and another drug are counted under the ambrisentan group only.

Note: Person Years = sum of days on study drug over all subjects, divided by 365.25. For ongoing subjects, date of last dose is estimated.

Table 12A Estimated Cumulative Duration of Exposure to Ambrisentan in Ambrisentan Clinical Trials (GSK sponsored) through 14 June 2019 by Age Group and Sex

	Double-Blind Phase (Exposure to Blinded Treatment)				Open Label/Completed (Exposure to Ambrisentan)			
	Patient [N]		Patient Year[1]		Patient [N]		Patient Year[1]	
Age Group	M	F	M	F	M	F	M	F
Children (2-11 years)	5	9	2.3	4.0	5	9	27.7	39.3
Adolescents (12-17 years)	9	18	4.0	7.8	8	16	24.4	53.1
Adults (18-64 years)	5	4	1.5	1.2	144	161	24.5	110.4
Elderly people (65-74 years)	1	3	0.3	0.9	2	6	1.9	5.3
Elderly people (75-84 years)	3	1	0.8	0.3	1	2	0.2	0.8
Missing	0	0	0	0	0	0	0	0
Total	23	35	9.0	14.2	160	194	78.6	209.0

[1]Patient-years = sum of days on study drug over all patients / 365.2422

Included studies are AMB115812, AMB112529, AMB114588, AMB115811, AMB116457, 201964, AMB107623 and AMB107816.

Table 13 Estimated Cumulative Duration of Exposure to Ambrisentan in Ambrisentan Clinical Trials (sponsored by Gilead) through 14 June 2019 by Indication and Race

		Double-Blind in Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Indication	Race	N	Person-Years	N	Person-Years
Chronic Allograft Injury	White	0	0	69	1.5
	Black or African American	0	0	18	0.4
	Asian	0	0	0	0
	American Indian or Alaska Native	0	0	0	0
	Native Hawaiian or Other Pacific Islander	0	0	0	0
	Other	0	0	0	0
	Not Permitted	0	0	0	0
	Multiple	0	0	0	0
	Missing	0	0	0	0
	Total	0	0	87	2
Idiopathic Pulmonary Fibrosis	White	0	0	293	205.1
	Black or African American	0	0	1	0.9
	Asian	0	0	4	2.3
	American Indian or Alaska Native	0	0	1	0.2
	Native Hawaiian or Other Pacific Islander	0	0	0	0

		Double-Blind in Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Indication	**Race**	**N**	**Person-Years**	**N**	**Person-Years**
	Other	0	0	27	25.7
	Not Permitted	0	0	3	1.3
	Multiple	0	0	0	0
	Missing	0	0	0	0
	Total	0	0	329	235.6
Pulmonary Arterial Hypertension	White	0	0	982	2006.5
	Black or African American	0	0	70	96.6
	Asian	0	0	24	76.3
	American Indian or Alaska Native	0	0	2	3.5
	Native Hawaiian or Other Pacific Islander	0	0	2	4.1
	Other	0	0	85	306.1
	Not Permitted	0	0	0	0
	Multiple	0	0	3	8.3
	Missing	0	0	3	1.9
	Total	0	0	1171	2503.4
Pulmonary Hypertension	White	0	0	193	367
	Black or African American	0	0	23	28.3
	Asian	0	0	5	5.6

		Double-Blind in Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Indication	**Race**	**N**	**Person-Years**	**N**	**Person-Years**
	American Indian or Alaska Native	0	0	0	0
	Native Hawaiian or Other Pacific Islander	0	0	0	0
	Other	0	0	3	11.8
	Not Permitted	0	0	0	0
	Multiple	0	0	0	0
	Missing	0	0	0	0
	Total	0	0	224	412.8
Pulmonary Hypertension Associated with Idiopathic Pulmonary Fibrosis	White	0	0	25	9.9
	Black or African American	0	0	0	0
	Asian	0	0	0	0
	American Indian or Alaska Native	0	0	0	0
	Native Hawaiian or Other Pacific Islander	0	0	0	0
	Other	0	0	0	0
	Not Permitted	0	0	0	0
	Multiple	0	0	0	0
	Missing	0	0	0	0
	Total	0	0	25	9.9

Note: Studies included are AMB-220, AMB-220E, AMB-222, AMB-320, AMB-321, AMB-320/321, AMB-323, GS-US-300-0111, GS-US-300-0112, GS-US-300-0113, GS-US-300-0116, GS-US-300-0117, GS-US-300-0124, GS-US-300-0128, GS-US-300-0139, GS-US-300-0140, GS-US-231-0101, GS-US-244-0102, GS-US-244-0103.

Note: Subjects receiving ambrisentan and another drug are counted under the ambrisentan group only.

Note: Person Years = sum of days on study drug over all subjects, divided by 365.25. For ongoing subjects, date of last dose is estimated.

Table 13A Estimated Cumulative Duration of Exposure to Ambrisentan in Ambrisentan Clinical Trials (GSK sponsored) through 14 June 2019 by Indication and Race

		Double-Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Indication	**Race**	**Patient (N)**	**Patient Years[1]**	**Patient (N)**	**Patient Years[1]**
CTEPH	White	11	3.3	13	10.9
	Black	0	0	0	0
	Asian	6	1.8	6	2.1
	Other	0	0	0	0
	Missing	0	0	0	0
	Total	17	5.0	19	13.0
Healthy Volunteers	White	0	0	74	0.8
	Black	0	0	12	0.1
	Asian	0	0	27	0.2
	Other	0	0	0	0
	Missing	0	0	0	0

		Double-Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Indication	**Race**	**Patient (N)**	**Patient Years[1]**	**Patient (N)**	**Patient Years[1]**
	Total	0	0	113	1.2
Pediatric Pulmonary Arterial Hypertension	White	30	13.0	27	99.4
	Black	2	1.0	2	4.5
	Asian	8	3.7	8	35.7
	Other	1	0.5	1	5.1
	Missing	0	0	0	0
	Total	41	18.1	38	144.6
Pulmonary Arterial Hypertension	White	0	0	0	0
	Black	0	0	0	0
	Asian	0	0	184	128.9
	Other	0	0	0	0
	Missing	0	0	0	0
	Total	0	0	184	128.9

[1]Patient-years = sum of days on study drug over all patients / 365.2422

Included studies are AMB115812, AMB112529, AMB114588, AMB115811, AMB116457, 201964, AMB107623 and AMB107816.

Table 14 Estimated Cumulative Duration of Exposure to Ambrisentan in Ambrisentan Clinical Trials (sponsored by Gilead) through 14 June 2019 by Race

	Double-Blind in Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Race	N	Patient-Years	N	Person-Years
White	0	0	1562	2590.2
Black or African American	0	0	112	126.3
Asian	0	0	33	84.2
American Indian or Alaska Native	0	0	3	3.7
Native Hawaiian or Other Pacific Islander	0	0	2	4.1
Other	0	0	115	343.6
Not Permitted	0	0	3	1.3
Multiple	0	0	3	8.3
Missing	0	0	3	1.9
Total	0	0	1836	3163.7

Note: Studies included are AMB-220, AMB-220E, AMB-222, AMB-320, AMB-321, AMB-320/321, AMB-323, GS-US-300-0111, GS-US-300-0112, GS-US-300-0113, GS-US-300-0116, GS-US-300-0117, GS-US-300-0124, GS-US-300-0128, GS-US-300-0139, GS-US-300-0140, GS-US-231-0101, GS-US-244-0102, GS-US-244-0103.

Note: Subjects receiving ambrisentan and another drug are counted under the ambrisentan group only.

Note: Person Years = sum of days on study drug over all subjects, divided by 365.25. For ongoing subjects, date of last dose is estimated.

Table14A Estimated Cumulative Duration of Exposure to Ambrisentan in Ambrisentan Clinical Trials (GSK sponsored) through 14 June 2019 by Race

	Double-Blind Phase (Exposure to Blinded Treatment)		Open Label/Completed (Exposure to Ambrisentan)	
Race	**Patient (N)**	**Patient Years[1]**	**Patient (N)**	**Patient Years[1]**
White	41	16.2	114	111.1
Black	2	1.0	14	4.6
Asian	14	5.5	225	166.9
Other	1	0.5	1	5.1
Missing	0	0	0	0
Total	58	23.2	354	287.7

[1]Patient-years = sum of days on study drug over all patients / 365.2422

Included studies are AMB115812, AMB112529, AMB114588, AMB115811, AMB116457, 201964, AMB107623 and AMB107816.

PART II: MODULE SIV - POPULATIONS NOT STUDIED IN CLINICAL TRIALS

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

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
Adults: excluded subjects if serum alanine aminotransferase (ALT) or aspartate aminotransferase (AST) >1.5x upper limit of normal (ULN) or a SAE attributed to previous treatment with an ERA. Paediatrics: (AMB112529 and ongoing AMB114588 with interim data up to 23 August 2019): subjects were excluded if clinically significant hepatic enzyme elevation (i.e. ALT, AST or alkaline phosphatase >3 x ULN) was	ERAs are known to cause AST/ALT elevations.	No	Baseline values of hepatic aminotransferases (aspartate aminotransferases (AST) and/or alanine aminotransferases (ALT) >3xULN are contraindicated in the Product Label as well as in patients with severe hepatic impairment. Implications for target population are limited as there are a number of other licensed PAH treatments in different drug classes that may be given to this group of patients.

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
present at screening.			
Pregnancy and breast-feeding	Endothelin receptor antagonist (ERA)s have been shown to be teratogenic in animals.	No	PAH affects people of all ages, and women more than men, therefore a number of PAH patients will be women of child bearing potential (WCBP). In addition, pregnancy carries a significant mortality to the mother in patients with PAH and is therefore not recommended in this population. Ambrisentan, as well as other ERA, have been shown to be teratogenic in animal studies, though may be given to WCBP as long as they are practicing reliable contraception and monthly pregnancy tests are recommended, Ambrisentan does not interact with oral contraceptive pills.
PAH due to or associated with congenital heart disease, coronary artery disease, left heart disease, interstitial lung disease (ILD),	PAH associated with congenital heart disease was excluded as this is a diverse population and a number of the efficacy surrogates may	No	Ambrisentan is indicated in subjects with PAH. The classification of PAH has changed since the trials were designed. PAH associated with Congenital Heart

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
chronic obstructive pulmonary disease (COPD), veno-occlusive disease, chronic thrombotic and/or embolic disease, or sleep apnoea	be different in this group. *(Subjects with congenital heart disease were not excluded from AMB112565 [AMBITION] study).* PH associated with other conditions were excluded to ensure ambrisentan was studied in the target population of Pulmonary Hypertension WHO Group 1: PAH.		Disease is considered part of the classification of PAH as it shares similar underlying pathophysiology. The ambrisentan label states that efficacy has only been demonstrated in patients with iPAH and PAH-CTD. PH associated with left heart disease, ILD, COPD, chronic thrombotic and/or embolic disease and sleep apnoea are not classified as PAH and therefore ambrisentan is not licensed in these indications. There is a special warning and precaution about pulmonary veno-occlusive disease (PVOD) in the Product Label. The use of ambrisentan in patients with idiopathic pulmonary fibrosis (IPF) is contraindicated.
Portopulmonary hypertension	Excluded due to potential for co-existing liver disease.	No	Contraindications about use of ambrisentan in patients with severe hepatic impairment and those with clinically abnormal

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			aminotransferase levels are present in the label.
Patients below 8 years of age	Studies for initial registration were adult only. Subsequent study AMB112529 and ongoing AMB114588 with interim data up to 23 August 2019, evaluated paediatric subjects aged 8 to less than 18 years of age.	No	Ambrisentan is not licensed for use in patients below 8 years of age.
Abnormal lung function- TLC <70% predicted; FEV1 <65% of predicted in adult trials	To exclude subject with significant lung involvement which may confuse diagnosis between PAH and PH associated with significant lung disease.	No	Ambrisentan is only licensed in patients with PAH. There is a contraindication for use in patients with IPF.
Concomitant use of bosentan or chronic prostanoid therapy. In paediatric study	To ensure patient population in the registration trials was treatment naive.	No	The potential for interaction with other PAH medications is limited, and ambrisentan interaction has been studied in healthy volunteer studies with both

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
AMB112529, subjects were excluded who were currently on ERA therapy for PAH or who were not on a stable dose of other PAH therapy for at least one month prior to screening.			sildenafil and tadalafil. Additionally, other PAH medications were allowed in the AMB320E/321E long-term extension studies.
Haemoglobin concentration <10 g/dL or haematocrit <30%	Ambrisentan, as with other ERAs, has a known impact on haemoglobin levels, therefore this was a safety exclusion criterion.	No	The Product Label already contains a special warning and precaution: initiation of ambrisentan is not recommended for patients with clinically significant anaemia and it is recommended that haemoglobin and/or haematocrit levels are measured during treatment with ambrisentan, for example at 1 month, 3 months and periodically thereafter in line with clinical practice. If a clinically significant decrease in haemoglobin or haematocrit is observed, and other causes have been excluded, dose reduction or discontinuation of

Criterion	Reason for exclusion	Is it considered to be included as missing information (YES/NO)	Rationale
			treatment should be considered.

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

The clinical development programme is unlikely to detect certain types of adverse reactions such as rare adverse reactions, adverse reactions with a long latency, or those caused by prolonged or cumulative exposure.

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

Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant women	Not included in the clinical development program.
Breastfeeding women	Not included in the clinical development program.
Patients with relevant comorbidities: • Patients with hepatic impairment • Patients with renal impairment • Patients with cardiovascular impairment • Immunocompromised patients • Patients with a disease severity different from inclusion criteria in clinical trials	**Patients with hepatic impairment** Patients with portopulmonary hypertension, severe hepatic impairment, cirrhosis, or clinically significant elevated hepatic transaminases were not included in the pre-registration studies. **Patients with renal impairment** Not included in the clinical development program.

	Patients with cardiovascular impairment Subjects with three or more risk factors for left ventricular disease or dysfunction were not included in the clinical development program. These were not exclusion criteria for subjects aged 8 to less than 18 years of age (AMB112529 and AMB114588). **Immunocompromised patients** Not included in the clinical development program. These were not exclusion criteria for subjects aged 8 to less than 18 years of age (AMB112529 and AMB114588). **Patients with a disease severity different from inclusion criteria in clinical trials** In the Phase 3 clinical studies, nearly all of the subjects in these studies had either WHO functional class II (38.4%) or class III (55.0%) symptoms at baseline. Due to the small numbers in groups I and IV, the efficacy and safety of ambrisentan is much less well characterized in these groups; however, these patients were observed to have a therapeutic response. Ambrisentan is only licensed for those patients with WHO Functional Class II and III symptoms at initiation of treatment.
Population with relevant different ethnic origin	A majority of patients exposed to ambrisentan were White. No ethnicities were excluded from the clinical development program.
Subpopulations carrying relevant genetic polymorphisms	Not included in the clinical development program.
Other: • Children under 8 years of age	Children under the age of 8 years are not included in the clinical development program.

PART II: MODULE SV - POST-AUTHORISATION EXPERIENCE

SV.1 Post-authorisation exposure

Changes to the cumulative post-marketing exposure do not alter considerations on the risk evaluation for ambrisentan.

SV.1.1 Method used to calculate exposure

Patient exposure to ambrisentan is estimated from enrollment numbers in the Letairis Education and Access Program (LEAP) for the US and from sales data (IMS Health) for the rest of the world (ROW). It should be noted that the use of sales data for patient exposure calculations will generally overestimate patient exposure due to the accumulation of drug stocks at pharmacies/distributors and wastage.

Exposure estimates are based on the assumption that a patient receives two ambrisentan 2.5 mg tablets (2.5 mg tablet strength not available in all countries), or one tablet of 5 mg or 10 mg daily for 365 days (ROW) or 365.25 days (US) in a year (i.e., 1825 mg/patient/year [ROW] or 1826.25 mg/patient/year [US] for the 2.5 mg and 5 mg tablet strengths, and 3650 mg/patient/year [ROW] or 3652.5 mg/patient/year [US] for the 10 mg tablet strength, respectively).

SV.1.2 Exposure

Ambrisentan is indicated for treatment of pulmonary arterial hypertension (PAH) in adult patients of WHO Functional Class (FC) II to III, including use in combination treatment.

Worldwide

Cumulative patient exposure to marketed ambrisentan since first marketing approval in the US on 15 June 2007 to 14 June 2019 is estimated to be 171,431 patient-years (see Table 15).

Table 15 Estimated Worldwide Patient Exposure to Marketed ambrisentan from 15 June 2007 to 14 June 2019 and Cumulatively

Geographic Area	Cumulative Patient Exposure to 31 March 2019 (Patient-Years) (rounded to nearest whole number)
US	98,931
ROW[a]	72,500[b]
Total	**171,431**

[a] ROW markets include Germany, France, Japan, Italy, Spain, Australia, Canada, the United Kingdom, Austria, Belgium, Greece, Sweden, Norway, Finland, Ireland, Denmark, Switzerland, the Slovak Republic, China, Slovenia, Hungary, Malaysia, Netherlands, Czech Republic, Brazil, New Zealand, South Korea, Croatia, Romania, Bulgaria, Poland, India, Turkey, Russia, Thailand, Latvia, Argentina, Columbia, Ecuador, Saudi Arabia, United Arab Emirates, Hong Kong and Mexico.
[b] Cumulative to 31 March 2019.

United States

Cumulative patient exposure to ambrisentan since first marketing approval in the US on 15 June 2007 to 14 June 2019 is 43,394 patients (approximately 98,931 patient-years).

Note: US patient-year exposure estimates based on data from the LEAP program account for leap years; therefore, a year is presumed to be 365.25 days long. The estimated patient exposure to marketed ambrisentan in the US, in patient-years, is provided below:

Table 16 Estimated Patient Exposure to Marketed Ambrisentan in the US

Tablet Strength (mg)	Patient Exposure Cumulative to 14 June 2019 (patient-years) (rounded to the nearest whole number)
2.5	N/A
5	22,160
10	76,771

Tablet Strength (mg)	Patient Exposure Cumulative to 14 June 2019 (patient-years) (rounded to the nearest whole number)
Total	98,931

Rest of the World

Rest of the World (ROW) patient exposure to marketed ambrisentan is estimated from sales data provided by IMS Health. The IMS Health database is updated quarterly and, at the time of this report, had been updated to 31 March 2019. First approval and launch of ambrisentan in the ROW occurred on 20 March 2008 (Canada) and 16 June 2008 (Germany), respectively.

Exposure estimates for the European Union are included in the ROW exposure below. From initial launch to 31 March 2019, there was a total of 31,508 patient-years exposure in the EU.

IMS's "Prescribing Insights data" (PI) is not appropriate to represent demographic exposure to ambrisentan in the EU, as prescribing is restricted to specialty prescribers and pharmacies. Depending upon the country, these data may not be available through IMS PI. Hence, demographic data is not available for the majority of EU countries. Additionally, IMS PI does not include hospital-based doctors, which would be applicable to ambrisentan.

From initial launch to 31 March 2019, there was a total of 72,500 patient-years exposure in the ROW. The estimated patient exposure to marketed ambrisentan in the ROW, in patient-years, is provided below:

Table 17 Estimated Patient Exposure to Marketed Ambrisentan in ROW

Tablet Strength (mg)	Cumulative to 31 March 2019	
	Number Tablets Sold	Patient Exposure (patient-years) (rounded to the nearest whole number
2.5	[redacted]	30,602
5		22,919
10	4,211,857	18,979
Total	**18,718,001**	**72,500**

Markets included in the patient estimates provided above include: Germany, France, Japan, Italy, Spain, Australia, Canada, the United Kingdom, Austria, Belgium, Greece, Sweden, Norway, Finland, Ireland, Denmark, Switzerland, the Slovak Republic, China, Slovenia, Hungary, Malaysia, Netherlands, Czech Republic, Brazil, New Zealand, South Korea, Croatia, Romania, Bulgaria, Poland, India, Turkey, Russia, Thailand, Latvia, Argentina, Columbia, Ecuador, Saudi Arabia, United Arab Emirates, Hong Kong and Mexico.

PART II: MODULE SVI - ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

Potential for misuse for illegal purposes

Due to its mechanism of action, the potential for illegal use or abuse potential of ambrisentan is not expected.

PART II: MODULE SVII - IDENTIFIED AND POTENTIAL RISKS

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

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable. This is in line with GVP module V revision 2 which states that the initial identification of safety concerns is expected to be populated with the initial submission of an RMP, either at the time of initial marketing authorization or post-authorisation for approved products that previously did not have an RMP.

The initial EU-RMP was approved on (as part of the initial marketing authorisation - Commission Decision) 21 April 2008.

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

This section is not applicable. This is in line with GVP module V revision 2 which states that the initial identification of safety concerns is expected to be populated with the initial submission of an RMP, either at the time of initial marketing authorization or post-authorisation for approved products that previously did not have an RMP.

The initial EU-RMP was approved on (as part of the initial marketing authorisation - Commission Decision) 21 April 2008.

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

None.

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

SVII.3.1 Presentation of important identified risks and important potential risks

Important Identified Risk: Teratogenicity	
MedDRA terms	SMQ Broad - Reproductive toxicity SMQ Broad - Congenital, familial and genetic disorders SMQ Broad - Disorders of the offspring

	SMQ Broad - Pregnancy complications.
Potential mechanisms	Teratogenicity findings of ambrisentan appear to be pharmacologically-mediated and have occurred at clinically relevant exposures in animal models that are considered to have clinical relevance to humans.
Evidence source(s) and strength of evidence	Preclinical toxicology studies.
Characterisation of the risk	Teratogenicity is a class effect of ERAs. The effect of ambrisentan on embryo-fetal development has been assessed in rats and rabbits after oral dose administration on gestation days 6–17. In both species, abnormalities of the lower jaw, tongue, and/or palate were consistently observed at all doses. Additionally, the rat study showed an increased incidence of interventricular septal defects, trunk vessel defects, thyroid and thymus abnormalities, ossification of the basisphenoid bone, and the occurrence of the umbilical artery located on the left side of the urinary bladder instead of the right side. The potential for teratogenicity with ambrisentan is being closely monitored and is one of the key issues addressed in the Ambrisentan EU RMP. Ambrisentan use is contraindicated in pregnancy. Women of childbearing potential should be advised of the risk of fetal harm if ambrisentan is taken during pregnancy. Pregnancy must be excluded before the start of treatment with ambrisentan and prevented thereafter by reliable contraception. Monthly pregnancy tests during treatment with ambrisentan are recommended. Women of childbearing potential should be advised to contact their physician immediately if they become pregnant or suspect they may be pregnant. A total of 128 pregnancy cases involving 129 pregnancies (13 from clinical interventional studies, 92 from post-marketing reports in the US (Letairis REMS), 23 from post-marketing reports from ex-US), involving ambrisentan exposure have been reported world-wide between 15 June 2007 and 14 June 2019. Among the 129 pregnancies involving drug exposure during pregnancy there were 17 reports of live birth (with no fetal defects or unknown), 53 reports of termination of the pregnancy including 51 elective or therapeutic termination (with no fetal defects reported, or unknown); and 2 reports where termination method was not reported; 17 reports of miscarriage, spontaneous abortion, or missed abortion (1 of which may have been a case of stillbirth), 1 report of a nonviable fetus (with unknown further outcome or procedure), 31 reports without further information about the pregnancy outcome, and 8 reports in which the pregnancy was reported as ongoing at the time of report.
Risk factors and risk groups	Pregnant women and women of child-bearing potential

Preventability	Given the potential risk of teratogenicity based on non-clinical studies (see Part II: Module SII), the absence of relevant human data and the availability of alternative treatments for use in pregnancy (e.g., prostanoids), a contraindication for use in pregnant women and in women of child-bearing potential who are not using reliable contraception is included in the EU SmPC. In addition, monthly pregnancy tests during treatment with ambrisentan are recommended. To minimize the risk of foetal exposure and adverse foetal outcomes for female patients of child-bearing potential prescribed ambrisentan, a Patient Reminder Card (see Part V.2 for additional risk minimization measures), has been implemented and packing size has been limited to a 30-day supply.
Impact on the risk-benefit balance of the product	Benefit-risk remains positive due to implementation of the patient reminder card.
Public health impact	PAH is a rare disease with orphan indication status thus the potential public safety concern is low.
Important Identified Risk: Decreased haemoglobin/haematocrit/anaemia, including anaemia requiring transfusion	
MedDRA terms	HLGT - Anaemias nonhaemolytic and marrow depression PT - Haematocrit decreased PT - Haemoglobin decreased PT - Mean cell haemoglobin concentration decreased PT - Mean cell haemoglobin decreased PT - Red blood cell count decreased PT - Erythropenia
Potential mechanisms	The mechanism for decreases in haemoglobin and haematocrit has not been confirmed, although it is likely that intravascular volume expansion with these vasodilatory agents contributes some element of haemodilution. Of note, there is no evidence that the reduction in haemoglobin observed is the result of haemolysis or substantially reduced haemopoiesis.
Evidence source(s) and	Clinical trial and post-marketing data.

strength of evidence	
Characterisation of the risk	Decreases in haemoglobin concentrations and haematocrit have been observed with ERAs including ambrisentan, and there have been cases where this has resulted in anaemia, sometimes requiring transfusion (Barst, 2007; Tracleer SmPC, 2006a; Gilead, 2011; ARIES-C clinical study report, 2006). In clinical trials, decreases in haemoglobin and haematocrit were observed within the first few weeks of therapy and generally stabilized thereafter (ARIES-C clinical study report, 2006). The mean decrease in haemoglobin from baseline to the end of treatment for patients receiving ambrisentan in 12-week placebo-controlled studies was 0.8 g/dL (ARIES-C clinical study report, 2006). Mean decreases from baseline (ranging from 0.9 to 1.2 g/dL) in haemoglobin concentrations persisted for up to 4 years of treatment with ambrisentan in the long-term open-label extension of the pivotal Phase 3 clinical studies (ARIES-E clinical study report, 2010). In the AMB-320/321-E (ARIES-E) study, the mean (SD) ambrisentan exposure for the combined ambrisentan group was 144.6 (79.51) weeks, with maximum exposure of 295 weeks. For the combined ambrisentan group in this study, slight overall mean (SD) reductions in haemoglobin concentration (-0.88 ± 0.962 g/dL) were observed by Week 4; reductions in haemoglobin persisted through 4 years (204 weeks) of exposure to ambrisentan, reaching maximum mean reductions from baseline of -1.17 g/dL (at Week 108). Similarly, reductions in haematocrit (-0.03 [0.031] V/V), red blood cell count (-0.28 [0.333] x 10^{12}/L), and total white blood cell count (-0.72 [1.756] x 10^{9}/L) were observed by Week 4. These, too, persisted through 4 years of exposure to ambrisentan, with respective maximum mean reductions from baseline being -0.034 V/V in haematocrit (at Weeks 84 and 108), -0.30 x 10^{12}/L in red blood cell count (at Week 8), and -1.13 x 10^{9}/L in white blood cell count (at Week 108). There were no other clinically relevant changes in haematology parameters over time (ARIES-E clinical study report, 2010). In the AMB110094 (VOLT) study, in 998 subjects with a mean exposure of 2.2 years, 517 (55%) subjects were reported as having a non-clinically significant decrease in haemoglobin or haematocrit from previous visit at some point throughout the study, and a further 90 (10%) reported as experiencing a clinically-significant decrease in haemoglobin or haematocrit from previous visit at some point throughout the study. Overall 143 (14%) subjects reported 157 adverse events or serious adverse events related to haemoglobin or haematocrit disorders. Of the 157 events of haemoglobin or haematocrit abnormalities, most (137/157 events, 87%) were mild to moderate in intensity. The events were reported as SAEs for 32 subjects. The majority of these events (104) were resolved. Thirty-six events were

	considered by the investigator to be related to ambrisentan and 8 subjects withdrew from ambrisentan or the study, due to the adverse event. A cumulative review of anaemia requiring transfusion reported for ambrisentan was performed for data cumulative to 31 August 2010. A search of the Gilead safety database identified a total of 304 cases that contained anaemia-related events, of which 82 (27%) were cases of anaemia-related events requiring transfusion. Most of the cases requiring transfusion (69.5%) contained possible alternative aetiologies or did not provide sufficient information for assessment of causality. The remaining cases had a close temporal relationship with ambrisentan and were of unclear aetiology. Based on this review, it was concluded that there is sufficient evidence to support anaemia requiring transfusion as an adverse drug reaction (ADR) associated with ambrisentan therapy in addition to the listed ADR of anaemia. The Company Core Data Sheet (CCDS) was updated in May 2011 to add "anaemia requiring transfusion as an Undesirable Effect to the Post-Marketing Experience sub-section. In addition, an update to the EU SmPC to add "anaemia requiring transfusion" was approved in March 2012. In Study AMB112565 (AMBITION) a higher percentage of mITT subjects in COMB (20%) had AEs within the AESI category of anaemia compared with subjects in the AMB or TAD arms of the study (10% and 13%, respectively) during the period from Baseline to final assessment visit (FAV). However, ≤3% of subjects in each treatment group had severe anaemia, serious anaemia was reported in ≤4% of subjects, anaemia related to IP was reported in ≤6% of subjects, and withdrawals from the study or discontinuation of IP due to anaemia were reported in ≤2% of subjects. In the mITT population from Baseline to FAV, low haemoglobin values (< 100 G/L) were the only reported post-Baseline haematology values of potential clinical concern. Few subjects had such values at Baseline (0 to 4% of the subjects across treatment groups). From Baseline to FAV, 18% of subjects in the combination therapy group had a haemoglobin value of clinical concern compared with 7% of subjects in the ambrisentan monotherapy group and 13% of subjects in the tadalafil monotherapy group. In paediatric study AMB112529, in 41 subjects with a mean exposure of 161.5 days, there were no clinically relevant changes in blood haematology parameters over time other than a small mean reduction from Baseline in haemoglobin and haematocrit for both dose groups, which was consistently evident by Week 4 and remained stable thereafter. The mean (SD) change from Baseline at Week 24 across both dose groups was -12.1 (15.38) g/L and -0.0378 (0.04823) for haemoglobin and haematocrit, respectively. In ongoing paediatric study AMB114588 (interim data up to 23 August 2019), in 38 subjects with a mean exposure of 1238.5 days, there was a small mean reduction from Baseline in haemoglobin and haematocrit for all dose

	groups combined, which was most prominent at the Entry Visit and continued to be observed (to smaller magnitudes) until Month 60, when subject numbers became too small for meaningful interpretation. The mean change from Baseline in haemoglobin values was more marked for subjects in the 2.5 and 5 mg groups compared with the higher dose groups. The mean (SD) decrease from Baseline at the End of Study Visit across all subjects was 5.8 (20.29) and 0.0084 (0.05993), for haemoglobin (g/L) and haematocrit respectively. The most frequently reported AESI was anaemia (6 subjects, 11 events), with the majority resolving and none leading to withdrawal from ambrisentan or the study.
Risk factors and risk groups	Overall, anaemia is twice as prevalent in females as in males. This difference is significantly greater during the childbearing years. Anaemia of chronic disorders is more common in populations with a high incidence of chronic infectious disease (e.g., malaria, tuberculosis, acquired immunodeficiency syndrome Milman, 2011).
Preventability	Initiation of ambrisentan is not recommended for patients with clinically significant anaemia. It is recommended that haemoglobin is measured prior to initiation of ambrisentan, again at one month, and periodically thereafter. If a clinically significant decrease in haemoglobin is observed during therapy and other causes have been excluded, discontinuation of ambrisentan should be considered. Risk communication in the product labelling is considered to be the primary risk minimization tool.
Impact on the risk-benefit balance of the product	The anticipated benefits for PAH patients outweigh the identified risk of anemia associated with ambrisentan.
Public health impact	PAH is a rare disease with orphan indication status thus the potential public safety concern is low.
Important Identified Risk: Hepatotoxicity	
MedDRA terms	SMQ Broad - Drug related hepatic disorders-comprehensive search HLGT - Hepatic and hepatobiliary disorders
Potential mechanisms	Both the chemical structure and (ADME) absorption, distribution, metabolism and elimination profile of ambrisentan support a relatively lower risk of hepatotoxicity than either bosentan or sitaxentan. Ambrisentan is not an in vitro inhibitor of Bile Salt Export Protein (BSEP), which is hypothesized to be involved in the hepatic toxicity observed with bosentan. The acyl glucuronide of ambrisentan is stable and extractability of radioactivity from plasma samples is good, indicating a low potential for covalent binding to proteins. Furthermore, the daily dose of ambrisentan (10 mg or less) is much lower

<table>
<tr><td></td><td>than that of bosentan and sitaxentan further reducing the risk for hepatotoxicity. Overall, the weight of available ambrisentan preclinical ADME data does not indicate a potential for idiosyncratic drug toxicity and Drug Induced Liver Injury (DILI). Additionally, results of the toxicology studies do not predict a risk for clinical DILI.</td></tr>
<tr><td>Evidence source(s) and strength of evidence</td><td>Clinical trial and Post-marketing data</td></tr>
<tr><td>Characterisation of the risk</td><td>Placebo-controlled studies in PAH populations similar to those studied in the ambrisentan program have reported an incidence of aminotransferase abnormalities >3X ULN for the placebo population that ranged from 1.5-6% for drug exposures of 12 to 18 weeks (Barst, 2006; Rubin, 2002).

The below table describes the 12-week cumulative incidences of all clinically relevant serum aminotransferase abnormalities observed for all PAH studies as of the data cut-off of 30 November 2006.

Table 13 Serum Aminotransferase Abnormalities (ALT and/or AST) by Severity in All PAH Studies

<table>
<tr><th rowspan="3">ALT and/or AST</th><th colspan="2">≤12-week exposure</th><th colspan="5">Cumulative incidence for all PAH studies (>1 day)[1]</th></tr>
<tr><th>Placebo (N = 132)</th><th>AMB (N = 483)</th><th>AMB (N = 483)[2]</th><th colspan="4">Distribution by dose at event[3], n</th></tr>
<tr><th>n (%)</th><th>n (%)</th><th>n (%)</th><th>1 mg</th><th>2.5 mg</th><th>5 mg</th><th>10 mg</th></tr>
<tr><td>>3xULN and ≤5xULN</td><td>1 (0.8)</td><td>3 (0.6)</td><td>13 (2.7)</td><td>1</td><td>3</td><td>5</td><td>4</td></tr>
<tr><td>>5xULN and ≤8xULN</td><td>2 (1.5)</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td><td>0</td></tr>
<tr><td>>8xULN</td><td>0</td><td>1 (0.2)</td><td>4 (0.8)</td><td>0</td><td>0</td><td>1</td><td>3</td></tr>
<tr><td>All >3xULN</td><td>3 (2.3)</td><td>4 (0.8)</td><td>17 (3.5)</td><td>1</td><td>3</td><td>6</td><td>7</td></tr>
<tr><td>Mean exposure (weeks)</td><td>11.4</td><td>47.4</td><td>79.5</td><td colspan="4" rowspan="2"></td></tr>
<tr><td>All > 3X ULN rate per 100 patient years exposure</td><td>10.3</td><td>3.0</td><td>2.3</td></tr>
</table>
1. Mean exposure 79.5 ± 50.28 and maximum exposure 212.3 weeks as of 30 November 2006.
2. Total number of subject does not include the 14 subjects ongoing in Study AMB-323 as of 30 November 2006. None of these subjects developed ALT/AST >3x ULN at the time of data cut-off.
3. Majority of patients were treated with ambrisentan 5 mg and 10 mg in the long term.
Source: The Clinical Safety Update Section 5.1.1 and Table 25

At the time of data-lock for the Marketing Authorisation Application MAA) (16 February 2006; mean exposure 47.4 weeks) across all of the phase 2 and 3 studies, the rate of ALT/AST >3X ULN for ambrisentan-treated patients was 3.0 events per 100 patient years of exposure. Following integration of data through 30 November 2006 (mean ambrisentan exposure 79.5 weeks and occurrence of 4 additional events), the rate of ALT/AST >3X ULN was 2.3 events per 100 patient years of exposure.</td></tr>
</table>

As of December 2010, the clinical trial experience for ambrisentan (over 700 subjects exposed), including the long-term extension trials, indicated that the incidence of hepatic enzyme elevations continued to be low and was consistent with the rate seen in the placebo groups in the short term pivotal phase III studies. There were a few events of severe hepatic enzyme elevations temporally associated with ambrisentan therapy with a positive dechallenge; however, these cases were largely confounded by other medical conditions or concomitant medications. There was one report of a fatal outcome in a patient with a liver event; however, insufficient data was available for this case to establish causality of the liver event. There were four reports lacking significant confounding factors with features suggestive of a drug-related liver event in which, without further information, a role for ambrisentan cannot be excluded. Three cases consistent with autoimmune hepatitis (AIH), including two cases in which AIH was diagnosed during the period after initiation of ambrisentan have also been identified.

The cumulative incidence of serum aminotransferase abnormalities>3xULN in all Phase 2 and 3 studies (including respective open label extensions) was 17 of 483 subjects over a mean exposure duration of 79.5 weeks. This is an event rate of 2.3 events per 100 patient years of exposure for Volibris. In the ARIES E open label long term extension study, the 2 year risk of developing serum aminotransferase elevations >3xULN in patients treated with ambrisentan was 3.9%.

Postmarketing Surveillance Program, AMB110094, (VOLT):

Incidence of aminotransferase abnormalities

INCIDENCES OF AMINOTRANSFERASE ELEVATIONS >3XULN AT ANY POST-BASELINE VISIT

LFT abnormalities	Cumulative Incidence		Incidence rates by 100 patient-year	
>3 x ULN	Number subjects n=998	% (95%CI)	Number subjects/number subject years	Event rate (95%CI)
ALT>3 x ULN	43	4.3 (3.1, 5.8)	43/2132	0.02 (0.01, 0.03)
AST>3 x ULN	43	4.3 (3.1, 5.8)	43/2129	0.02 (0.01, 0.03)

ALT and AST>3 x ULN	30	3.0 (2.0, 4.3)	30/2149	0.01 (0.01, 0.02)
ALT and /or AST>3 x ULN	55	5.5 (4.2, 7.1)	55/2112	0.03 (0.02, 0.03)
Source tables 13.7302 and 13.7402				

In study AMB110094, only 57 of 998 subjects had elevation of >3 x ULN of ALT or AST or both at any post baseline visit, of whom 15 permanently discontinued ambrisentan as a result. The safety population (n=998) included not only ambrisentan naive subjects (n=431), but also ambrisentan experience patients (n-567). This heterogeneity might lead to an underestimation of the incidence of aminotransferase elevations. A further limitation of this study was there were no protocol specified requirements for laboratory investigations, but there were protocol specified requirements for AE collection.

In the AMB112565 (AMBITION) study, ALT and AST values were set at 2x ULN as exclusion values. In the mITT population, from Baseline to FAV, the percentage of subjects with any liver AESI on randomized treatment was 7% in the combination therapy group, 2% in the ambrisentan monotherapy group, and 5% in the tadalafil monotherapy group. No single liver AE was reported in >2% of subjects in any of the randomized treatment groups.

In paediatric study AMB112529, there were no liver events as defined in Protocol. One subject in the Low dose group had a total bilirubin value of potential clinical concern reported at Baseline and Week 4 (high of reference range [<34.2]. There were no subjects with values of potential clinical concern for ALT and AST hepatic transaminases.

In ongoing paediatric study AMB114588 (interim data up to 23 August 2019), there were 4 subjects who had a TEAE related to liver parameters, one event of ALT increased was classified as an SAE that met protocol-defined stopping criteria and led to temporary dose reduction, however, none led to permanent withdrawal from ambrisentan or the study. An additional 4 subjects had a liver function parameter value of PCC (limited to bilirubin or GGT only) but did not have a corresponding TEAE reported and were noted as elevated at Study AMB112529 Baseline in all but 1 subject.

Risk factors and risk groups	One of the challenges of analyzing reports of liver related events in patients with PAH is that this patient population has an underlying risk of liver disease. One of the most common causes of elevated liver enzymes in pulmonary hypertension patients is liver congestion associated with severe pulmonary hypertension or right heart failure. In addition to congestive hepatopathy, since the liver typically receives 20% of cardiac output, circulatory failure, which can occur in PAH patients with decompensated heart failure, can be associated with ischemic hepatitis, especially if the cardiac index <1.5 liters/min/m2 (Naschitz, 2000). Hypoxic hepatitis is associated with PaO2 < 45 mmHg (which may also occur in severe or end stage PAH patients) and results in a high (62%) in-hospital mortality. Hypoxic hepatitis is rare and has similar findings to ischemic hepatitis: abrupt, marked ALT & AST elevations (10-20 fold normal) which resolve rapidly, with centrilobular necrosis on liver biopsy. (Henrion, 2012). Additionally, hepatitis in PAH patients may be associated with underlying diseases (e.g., autoimmune hepatitis, HIV co-infected viral hepatitis, connective tissue disease associated hepatitis and existing liver disease resulting in portopulmonary hypertension). A review of placebo data in ambrisentan, bosentan and sitaxentan clinical studies in PAH patients indicated that elevated aminotransferase levels of greater than three times the upper limit of normal (ULN) occurred in placebo patients at an incidence of between 1.5 and 6% over a 12 to 24 week period (Galiè, 2008a; Rubin, 2002; Barst, 2004; Barst, 2006; Oudiz, 2006; Galiè, 2008b). The background rate of liver dysfunction in PAH patients makes it challenging to disentangle a possible causal association with ambrisentan from the underlying predisposition of PAH patients to experience liver events. It is not clear whether a history of transaminase elevations prior to initiation of ambrisentan constitutes a risk factor for hepatotoxicity with ambrisentan. At the time of submission for marketing authorisation the assessment of liver safety also included a cohort of patients who had discontinued other ERAs due to elevations in hepatic transaminases previously. Over a period of exposure (mean 52.9 weeks, maximum exposure 76 weeks) none of the 36 patients enrolled had LFT abnormalities that required permanent discontinuation of ambrisentan. In this study the duration of exposure to ambrisentan is considerably longer than the median time to discontinuation of bosentan or sitaxentan (14 and 29 weeks respectively).
Preventability	Use of ambrisentan is contraindicated in patients with severe hepatic impairment (with or without cirrhosis) and in patients with baseline values of hepatic aminotransferases (AST and/or ALT) >3X ULN. Hepatic alanine aminotransferase and aspartate aminotransferase should be evaluated prior to initiation of ambrisentan.

	Patients should continue to be monitored for signs of hepatic injury with monthly on-therapy monitoring of ALT and/or AST. If patients develop sustained, unexplained clinically significant ALT and/or AST elevation or if ALT and/or AST elevation is accompanied by signs or symptoms of hepatic injury (e.g. jaundice), ambrisentan therapy should be discontinued. In patients without clinical symptoms of hepatic injury or jaundice, re-initiation of ambrisentan may be considered following resolution of hepatic enzyme abnormalities. When appropriate, case reports will be evaluated by GSK's Hepatotoxicity Panel, which contains internal and external experts of hepatotoxicity. To minimize the potential of hepatotoxicity in patients prescribed ambrisentan, a Patient Reminder Card has been developed and distributed to prescribers to give to their patients (see Part V.2, additional risk minimization measures). Ambrisentan packaging is limited to a 30-day supply.
Impact on the risk-benefit balance of the product	Benefit-risk remains positive due to proper implementation of educational materials regarding hepatotoxicity.
Public health impact	PAH is a rare disease with orphan indication status thus the potential public safety concern is low.
Important Potential Risk: Testicular tubular atrophy/Male infertility	
MedDRA terms	HLT- Testicular and epididymal disorders NEC HLT - Spermatogenesis and semen disorders PT-Infertility male PT - Aspermia PT - Infertility PT - Azoospermia PT - Sperm count decreased PT - Sperm count zero PT - Dihydrotestosterone abnormal

	PT - Blood testosterone decreased PT - Blood testosterone free abnormal PT - Blood testosterone free decreased PT - Androgens decreased PT - Androgens abnormal
Potential mechanisms	Testicular tubular atrophy, which was occasionally associated with aspermia, was observed in oral repeat dose toxicity and fertility studies with male rats and mice without safety margin. The testicular changes were not fully recoverable during the off-dose periods evaluated. However, no testicular changes were observed in dog studies of up to 39 weeks duration at an exposure 35–fold that seen in humans based on AUC. In male rats, there were no effects of ambrisentan on sperm motility at all doses tested (up to 300 mg/kg/day). A slight (<10%) decrease in the percentage of morphologically normal sperms was noted at 300 mg/kg/day but not at 100 mg/kg/day (>9-fold clinical exposure at 10 mg/day). Data from analysis of a limited number of semen samples show no clear effect of ambrisentan on sperm count over an extended period of observation. The clinical inhibin B data from the whole male cohort in phase 3 studies indicate there is some effect of ambrisentan on Sertoli cell function but given the observations from semen analysis the magnitude of this effect is clinically small. The testosterone data show that ambrisentan is not associated with a risk of endocrine hypogonadism through effects on Leydig cells.
Evidence source(s) and strength of evidence	Pre-clinical data and clinical trial data
Characterisation of the risk	Although there is no direct human data on testicular tubular atrophy, semen analysis has been collected in a small number of subjects during the clinical development program. Only a relatively small proportion (31/97) of male subjects in phase 2 and 3 studies have been willing to date to provide semen samples for analysis. Of these 31 subjects, eight had a total sperm count less than 40 million at baseline. A baseline and at least one follow-up sample is not available for a further four subjects. Because the collection of data is challenging, data from all patient studies have been pooled. The data show that in subjects with a total count >40 million at baseline there is no trend to a reduction in count with one year's exposure to ambrisentan.

	The data from all subjects are consistent with this observation. The data have also been examined in terms of the absolute count scatter and the change from baseline. These are reassuring, showing that there are very few on-treatment samples (n=8 from 6 subjects) with a count <40 million among those with a count >40 million at baseline. In 5 of the 6 subjects they have a subsequent sample with a total count >40 million; in the sixth case no additional sample is available. Overall the data show no clear evidence of a detrimental effect of ambrisentan on sperm count over a one year period of observation. A high degree of variability is observed (higher than in reference series) but this is consistent with the severity of the disease state and is considered a feature of the patient population rather than the method of assessment. The analyses presented here are consistent with the conclusion of an independent fertility expert who reviewed the data available at the MAA cut off and concluded that there was no definitive evidence of de novo effect of ambrisentan on male reproductive potential. During the AMB112565 (AMBITION) trial, the following laboratory tests of testicular function were performed in some male subjects: Total testosterone, sex hormone-binding globulin (SHBG – needed to calculate free testosterone), follicle stimulating hormone (FSH), luteinizing hormone (LH), and inhibin B comprised the tests of testicular function in male subjects. Caution should be used interpreting the results as they are confounded by variable hypogonadism in this ill population of subjects. The values of potential clinical concern for testicular function (free testosterone, inhibin B, and FSH) were values less than 80% of the lower limit of normal and values more than 120% of upper limit of normal. Across the 3 study populations there was a single Baseline FSH value of clinical concern (low; in the combination therapy group). There were no FSH values of clinical concern from Baseline to FAV. In each of the 3 study populations (at Baseline, and from Baseline to FAV) and in the 3 randomized treatment groups, there were testosterone values (mostly low) of potential clinical concern. In paediatric study (AMB112529), no clinically relevant change from baseline was observed in testicular volume or in male endocrine parameters (FSH, total testosterone and inhibin B). In ongoing paediatric study AMB114588 (interim data up to 23 August 2019), subjects had pubertal development assessments (change from Study AMB112529 Baseline in endocrinology assessments) every 6 months and at 20 years of age. There was no clear evidence or pattern of change from Baseline in endocrinology or plasma endocrine parameters at the post-Baseline visits.

Risk factors and risk groups	Alterations in sperm count have been reported in men with severe chronic diseases such as PAH. No specific risk factors for reduction in sperm count have been identified.
Preventability	Risk communication in the product labelling is considered to be the primary routine risk minimization tool. The effect on male human fertility is not known but a deterioration of spermatogenesis cannot be excluded.
Impact on the risk benefit balance of the product	The overall benefit to patients with PAH outweighs the potential risk of testicular tubular atrophy.
Public health impact	The potential public health impact of testicular tubular atrophy/male infertility is believed to be low.

SVII.3.2 Presentation of the missing information

There is no missing information for ambrisentan.

PART II: MODULE SVIII - SUMMARY OF THE SAFETY CONCERNS

Table 18 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Teratogenicity • Decreased haemoglobin/haematocrit, anaemia, including anaemia requiring transfusion • Hepatotoxicity
Important potential risks	• Testicular tubular atrophy/ Male infertility
Missing information	• None

PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST AUTHORISATION SAFETY STUDIES)

III.1 Routine pharmacovigilance activities

Routine pharmacovigilance activities beyond adverse reaction reporting and signal detection are required:

Specific adverse reaction follow-up questionnaires for the following safety concerns will be used:

- To obtain additional information for individual pregnancy reports for teratogenicity risk.
- To obtain additional information regarding individual adverse events of decreased haemoglobin/haematocrit/anaemia, including anaemia requiring transfusion risk.
- To obtain additional information regarding individual adverse events of hepatotoxicity.

Other forms of routine pharmacovigilance activities for the following safety concerns will be used:

Analysis of additional safety data that may arise from any future studies related to the following risks:

- Pregnancy and pregnancy outcome
- Decreased haemoglobin/haematocrit/anaemia, including anaemia requiring transfusion risk
- Hepatotoxicity*
- Testicular tubular atrophy/ Male infertility

* When appropriate, case reports will be evaluated by GSK's Hepatotoxicity Panel which contain internal and external experts on hepatotoxicity.

III.2 Additional pharmacovigilance activities

Currently, there are no ongoing pharmacovigilance studies for ambrisentan. Tabulated summaries of the completed studies are presented in ANNEX 2.

III.3 Summary Table of additional Pharmacovigilance activities

Not applicable.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

There are currently no imposed post-authorisation efficacy studies for ambrisentan.

PART V: RISK MINIMISATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMISATION ACTIVITIES)

Risk Minimisation Plan

V.1. Routine Risk Minimisation Measures

Table 19 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important Identified Risk: Teratogenicity	**Routine risk communication:** SmPC Sections 4.2, 4.3, 4.4, 4.6 and 5.3 of the EU SmPC PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendation for monthly pregnancy tests during treatment with ambrisentan in section 4.4 and 4.6 of the SmPC • Need for exclusion of pregnancy and practice reliable contraception before initiating ambrisentan in section 4.4 of the SmPC **Other routine risk minimisation measures beyond the Product Information:** Limited package supply Restricted medical prescription
Important Identified Risk: Decreased haemoglobin/haematocrit/anaemia, including anaemia requiring transfusion	**Routine risk communication:** Text within Sections 4.4, 4.8, and 5.1 of the EU SmPC PL Sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Recommendations to not initiate ambrisentan for patients with clinically significant anaemia; and for monitoring haemoglobin and/or haematocrit levels during ambrisentan treatment in section 4.4 of the SmPC

	• Recommendation to consider dose reduction or discontinuation if a clinically significant decrease in haemoglobin and/or haematocrit is observed and other causes have been excluded in section 4.4 of the SmPC **Other routine risk minimisation measures beyond the Product Information:** Limited package supply Restricted medical prescription
Important Identified Risks: **Hepatotoxicity**	**Routine risk communication:** Text within Sections 4.2, 4.3, 4.4, 4.8, 5.1. and 5.2 of the EU SmPC PL Sections 2 and 4 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** • Need for hepatic aminotransferases evaluation prior to initiation of ambrisentan in section 4.4 of the SmPC • Need for exclusion of patients with severe hepatic impairment and with baseline values of ALT and/or AST >3xULN in sections 4.2, 4.3, and 4.4 of the SmPC • Recommendations to monitor patients for signs of hepatic injury and monthly monitoring of ALT and AST in section 4.4 of the SmPC • Need to discontinue ambrisentan therapy if patients develop sustained, unexplained, clinically significant ALT and/or AST elevation, or if ALT and/or AST elevation is accompanied by signs or symptoms of hepatic injury (e.g., jaundice) in section 4.4 of the SmPC • Recommendation on re-initiation of ambrisentan therapy in patients without clinical symptoms of hepatic injury or jaundice, following resolution of hepatic enzyme abnormalities with the advice of a hepatologist in section 4.4 of the SmPC **Other routine risk minimisation measures beyond the Product Information:**

	Limited package supply Restricted medical prescription
Important Potential Risk: Testicular tubular atrophy/male infertility	**Routine risk communication:** Text within Sections 4.6 and 5.3 of the EU SmPC PL Section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Limited package supply Restricted medical prescription

V.2. Additional Risk Minimisation Measures

The following additional risk minimisation measure for VOLIBRIS is presented below:

Patient Reminder Card

Objectives:

To eliminate the possible risks of teratogenicity/pregnancy and hepatotoxicity in patients taking Volibris.

Rationale for the additional risk minimisation activity:

To help patients understand the risks to an unborn child, due to a pregnant patient taking Volibris and the risks of hepatotoxicity, and to take steps to manage the risks.

Target audience and planned distribution path:

Patients taking Volibris will receive a reminder card from their physician focusing on the risks of teratogenicity/pregnancy and hepatotoxicity and the main required actions to be taken in order to prevent and minimize these risks. Details of the distribution system should be agreed with the National Competent Authorities (NCA) of Member States (MS).

Plans to evaluate the effectiveness of the interventions and criteria for success:

Routine pharmacovigilance: ongoing monitoring of pregnancy reports and liver-related adverse events from all sources (spontaneous, clinical trials, post-marketing surveillance) with special attention to compliance with labelling recommendations.

Criteria for success of the patient reminder card:

A patient reminder card will be provided to all patients by the prescriber. Well-documented pregnancy and liver-related adverse event reports will demonstrate that clinical outcomes are not due to failure of the patient reminder card distribution.

Removal of additional risk minimisation activities

Educational materials for healthcare professionals (including pre-prescription checklist and prescriber advice) and for male partners of women with child-bearing potential are no longer required given the availability of the SmPC and the experience using ambrisentan. Additionally, a formal "controlled distribution system" is no longer required; however, the MAH will ensure that in each Member State where Volibris is marketed, the patient reminder card is made available to all prescribers to give to all patients who are prescribed Volibris.

V.3 Summary of risk minimisation measures

Table 20 Summary table of pharmacovigilance activities and risk minimisation activities by safety concern

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important Identified Risks		
Teratogenicity	**Routine risk minimisation measures** Text within Sections 4.2, 4.3, 4.4, 4.6 and 5.3 of the EU SmPC PL section 2 Limited package supply Restricted medical prescription **Additional risk minimisation measures** Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted Follow-up Questionnaires • Analysis of additional safety data that may arise from any ongoing or future studies Additional pharmacovigilance activities: None

Decreased haemoglobin/haematocrit/ anaemia, including anaemia requiring transfusion	**Routine risk minimisation measures** Text within Sections 4.4, 4.8 and 5.1 of the EU SmPC PL sections 2 and 4 Limited package supply Restricted medical prescription **Additional risk minimisation measures** None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted Follow-up Questionnaires • Analysis of additional safety data that may arise from any ongoing or future studies Additional pharmacovigilance activities: None

Hepatotoxicity	**Routine risk minimisation measures** Text within Sections 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the EU SmPC PL Sections 2 and 4 Limited package supply Restricted medical prescription **Additional risk minimisation measures** Patient Reminder Card	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Targeted Follow-up Questionnaires • Analysis of additional safety data that may arise from any ongoing or future studies Additional pharmacovigilance activities: None

Important Identified Potential Risks		
Testicular tubular atrophy/Male infertility	**Routine risk minimisation measures** Text within Sections 4.6 and 5.3 of the EU SmPC PL Section 2 Limited package supply Restricted medical prescription **Additional risk minimisation measures** None	Routine pharmacovigilance activities beyond adverse reactions reporting and signal detection: • Analysis of hormone data from ongoing studies including Paediatric Studies. • Analysis of additional safety data that may arise from any ongoing or future studies Additional pharmacovigilance activities: None

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for VOLIBRIS (ambrisentan)

This is a summary of the risk management plan (RMP) for VOLIBRIS. The RMP details important risks of VOLIBRIS, how these risks can be minimised, and how more information will be obtained about VOLIBRIS's risks and uncertainties (missing information).

VOLIBRIS's summary of product characteristics (SmPC) and its package leaflet give essential information to healthcare professionals and patients on how VOLIBRIS should be used.

This summary of the RMP for VOLIBRIS should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all which is part of the European Public Assessment Report (EPAR).

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

I. The medicine and what it is used for

VOLIBRIS is authorised for treatment of pulmonary arterial hypertension (PAH) in adult and paediatric patients aged 8 and over (see SmPC for the full indication). It contains ambrisentan as the active substance and it is given by oral route.

Further information about the evaluation of VOLIBRIS's benefits can be found in VOLIBRIS's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage:

http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000839/human_med_001151.jsp&mid=WC0b01ac058001d124

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

Important risks of VOLIBRIS, together with measures to minimise such risks and the proposed studies for learning more about VOLIBRIS 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 the case of VOLIBRIS, these measures are supplemented with *additional risk minimization measures* mentioned under relevant important risks, below.

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including PSUR assessment - 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 VOLIBRIS is not yet available, it is listed under 'missing information' below.

II.A List of important risks and missing information

Important risks of VOLIBRIS are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken. Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of VOLIBRIS. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation. Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected (e.g. on the long-term use of the medicine);

List of important risks and missing information	
Important identified risks	Teratogenicity Decrease haemoglobin/haematocrit, anaemia, including anaemia requiring transfusion Hepatotoxicity
Important potential risks	Testicular tubular atrophy/Male infertility
Missing information	None

II.B Summary of important risks

Important identified risk: **Teratogenicity**

Evidence for linking the risk to the medicine	Preclinical toxicology studies
Risk factors and risk groups	Pregnant women and women of child-bearing potential
Risk minimisation measures	**Routine risk minimisation measures** Text within Sections 4.2, 4.3, 4.4, 4.6 and 5.3 of the EU SmPC PL Section 2 Limited package supply Restricted medical prescription **Additional risk minimisation measures** Patient Reminder Card
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** None
Decreased haemoglobin/haematocrit/anaemia, including anaemia requiring transfusion	
Evidence for linking the risk to the medicine	Clinical Trial and Post-marketing data
Risk factors and risk groups	Overall, anaemia is twice as prevalent in females as in males. This difference is significantly greater during the childbearing years. Anaemia of chronic disorders is more common in populations with a high incidence of chronic infectious disease (e.g., malaria, tuberculosis, acquired immunodeficiency syndrome Milman, 2011).
Risk minimisation measures	**Routine risk minimisation measures** Text within Sections 4.4, 4.8 and 5.1 of the EU SmPC PL Sections 2 and 4 Limited package supply Restricted medical prescription **Additional risk minimisation measures** None
Hepatotoxicity	

Evidence for linking the risk to the medicine	Clinical trials and post-marketing data
Risk factors and risk groups	One of the challenges of analyzing reports of liver related events in patients with PAH is that this patient population has an underlying risk of liver disease. One of the most common causes of elevated liver enzymes in pulmonary hypertension patients is liver congestion associated with severe pulmonary hypertension or right heart failure. In addition to congestive hepatopathy, since the liver typically receives 20% of cardiac output, circulatory failure, which can occur in PAH patients with decompensated heart failure, can be associated with ischemic hepatitis, especially if the cardiac index <1.5 liters/min/m2 (Naschitz, 2000). Hypoxic hepatitis is associated with PaO2 < 45 mmHg (which may also occur in severe or end stage PAH patients) and results in a high (62%) in-hospital mortality. Hypoxic hepatitis is rare and has similar findings to ischemic hepatitis: abrupt, marked ALT & AST elevations (10-20 fold normal) which resolve rapidly, with centrilobular necrosis on liver biopsy. (Henrion, 2012). Additionally, hepatitis in PAH patients may be associated with underlying diseases (e.g., autoimmune hepatitis, HIV co-infected viral hepatitis, connective tissue disease associated hepatitis and existing liver disease resulting in portopulmonary hypertension). A review of placebo data in ambrisentan, bosentan and sitaxentan clinical studies in PAH patients indicated that elevated aminotransferase levels of greater than three times the upper limit of normal (ULN) occurred in placebo patients at an incidence of between 1.5 and 6% over a 12 to 24 week period (Galiè, 2008a; Rubin, 2002; Barst, 2004; Barst, 2006; Oudiz, 2006; Galiè, 2008b). The background rate of liver dysfunction in PAH patients makes it challenging to disentangle a possible causal association with ambrisentan from the underlying predisposition of PAH patients to experience liver events. It is not clear whether a history of transaminase elevations prior to initiation of ambrisentan constitutes a risk factor for hepatotoxicity with ambrisentan. At the of submission for marketing authorisation the assessment of liver safety also included a cohort of patients who have discontinued other ERAs due to elevations in hepatic transaminases previously. Over a period of exposure (mean 52.9 weeks, maximum exposure 76

	weeks) none of the 36 patients enrolled had LFT abnormalities that required permanent discontinuation of ambrisentan. In this study the duration of exposure to ambrisentan is considerably longer than the median time to discontinuation of bosentan or sitaxentan (14 and 29 weeks respectively).
Risk minimisation measures	**Routine risk minimisation measures** Text within Sections 4.2, 4.3, 4.4, 4.8, 5.1 and 5.2 of the EU SmPC PL Sections 2 and 4 Limited package supply Restricted medical prescription **Additional risk minimisation measures** Patient Reminder Card
Important potential risk:	
Testicular tubular atrophy/Male infertility	
Evidence for linking the risk to the medicine	Pre-clinical and clinical trial data
Risk factors and risk groups	Alterations in sperm count have been reported in men with severe chronic diseases such as PAH. No specific risk factors for reduction in sperm count have been identified.
Risk minimisation measures	**Routine risk minimisation measures** Text within Sections 4.6 and 5.3 of the EU SmPC PL section 2 Limited package supply Restricted medical prescription **Additional risk minimisation measures** None
Missing information:	

None

II.C Post-authorisation development plan

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

There are no studies which are conditions of the marketing authorisation or specific obligation of VOLIBRIS.

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

There are no studies required for VOLIBRIS.

PART VII: ANNEXES

LIST OF ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Table of contents:

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Targeted Follow Up Questionnaire
Ambrisentan and Decreased Hemoglobin/Hematocrit

Patient/subject ID, DOB:	**Sex** ☐ M ☐ **F**	**GSK OCEANS CASE No:**
Weight: Kg	**Height:** Centimeters	**Obese?(BMI >30)** ☐ Yes ☐ No

Description of the Event:

	Yes	**No**
Was the patient symptomatic with anemia? • If *yes*, please tick all that apply: ☐ Fatigue/malaise (worsening from baseline) ☐ Dyspnea (worsening from baseline) ☐ Pallor ☐ Syncope/near syncope ☐ Dizziness ☐ Symptomatic hypotension (worsening from baseline) ☐ Tachycardia/palpitations ☐ Other, please specify:	☐	☐
Did the patient require treatment or intervention for anemia? • If *yes*, please tick all that apply ☐ Iron Supplement ☐ Transfusion ____ units ☐ Treatment with hematopoetic growth factors ☐ Other, please specify: (i.e. B12, folate)	☐	☐
Did event resolve? • If yes, please specify time to resolution: • If no, please specify outcome:	☐	☐
When did the patient develop anemia relative to first dose of ambrisentan therapy? ☐ within 1 week ☐ within 2 weeks ☐ within 4 weeks ☐ within 8 weeks ☐ other: please specify		
Did the patient have evidence of new or worsening fluid retention?	☐	☐
Action Taken with ambrisentan		
Was ambrisentan therapy withdrawn?	☐	☐
• If *yes*, did events resolve following this action?	☐	☐
• If events resolved, please specify time to resolution:		
Was ambrisentan dose was **reduced**?	☐	☐
• If *yes*, did events resolve following this action?	☐	☐
• If events resolved, please specify change in dose and time to resolution:		
Was the patient was **rechallenged** with ambrisentan?	☐	☐
• If yes, did the events recur with rechallenge?	☐	☐
• If events recurred, please specify time to recurrence:		

Diagnostic tests:

Did the patient have baseline hemoglobin/hematocrit level before initiation of Ambrisentan? ☐ Yes ☐ No
If yes, please specify hemoglobin/hematocrit level: Date:

Please provide value for lowest hemoglobin/hematocrit level measured thus far: Date:

Please characterize the type of anemia at the time of the event:
☐ **Hypochromic, microcytic**
☐ **Macrocytic**
☐ **Normochromic, normocytic**
Was there evidence of hemolysis? ☐ Yes ☐ No If yes, please specify

Additional Laboratory Tests	Normal	Abnormal	Test Not Done	Results/Date
WBC count	☐	☐	☐	
Platelet Count	☐	☐	☐	
BUN	☐	☐	☐	
Creatinine	☐	☐	☐	

Was a work-up for a possible gastrointestinal source of bleeding done (e.g. hemoccult stool/rectal exam, etc)? ☐ Yes ☐ No

If *yes*, indicate results with date:

Was a bone marrow biopsy performed at the time of the event? ☐ Yes ☐ No

If yes, indicate results with date:

Were any other diagnostic tests conducted? ☐ Yes ☐ No

If *yes*, please specify and give results with dates:

History:

Did the patient have a history of any of the following prior to starting therapy with ambrisentan?

	Yes	No		Yes	No
Blood loss/Acute Hemorrhage			**Immune Mediated Disorders**		
• Gastrointestinal *(i.e. ulcer, diverticulosis)* Please specify:	☐	☐	• Autoimmune hemolysis	☐	☐
• Genitourinary *(i.e. menorrhagia, dysfunctional uterine bleeding)* Please specify:	☐	☐	• Autoimmune disease *(e.g. Systemic Lupus Erythematosus, Sarcoidosis)* Please specify:	☐	☐
Hematologic Disorders			**Chronic Diseases and Malignancies**		
• Primary bone marrow disorder *(i.e. multiple myeloma, leukemia, metastatic cancer, myelofibrosis)* Please specify:	☐	☐	• Non- hematologic malignancy Please specify:	☐	☐
• Microangiopathic hemolytic anemia	☐	☐	• Anemia of Chronic disease	☐	☐
• Thalassemias/hemoglobinopathies	☐	☐	• History of cirrhosis	☐	☐
• Congenital *(i.e. cytoskeleton defects/ dyserythropoiesis/ or enzymatic deficiencies)*	☐	☐	• History of renal insufficiency/failure Please specify etiology if known:	☐	☐
Nutritional			**Infectious**		
• Iron deficiency	☐	☐	• Recent infection (e.g. cytomegalovirus, EBV, malaria, clostridia, other) Please specify:	☐	☐
• Vitamin B-12 deficiency	☐	☐	• HIV	☐	☐
• Folate deficiency	☐	☐	• Prior to the current event, any history of transfusion? If yes, specify reason and date:	☐	☐
• Malnutrition	☐	☐			
Other					

• Recent pregnancy	☐	☐			

Other relevant history, please specify:

Other medications added prior to event, including chronic or intermittent therapy? ☐ **Yes** ☐ **No**

☐ Immunosuppressive agents ☐ Methotrexate ☐ Coumadin/anticoagulant ☐ Thiazolidinediones

☐ Other (including over-the-counter or herbal remedies)

Please specify:

If patient has Pulmonary Artery Hypertension (**PAH), please specify etiology if known**:

☐ Idiopathic ☐ Connective Tissue Disease associated, please specify:

☐ HIV ☐ Other, please specify:

PAH-WHO functional class at time of Ambrisentan initiation	**PAH-WHO functional class at time of event**
☐ I ☐ II ☐ III ☐ IV	☐ I ☐ II ☐ III ☐ IV

Personal and medical information may be made available to GlaxoSmithKline to provide and support the services that GlaxoSmithKline uses to process such information in order to meet its legal and regulatory obligations. GlaxoSmithKline takes steps to ensure that these service providers protect the confidentiality and security of this personal and medical information, and to ensure that such information is processed only for the provision of the relevant services to GlaxoSmithKline and in compliance with applicable law.

GlaxoSmithKline

Targeted Follow Up Questionnaire

Ambrisentan and Hepatobiliary Adverse Events

Patient/subject ID, DOB:	**Sex:** ☐ **M** ☐ **F**	**GSK OCEANS CASE No:**
Weight : _____ Kg	**Height** _____ Centimeters	**Obese?(BMI >30)** ☐ yes ☐ no

Description of the Event:

	Yes	**No**
Did the patient present with any of the following? ☐ Right upper quadrant pain (RUQ)/abdominal pain ☐ Nausea/vomiting ☐ Rash ☐ Anorexia ☐ Jaundice ☐ Fever ☐ Altered mental status/confusion ☐ Other: *please describe*	☐	☐
How soon after initiation of Ambrisentan therapy did event occur? ☐ within 24 hours ☐ within 1 week ☐ other: *please specify*	☐	☐
Did the patient develop fulminant liver failure? (e.g. jaundice, encephalopathy, elevated prothrombin time)	☐	☐
• If yes, did the patient require liver transplantation?	☐	☐
Were there any other contributing factors? ☐ concomitant acute illness (e.g. acute pancreatitis) ☐ worsening of underlying pulmonary artery hypertension ☐ other: *please specify*		
Did the patient initiate or change therapy with any medications other than ambrisentan just prior to the event?	☐	☐
• If yes, please specify medication, dosage, and timing relative to the event:		

Action Taken with ambrisentan	Yes	No
Was ambrisentan therapy withdrawn?	☐	☐
• If *yes,* did events resolve following this action?	☐	☐
• If events resolved, please specify time to resolution:		
Was ambrisentan dose was **reduced?**	☐	☐
• If *yes*, did events resolve following this action?	☐	☐
• If events resolved, please specify change in dose and time to resolution:		
Was the patient **rechallenged** with ambrisentan?	☐	☐
• If yes, did the events recur with rechallenge?	☐	☐
• If events recurred, please specify time to recurrence:		

Diagnostic Tests

Laboratory tests* (at time of event)	**Normal**	**Abnormal**	**Test Not Done**	**Results/Date**
Alanine Aminotransferase (ALT/SGPT)	☐	☐	☐	
Aspartate Aminotransferase (AST/SGOT)	☐	☐	☐	
Lactate Dehydrogenase (LDH)	☐	☐	☐	
Alkaline Phosphatase	☐	☐	☐	

Gamma Glutamyltransferase (GGT)	☐	☐	☐	
Total Bilirubin	☐	☐	☐	
Direct (Conjugated) Bilirubin	☐	☐	☐	
Prothrombin Time (PT)	☐	☐	☐	
Creatinine Phosphokinase (CPK)	☐	☐	☐	
Eosinophil count	☐	☐	☐	
Albumin level	☐	☐	☐	

***If tests performed on more than one occasion, please attach results for *all* dates available.**

Are pre-ambrisentan baseline liver enzyme and function tests available? ☐ YES ☐NO

- If yes, please specify type of test, date performed and results:

Were tests for viral hepatitis performed at the time of the event? ☐ YES ☐NO

☐ Hepatitis A	☐ Hepatitis C	☐ Hepatitis E	☐ Epstein-Barr Virus
☐ Hepatitis B	☐ Hepatitis D	☐ Herpes Viruses	☐ Cytomegalovirus

- Please indicate date and results:

Did the patient have evidence of autoimmune disease at the time of the event? ☐ YES ☐NO

☐ ANA (anti-nuclear antibody)
☐ SMA (anti-smooth muscle antibody)
☐ anti-LKM (Type 1 anti-liver-kidney microsomal antibody)
☐ Other, please specify:

Were any imaging or other diagnostic tests performed at the time of the event (e.g. ultrasonography, computed tomography (CT) scan, magnetic resonance imaging)**?**

- If *yes*, please indicate type of test, date performed and results:

Was a liver biopsy performed? ☐ YES ☐NO

- If *yes*, please indicate date and attach copy of results.

Were any other relevant laboratory investigations performed? ☐ YES ☐NO

- *If yes*, please specify date and results:

History:

Has the patient ever taken (include dates) any of these medications for pulmonary arterial hypertenstion (PAH)?
☐ YES ☐ NO

☐ Bosentan (Tracleer)	☐ Sitaxsentan (Thelin)
☐ Sildenafil (Revatio)	☐ Treprostinil (Remodulin)
☐ Epoprostenol (Flolan)	☐ Iloprost (Ventavis)
☐ Other: please specify	

Has the patient ever discontinued any of the above medications due hepatotoxicity? ☐ YES ☐NO

- If yes, please specify medication(s) and outcome:

Concomitant medications at the time of the event (Please indicate name of medication and dosage if known)

☐ Non-steroidal Anti-inflammatory medications

☐ Acetaminophen (indicate g/day if known):

☐ Over-the counter products or herbal supplements:

☐ **Other** chronic or intermittent medications, especially those with known hepatotoxicity:

Did the patient have a history of any of the following prior to initiation of ambrisentan therapy?

Hepatobiliary Disease	Yes	No	Other Systemic Disorders	Yes	No
Gilbert's disease	☐	☐	Wilson's Disease	☐	☐
Non-alcoholic fatty liver	☐	☐	Hemochromatosis	☐	☐
Cirrhosis	☐	☐	Alpha-1 Antitrypsin deficiency	☐	☐
Hepatic Failure	☐	☐	Granulomatous disease (i.e. Sarcoidosis)	☐	☐
Gallbladder Disease	☐	☐	Autoimmune Disease Please specify:	☐	☐
Pancreatitis	☐	☐	**Infections**	☐	☐
Substance Abuse	☐	☐	Hepatitis A	☐	☐
Sympathomimetics (i.e. cocaine, methamphetamines)	☐	☐	Hepatitis B	☐	☐
Alcohol Use			Hepatitis C		
Intravenous Drug Use			HIV		
Cardiac			Known close contact with a person with acute viral hepatitis		
Right Sided Heart Failure			Recent travel to or domicile in a developing country within 3 months		

Other pertinent medical history, please specify:

Etiology of PAH: ☐ Idiopathic ☐ Connective Tissue Disease Associated, please specify
☐ HIV ☐ Other, please specify:

PAH-WHO Functional Class at time Ambrisentan initiated ☐ I ☐ II ☐ III ☐ IV

PAH-WHO Functional Class at time of event ☐ I ☐ II ☐ III ☐ IV

Personal and medical information may be made available to GlaxoSmithKline to provide and support the services that GlaxoSmithKline uses to process such information in order to meet its legal and regulatory obligations. GlaxoSmithKline takes steps to ensure that these service providers protect the confidentiality and security of this personal and medical information, and to ensure that such information is processed only for the provision of the relevant services to GlaxoSmithKline and in compliance with applicable law.

GlaxoSmithKline

Targeted Follow Up Questionnaire

Ambrisentan Pregnancy Report

Patient/subject ID:	**DOB:**	**GSK OCEANS CASE No:**
Weight: _____ Kg	**Height** _____ Centimeters	**Obese?(BMI >30)** ☐ Yes ☐ No

Description of the Event:

	Yes	**No**
1. Was patient assessed to be a female of child bearing potential prior to initiation of ambrisentan therapy? • If no, please explain circumstances	☐	☐
2. **Was counseling provided to the patient concerning risk of fetal harm and importance of using reliable contraception prior to initiation of ambrisentan therapy?** • If no, please explain circumstances.	☐	☐
3. **Were supplementary educational materials, if available, regarding teratogenicity and pregnancy prevention provided to the patient prior to initiation of ambrisentan therapy?** • If no, please explain circumstances.	☐	☐
4. **Were the partners of women of childbearing potential provided supplementary educational materials regarding teratogenicity and pregnancy prevention?**	☐	☐
5. **Did the patient appear to understand the importance of contraception and the recommended contraceptive methods prior to initiation of ambrisentan therapy?**	☐	☐
6. **When prescribing ambrisentan for this patient, did you routinely limit the prescription to a one month supply?**	☐	☐

7. **Were you able to identify possible contributory factors for failure to avoid pregnancy?**

☐ Patient intended to become pregnant

☐ Non-compliance with use of reliable contraceptive method

☐ Patient selected unreliable contraceptive method (i.e. not a method recommended in educational materials, if available)

☐ Patient did not understand how to use the particular contraceptive method selected

☐ Patient had difficulty obtaining access to a reliable contraceptive method

- Please explain:

☐ Failure of physical contraceptive method (e.g. condom, diaphragm)

- Please specify:

☐ Failure of hormonal contraceptive method (e.g. oral contraceptive, injectable or implanted hormonal method)

- Please specify:

☐ Other, please describe:

Diagnostic Tests		
	Yes	**No**
Was a pregnancy test performed prior to initiation of ambrisentan therapy? If yes, please specify results (Day/Month/Year):	☐	☐
Were monthly pregnancy tests performed during treatment with ambrisentan?	☐	☐
Date of last negative pregnancy test (Day/Month/Year):		
Date of positive pregnancy test (Day/Month/Year):		
Were any other relevant laboratory investigations performed? Please specify:	☐	☐

History	
Was the patient using any method of contraception when pregnancy occurred? YES ☐ NO ☐	
Which method(s) of contraception? (Please provide specific brand where applicable)	
☐ Oral Contraceptive	☐ Intrauterine device (IUD) or intrauterine system (IUS)
☐ Injectable progestogen	☐ Male partner sterilization (vasectomy with documentation of azoospermia)
☐ Implants of levonorgestrel	☐ Double barrier method: condom or occlusive cap (diaphragm or cervical/vault caps) plus spermicidal agent (foam/gel/film/cream/suppository)
☐ Oestrogenic vaginal ring	☐ Abstinence
☐ Percutaneous contraceptive patches	☐ Other, please specify:

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ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMISATION ACTIVITIES (IF APPLICABLE)

Key messages of the additional risk minimisation measures

- Patient Reminder Card
  - That Volibris treatment may increase the risk of teratogenicity and liver injury as described in the patient leaflet:
  - That Volibris is teratogenic in animals;
  - That pregnant women must not take Volibris;
  - That women of reproductive potential must use effective contraception;
  - The need for monthly pregnancy tests;
  - The need for regular monitoring of liver function because Volibris may cause liver injury.