Australian Government
Department of Health
Therapeutic Goods Administration

Australian Public Assessment Report for Riociguat

Proprietary Product Name: Adempas

Sponsor: Bayer Australia Ltd

June 2014

TGA Health Safety Regulation

About the Therapeutic Goods Administration (TGA)

- The Therapeutic Goods Administration (TGA) is part of the Australian Government Department of Health and is responsible for regulating medicines and medical devices.
- The TGA administers the *Therapeutic Goods Act 1989* (the Act), applying a risk management approach designed to ensure therapeutic goods supplied in Australia meet acceptable standards of quality, safety and efficacy (performance), when necessary.
- The work of the TGA is based on applying scientific and clinical expertise to decision-making, to ensure that the benefits to consumers outweigh any risks associated with the use of medicines and medical devices.
- The TGA relies on the public, healthcare professionals and industry to report problems with medicines or medical devices. TGA investigates reports received by it to determine any necessary regulatory action.
- To report a problem with a medicine or medical device, please see the information on the TGA website <http://www.tga.gov.au>.

About AusPARs

- An Australian Public Assessment Record (AusPAR) provides information about the evaluation of a prescription medicine and the considerations that led the TGA to approve or not approve a prescription medicine submission.
- AusPARs are prepared and published by the TGA.
- An AusPAR is prepared for submissions that relate to new chemical entities, generic medicines, major variations, and extensions of indications.
- An AusPAR is a static document, in that it will provide information that relates to a submission at a particular point in time.
- A new AusPAR will be developed to reflect changes to indications and/or major variations to a prescription medicine subject to evaluation by the TGA.

Contents

List of commonly used abbreviations

Abbreviation	Meaning
6MWD	6 minute walk distance
6MWT	6 minute walk test
AE	adverse event
AFIB	atrial fibrillation
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the concentration versus time curve from zero to infinity
BID	bis in die (twice a day)
BNP	brain natriuretic peptide
BP	blood pressure
bpm	beats per minute
CHMP	Committee for Medicinal Products for Human Use
CI	confidence interval
cGMP	cyclic guanosine monophosphate
CLCR	creatinine clearance
CLR	clearance of riociguat
C_{max}	maximum drug concentration in measured matrix after single dose administration
C_{max}/D	maximum drug concentration in measured matrix after single dose administration divided by dose
CO	cardiac output
CSR	clinical study report
CTEPH	chronic thromboembolic pulmonary hypertension
CTX	type I collagen C-telopeptides
CV	coefficient of variation

Abbreviation	Meaning
CYP	cytochrome P450 isoenzyme
CYP1A1	cytochrome P450 isoenzyme 1A1
CYP1A2	cytochrome P450 isoenzyme 1A2
CYP2C8	cytochrome P450 isoenzyme 2C8
CYP2C9	cytochrome P450 isoenzyme 2C9
CYP2J2	cytochrome P450 isoenzyme 2J2
CYP3A4	cytochrome P450 isoenzyme 3A4
DBP	diastolic blood pressure
ECG	electrocardiogram
EMA	European Medicines Agency
EQ-5D	European quality of life 5-dimensions instrument
ERA	endothelin receptor antagonist
EU	European Union
FDA	Food and Drug Administration
H	h (s)
HR	heart rate
ICH	International Conference on Harmonisation
IDT	individual dose titration
ILD	interstitial lung disease
IPAH	idiopathic pulmonary arterial hypertension
IR	immediate release
ITT	Intention-to-Treat
LFT	liver function test
LPH	Living with Pulmonary Hypertension
LS mean	last square mean
LTE	long term extension

Abbreviation	Meaning
MAP	mean arterial pressure
MedDRA	Medical Dictionary for Regulatory Activities
N	number
NO	nitric oxide
NT-proBNP	N-terminal prohormone B-type natriuretic peptide
NTX	N-terminal cross-linking telopeptides of type I collagen
PAH	pulmonary arterial hypertension
PAP	pulmonary artery pressure
PCH	pulmonary capillary haemangiomatosis
PD	pharmacodynamic
PDE5	phosphodiesterase 5
PE	pulmonary embolism
P-gp	P-glycoprotein
PH	pulmonary hypertension
PK	pharmacokinetic
PP	per protocol
PPH	primary pulmonary hypertension
PVOD	pulmonary veno-occlusive disease
PVR	pulmonary vascular resistance
RMP	risk management plan
RV	right ventricle
RVF	right ventricular failure
RVH	right ventricular hypertrophy
RVSP	right ventricular systolic pressure
SAE	serious adverse event
SBP	systolic blood pressure

Abbreviation	Meaning
SD	standard deviation
sGC	soluble guanylate cyclase
SOC	system organ class
SVR	systemic vascular resistance
SVRI	systemic vascular resistance index
TEAE	treatment emergent adverse event
TESAE	treatment emergent serious adverse event
TDS	ter in die (3 times a day)
Tmax	time to reach maximum drug concentration in plasma after single (first) dose
TPR	total peripheral resistance
TTCW	time to clinical worsening
ULN	upper limit of normal
US(A)	United States (of America)
Vss	apparent volume of distribution at steady state
VTE	venous thromboembolism
WHO	World Health Organization
WHO FC	World Health Organization functional class

I. Introduction to product submission

Submission details

Type of submission:	New chemical entity
Decision:	Approved
Date of decision:	7 April 2014
Active ingredient:	Riociguat
Product name:	Adempas
Sponsor's name and address:	Bayer Australia Ltd PO Box 903 Pymble NSW 2073
Dose form:	Film coated tablets
Strengths:	0.5, 1, 1.5, 2 and 2.5 mg
Container:	Blister pack
Pack sizes:	21 (sample pack), 42 and 84 tablets
Approved therapeutic use:	***Pulmonary arterial hypertension*** *Adempas, as monotherapy or in combination with approved PAH treatments (endothelin receptor antagonists or inhaled or subcutaneous prostanoids), is indicated for the treatment of:* · *idiopathic pulmonary arterial hypertension* · *heritable pulmonary arterial hypertension* · *pulmonary arterial hypertension associated with connective tissue diseases or* · *pulmonary arterial hypertension associated with congenital heart disease* *in adult patients with WHO functional class II, III or IV symptoms* ***Chronic thromboembolic pulmonary hypertension*** *Adempas is indicated for the treatment of* · *Persistent or recurrent chronic thromboembolic pulmonary hypertension (CTEPH) after surgical treatment or* · *inoperable CTEPH* *in adult patients with WHO functional class II, III or IV symptoms*
Route of administration:	Oral (PO)
Dosage:	1 mg three times daily for 2 weeks and increased in 2-week intervals by 0.5 mg increments to a maximum of 2.5 mg three times daily

ARTG numbers: 207595-207599

Product background

This AusPAR describes the application by the Bayer Australia Ltd to register riociguat, a new chemical entity, for the treatment of inoperable or persistent or recurrent Chronic Thromboembolic Pulmonary Hypertension (CTEPH). It is also indicated for Pulmonary Arterial Hypertension (PAH).

The proposed indications were as follows:

Chronic thromboembolic pulmonary hypertension (CTEPH, WHO Group 4):

Adempas is indicated for the treatment of adult patients with

- *inoperable CTEPH,*
- *persistent or recurrent CTEPH after surgical treatment*

to improve exercise capacity and WHO functional class.

Pulmonary arterial hypertension (PAH, WHO Group 1):

Adempas is indicated for the treatment of adult patients with PAH to improve exercise capacity, WHO functional class and to delay clinical worsening.

Efficacy in PAH was shown in patients on riociguat monotherapy or in combination with endothelin receptor antagonists or prostanoids.

Studies establishing effectiveness in PAH predominately included patients with WHO functional class II-III and aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease.

It was designated by the TGA on 16 October 2012 as an Orphan Drug.

Riociguat is the first member of a novel class of compounds, the soluble guanylate cyclase (sGC) stimulators. It is a stimulator of soluble guanylate cyclase, an enzyme in the cardiopulmonary system, and increases production of the second messenger cyclic guanosine monophosphate (cGMP). It does this independent of nitric oxide (NO) and, in the presence of NO, it enhances the effects of NO. This mechanism of action is stated as unique in the setting of CTEPH and PAH.

Pulmonary arterial hypertension is thought to be mediated through an up-regulated endothelin-1 system, defective prostacyclin synthase activity and abnormalities of the nitric oxide pathway. Current treatments for PAH are aimed at these main pathways: endothelin receptor antagonists (inhibit the effects of elevated endothelin-1 and thus reduce vasoconstriction, smooth muscle cell proliferation and pulmonary vessel fibrosis), prostacyclin analogues (relax and reduce proliferation of vascular smooth muscle cells) and phosphodiesterase type 5 inhibitors (potentiate the anti-platelet, anti-proliferative and vasodilatory effects of nitric oxide).

Specific pharmaceutical treatments registered for the treatment of PAH include oral bosentan, ambrisentan, tadalafil and sildenafil, inhaled nitric oxide and iloprost, intravenous epoprostenol and subcutaneous treprostinil. A recent orphan designation for PAH included imatinib.

Chronic Thromboembolic Pulmonary Hypertension (CTEPH) is mainly treated with anticoagulants and then pulmonary endarterectomy surgery as the treatment of choice for patients with symptomatic, operable CTEPH. However there are 30 to 40% of patients who are not suitable for surgery or approximately 30% who have persistent pulmonary hypertension after surgery. There are currently no approved medicines to treat CTEPH.

Adempas has not been previously considered by the TGA's Advisory Committee for Prescription Medicines (ACPM).

There are two specific EU guidelines adopted by the TGA relevant to this submission, besides the general guidelines:

- EMEA/CHMP/EWP/356954/2008: Guideline on the Clinical Investigations of Medicinal Products for the Treatment of Pulmonary Arterial Hypertension. Effective: 28 May 2010
- EMEA/CHMP/EWP/644261/2008: Concept Paper on the Need for the development of a Paediatric Addendum to the CHMP Guideline on the Clinical Investigations of Medicinal Products for the Treatment of Pulmonary Arterial Hypertension. Effective: 1 May 2009.

Regulatory status

This is an application for a new chemical entity.

Riociguat was approved in USA in October 2013 (indication below). The CTEPH indication has been approved in Canada (September 2013) and Switzerland (November 2013). The PAH indication is under evaluation in Canada and was not submitted in Switzerland. The submission is under evaluation in the European Union (EU) and Japan (CTEPH only). The submission is proposed for New Zealand in 2014.

> FDA approved indication:
>
> *Chronic-Thromboembolic Pulmonary Hypertension*
>
> *Adempas is indicated for the treatment of adults with persistent/recurrent chronic thromboembolic pulmonary hypertension (CTEPH), (WHO Group 4) after surgical treatment, or inoperable CTEPH, to improve exercise capacity and WHO functional class [see Clinical Studies (14.1)].*
>
> *Pulmonary Arterial Hypertension*
>
> *Adempas is indicated for the treatment of adults with pulmonary arterial hypertension (PAH), (WHO Group 1), to improve exercise capacity, WHO functional class and to delay clinical worsening.*
>
> *Efficacy was shown in patients on Adempas monotherapy or in combination with endothelin receptor antagonists or prostanoids. Studies establishing effectiveness included predominately patients with WHO functional class II–III and etiologies of idiopathic or heritable PAH (61%) or PAH associated with connective tissue diseases (25%) [see Clinical Studies (14.2)].*

Product Information

The approved Product Information (PI) current at the time this AusPAR was prepared can be found as Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

II. Quality findings

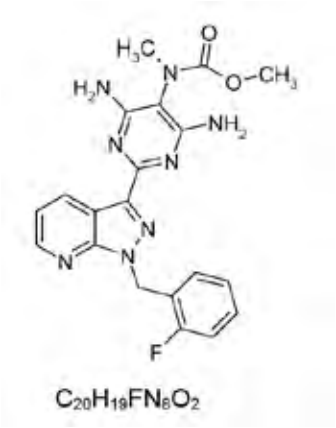
Drug substance (active ingredient)

Riociguat is made by chemical synthesis. It is an achiral molecule. Various polymorphic and pseudopolymorphic forms were shown to exist.

Riociguat used to manufacture ADEMPAS® tablets exists as the most thermodynamically stable form.

Riociguat was shown to be non-hygroscopic. The pKa of riociguat is 4.34 ± 0.02.

Figure 1. Chemical structure



It is not known to be structurally related to any other active moieties.

Riociguat is insoluble in aqueous solutions.

The drug substance is micronised. Due to the poor aqueous solubility of the drug substance, particle size control is considered to be significant as this may affect tablet dissolution. Appropriate particle size controls have been applied by the finished product manufacturer. Impurity controls are acceptable.

Drug product

The proposed Adempas® tablets are film-coated, immediate release tablets. They are not scored.

The formulation is conventional. They are presented in 21, 42 and 84 tablets in a blister pack. The 21 tablet pack size is considered to be a sample pack and is only being registered for the 0.5 mg strength. The 84 tablet pack size is only being registered for the 0.5 mg tablet strength.

Riociguat coated tablets are manufactured as immediate-release formulations with a fluid-bed granulation process followed by post blending, compression and film-coating in standard processes.

An intravenous solution was developed as a ready-to-use solution containing 0.5 mg of drug substance in 50 mL histidine buffer. It was used as an intravenous (IV) formulation in an absolute bioavailability study for the evaluation of immediate release tablets.

The start of Phase I dose finding studies was performed using an oral liquid formulation of riociguat micronised using a macrogol based solvent.

All other clinical trials were performed with immediate release tablet formulations of the various dose strengths and different colours. Throughout the whole clinical development

the tablet composition and manufacturing principles were not changed with only one exception regarding the colour of the film-coat: Whereas tablets used in clinical studies Phase I and II were coated in red (titanium dioxide and ferric oxide red as pigment), in clinical Phase III studies the colour was changed to pale orange (titanium dioxide and ferric oxide yellow and ferric oxide red as pigment), regardless of the dose strengths in order to maintain the blindness of the trials. The total amount of colour pigments and total amount of film coat were not changed. The change is considered to be very minor in nature and will not have any impact on bioavailability.

Various dissolution media were trialled during development and it was found that higher discriminatory power was achieved at higher pH values.

The proposed shelf life is 36 months, store below 30°C in blister packs. No physicochemical changes on storage were detected.

Chemistry and quality control aspects are considered acceptable.

Biopharmaceutics

The pharmacokinetics of riociguat are linear from 0.5 to 2.5 mg. Inter-individual variability (co variance (CV)%) of riociguat exposure (area under the concentration time curve (AUC)) across all doses is approximately 60%. Riociguat is rapidly absorbed with maximum plasma concentrations (Cmax) appearing 1 to 1.5 h after tablet intake.

An absolute bioavailability study (ING11910 [PH-36361]) was conducted to assess the pharmacokinetic profile of a 1 mg oral dose of riociguat (BAY 63-2521) in comparison to an intravenous solution of riociguat (planned dose 1 mg) given over 60 minutes in a randomised, non-blinded, not placebo controlled, 2-way crossover design in healthy male subjects. The absolute bioavailability of riociguat is high (94%).

A relative bioavailability study (ING11259 [PH-34409]) to investigate safety, tolerability and pharmacokinetics of 0.5 mg and 2.5 mg IR-tablets BAY 63-2521 in comparison to 2.5 mg solution of BAY 63-2521 and to investigate the food effect of a high fat, high calorie meal on a 2.5 mg tablet BAY 63-2521 in 12 healthy male subjects in a randomised, open-label, four-fold crossover design. There were no relevant differences in bioavailability for BAY 63-2521 (and BAY 60-4552) when 2.5 mg of the drug was given either as an oral solution or an immediate-release tablet. A slight reduction in mean C_{max} (approximately 25%) and AUC (approximately 15%) was observed for BAY 63-2521 when 2.5 mg of the drug was given as a tablet with a high fat, high calorie breakfast (see additional food effect study below).

A study (Study 13010 [PH-36249]) was conducted to investigate the effect of food on the pharmacokinetics of riociguat and its metabolite M1 (BAY 60-4552) in which subjects were administered a single oral dose of one 2.5 mg riociguat tablet in either the fasted state (after an at least 10 h fast) or fed state (dose administered 30 minutes after the start of a standardized high fat and high calorie American breakfast. The results of the statistical comparisons showed that riociguat was readily absorbed with a median time to C_{max} (T_{max}) of 1.0 h in the fasted state, whereas, in the fed state, riociguat absorption was delayed with a median T_{max} of 4.0 h. The 90% confidence intervals of the ratio "fed/fasted" for the AUC values of riociguat and BAY 60-4552 ([82.15; 94.96] and [89.43; 99.79]) were within the bioequivalence range of 80 to 125%. In contrast, the least squares (LS) mean C_{max} values of riociguat and BAY 60-4552 in the fed state were decreased by 35.3% and 20.5% compared to the LS-mean C_{max} values in the fasted state. The lower limits of the 90% confidence intervals of the ratio "fed/fasted" for the C_{max} values of riociguat and BAY 60-4552 (57.8% and 71.7%) were below the lower limit of the bioequivalence range, that is, 80%. This effect was irrespective of the smoking status. The PI states that *"Intake with food does not affect riociguat area under the concentration curve (AUC) or C_{max} to a clinically relevant*

extent. Riociguat can be taken with or without food." The Delegate and the ACPM should deliberate on the appropriateness of this statement in light of the delayed riociguat absorption and lower C_{max} values of riociguat and BAY 60-4552 observed in the fed state as compared to the fasted state.

Quality summary and conclusions

Registration is recommended with respect to chemistry, quality control and bioavailability aspects.

III. Nonclinical findings

Introduction

The overall quality of the nonclinical dossier was good with all pivotal studies conducted according to Good Laboratory Practice (GLP). The toxicity of riociguat in repeat dose studies limited the range of doses investigated; exposure ratios in most studies for total (bound +unbound) drug similar to or below the expected clinical exposure and exposure to the unbound drug generally < 5 times the expected clinical exposure.

The metabolite M1 (BAY 60-4552) underwent a development program as a separate new molecular entity for use as an antihypertensive agent. For this reason there was considerably more data submitted on BAY 60-4552 than is usual for a metabolite. Some of the results of these studies (Pharmacodynamics and Safety Pharmacology) were evaluated.

Riociguat is extensively bound to plasma proteins in animals and humans but there are some species differences. Exposure ratios (ER) quoted in this report compare the exposures to both the total (bound + unbound) [ER_{AUCT}] and unbound [ER_{AUCU}] forms of riociguat.

Pharmacology

Primary pharmacology

Soluble guanylate cyclase (sGC) is the most characterised receptor for nitric oxide (NO). Binding of L-arginine-derived NO to the haem group of sGC results in marked stimulation of the enzyme, increasing the intracellular concentration of the second messenger cyclic guanosine-3',5'-monophosphate (cGMP). cGMP plays an important role in the regulation of cellular functions in many tissues including regulation of vascular tone, cellular proliferation and inflammation. In blood vessels, NO dependent elevations in cGMP and kinase activity result in the phosphorylation of proteins that lead to reduced cytosolic calcium levels and subsequent reduced contraction of vascular smooth muscle. sGC stimulators are drugs which can sensitise sGC to low levels of bioavailable NO by stabilising the nitrosylhaem complex in sGC maintaining the enzyme in its active configuration. These stimulators can also increase sGC activity in the absence of NO. Riociguat is an orally active sGC stimulator.

Primary pharmacology studies *in vitro* explored the basic biochemical actions of riociguat on purified recombinant sGC and on recombinant sGC expressed in cultured cells. The effects on responses of isolated smooth muscle tissues to agonist stimulation were also investigated. Riociguat stimulated purified recombinant sGC and recombinant sGC in reporter cell lines and in cultured smooth muscle cells. Stimulation of purified

recombinant sGC by riociguat was blocked by removal of the haem group and by the sGC inhibitor ODQ and was enhanced in the presence of the NO donor DEA/NO. The 50% effective dose (EC_{50}) values for the stimulatory effects in cultured cells were in the 100-200 nM range (ER_{CmaxU} 5 to 10). These exposure ratio comparisons do not take account of possible binding in the *in vitro* experiments. The EC_{50} for stimulation of recombinant sGC in Chinese Hamster Ovary (CHO) cells by riociguat was reduced from 180 nM to 0.12 nM in the presence of the NO releasing drug SIN-1. Riociguat (0.1-1.0 μM) increased cGMP levels in porcine aortic endothelial cells in a concentration dependent manner. This stimulation of cGMP production was potentiated in the presence of the NO donor DEA/NO and when endogenous NO was released by bradykinin. In summary, these studies demonstrated that riociguat stimulates sGC directly and also sensitizes sGC to NO.

Riociguat also blocked the contractions induced by phenylephrine in a variety of isolated vascular smooth muscles (50% inhibitory concentration (IC_{50}) 4.8 to 380 nM) and reduced perfusion pressure in the rat heart Langendorff preparation (maximum effect at 1 μM).

Similar studies were performed on the same tissues using the M1 metabolite of riociguat (BAY 60-4552). M1 had essentially identical effects on stimulation of sGC and was also blocked by ODQ but was generally about 10 fold less potent than riociguat on a molar basis at stimulating sGC in all systems.

Single intravenous doses of riociguat ≥ 0.01 mg/kg reduced mean arterial pressure and increased coronary blood flow in anaesthetized dogs. These changes in pressure were accompanied by moderate increases in heart rate. Single intravenous doses (≥0.03 mg/kg) and single oral doses of riociguat ≥ 0.3 mg/kg reduced mean arterial pressure in anaesthetised rats. Significant increases in heart rate were seen only after 30 and 100 mg/kg intravenous doses. In conscious spontaneously hypertensive rats (SHR), single oral doses (0.03 to 3.0 mg/kg) decreased mean arterial pressures with accompanying tachycardia. Repeated daily doses of riociguat (0.1, 0.3 mg/kg for 4 days) to SHR produced similar reductions in arterial pressure and tachycardia following each dose. In published studies on animal models of pulmonary hypertension, riociguat reduced both pulmonary and systemic arterial pressures; with reduced right ventricular hypertrophy and structural remodelling of the lung in a chronic mouse model and reduced muscularisation of pulmonary arteries and right ventricular hypertrophy in a chronic rat model.

The profile of the metabolite M1 (BAY 60-4552) *in vivo* was generally similar to riociguat. A direct comparison of M1 and riociguat in anaesthetised dogs indicated that the two drugs had similar haemodynamic profiles but M1 was approximately 3 times less potent than riociguat.

Secondary pharmacodynamics and safety pharmacology

No significant interactions were identified following investigation of the pharmacological profile of riociguat was using radioligand binding assays. Riociguat caused measurable inhibition of one phosphodiesterase subtype (human PDE7B, IC_{50} 2.9 μM) but had no effect on 9 other phosphodiesterases tested. Riociguat had no effects on recombinant membrane bound guanylate cyclases GC-A, or GC-B expressed in CHO cells.

Soluble guanylate cyclase also plays an important role in platelet aggregation and adhesion. In platelets, high doses ($ERC_{max}T$ 50, $ERC_{max}U$ 1000) of riociguat increased Vasodilator-stimulated Phosphoprotein (VASP) phosphorylation and cGMP levels and inhibited the platelet aggregation induced by collagen, adenosine diphosphate (ADP) and Thrombin Receptor Activator for Peptide 6 (TRAP-6). Bleeding time was prolonged in mice (ER_{AUCU} approximately 3.2) but not in anaesthetised rats following single doses up to 3 mg/kg (ER_{AUCU} 0.7). Riociguat interaction studies with acetylsalicylic acid, rivarobaxan and clopidogrel only found significant prolongation of tail transection bleeding times with acetylsalicylic acid. Other haematological parameters were measured in blood taken from rats under anaesthesia. No effects were seen on leukocyte or platelet counts and there was

no effect on coagulation following single riociguat doses up to 3 mg/kg. Erythrocyte numbers were reduced following 1 and 3 mg/kg and haematocrit was reduced at all doses ≥ 0.3 mg/kg.

Riociguat (≥ 3 mg/kg PO) alone had no effect on erectile function in rabbits but caused erections in the presence of sodium nitroprusside. An *in vivo* adverse events profiling screen conducted in rats and mice (using single oral doses of 30 mg/kg) revealed prolonged bleeding time and transient increases in blood glucose in mice, reduced sodium excretion and urine volume in hydrated rats and reduced gastric irritation in fasted rats. In other studies blood glucose in fasted rats was increased following a dose of 3 mg/kg and in fed rats at doses ≥ 1 mg/kg. No effects on triglycerides or cholesterol were noted. Urine volume in rats was reduced at 3 mg/kg but electrolyte excretion was not affected.

Central nervous system (CNS) function was investigated in male rats at doses up to 3 mg/kg, (ER_{AUCU} 0.7). No effects were observed on open-field behaviour, body temperature or convulsive threshold to pentylenetetrazole. An increase in the latency of nociceptive responses was seen at 3 mg/kg. In CNS safety studies with the M1 metabolite BAY 60-4552 reduced body temperature, irregular breathing, hypoactivity, reduced muscle tone, ptosis, piloerection and tremor were seen following a dose of 10 mg/kg (ER_{AUCU} 14; based on averaged m/f values from 26 week repeat-dose BAY 60-4552 study).

Riociguat 10 µM (ER_{CmaxT} 20, ER_{CmaxU} 400) had no effect on hERG channel currents *in vitro* but this concentration caused a slight prolongation of Action Potential Duration At 90% Repolarisation (APD_{90}) in isolated rabbit cardiac Purkinje fibres. In conscious dogs riociguat at doses ≥ 0.05 mg/kg decreased blood pressure and increased heart rate. Some prolongation of QT intervals at high heart rates was seen using Bazett's (QT_{cB}) and Frederica's (QT_{cF}) correction formulae but no prolongation was apparent when QT intervals were corrected using van der Water's formula (QT_{cW}).[1] Similar effects were seen with the different correction formulae when applied to QT intervals at high heart rates in anaesthetised dogs. Given the lack of effect on hERG currents *in vitro* it seems unlikely that riociguat presents any risk of ventricular arrhythmias. In anaesthetised dogs the effects of riociguat on blood pressure and heart rate were attenuated with blood pressure affected at doses ≥ 0.1 mg/kg and heart rate at 0.3 mg/kg. In conscious telemetered female rats riociguat caused long lasting dose dependent decreases in arterial pressure and increases in heart rate but did not affect any electrocardiogram (ECG) parameters.

In vivo BAY 60-4552 had essentially similar cardiovascular effects to those of riociguat. BAY 60-4552 did cause some inhibition of hERG currents (IC_{50} 57 µmol/L) in HEK293 cells and prolonged APD_{90} and reduced maximal repolarization velocity, triangulation, and reverse frequency dependence in isolated rabbit cardiac Purkinje fibres at concentrations ≥10 µmol/L (ER_{CmaxU} 1000).

No effects were seen on respiration or lung mechanics in anaesthetised dogs with riociguat doses up to 0.3 mg/kg and BAY 60-4552 doses up to 1.0 mg/kg.

Gastrointestinal effects were examined both *in vitro* and *in vivo*. Riociguat did not affect tone in isolated guinea-pig ileal segments but decreased responses to acetylcholine and histamine at 1 µM. In male rats intestinal transit was inhibited by riociguat at 1 and 3 mg/kg.

[1] QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated.

Pharmacokinetics

A non-compartmental linear pharmacokinetic model most adequately described riociguat disposition in experimental animals.

Absorption

Oral absorption was rapid in rats with C_{max} being reached by between 0.5 and 1.5 h while in dogs slightly longer T_{max} values ranged from 0.91 h to 2.88 h. Oral bioavailability was moderate (35 to 66%) in rat and higher (50 to 80%) in dog. Exposure in terms of AUC increased more than dose-proportionally in rats from 0.3 mg/kg to 3 mg/kg following oral administration while in dogs the AUC increase was approximately dose proportional from 0.03 mg/kg to 0.6 mg/kg. Clearance following single intravenous dosing was moderate in rats and dogs, 1.3 and 0.3 L/(kg.h) respectively. The plasma elimination half-lives were short in the interval up to 8 h in rat (0.7 to 1.5 h) and dog (1.5 to 3.1 h). Exposure to the M1 (primary metabolite of riociguat in humans) following repeat-dosing of riociguat was close to equal with riociguat exposure in dogs but much lower in rats (approximately 10% of parent).

Distribution

Plasma protein binding was high in humans (approximately 95%) and rabbit (96%) and moderate in rat (84%), and dog (83%) in *in vitro* experiments. In human plasma, a1-acid-glycoprotein was the main serum component responsible for protein binding. Riociguat is distributed mainly in human plasma rather than in blood cells as indicated by the plasma/blood concentration ratio of 1.51 (human) while more equal distribution was seen in rat (1.10) and dog (1.15). Plasma protein binding of the primary metabolite M1 in experimental species and man was similar to that of riociguat. Steady state volume of distribution following intravenous dosing was moderate in rats and dogs, 1.2 and 0.7 L/kg respectively. Riociguat was distributed rapidly to peripheral organs in rat and higher concentrations (of radioactivity) were detected in well perfused tissues such as kidney and liver as well as bile duct, adrenals, aorta wall and GI mucosa. Exposure in terms of AUC was higher in thyroid, liver, kidney and outer renal medulla. Comparison of $AUC_{0\text{-}24\ h}$ values on Day 14 with Day 1 values indicated limited accumulation ratios (between 1.5 and 2.4 for most penetrated tissues and 2.6 for whole blood). Terminal elimination of the low residual radioactivity was slow in whole body autoradiography studies with long terminal half-lives. Affinity for pigmented tissues such as eye wall and pigmented tissues was seen in studies in Long-Evans rats. Riociguat exhibited low penetration of the blood/brain and blood/testes barriers. In females riociguat was readily distributed to reproductive organs and also cross the placental barrier and was excreted in milk.

Metabolism

N-demethylation of riociguat to M1 was the major metabolic pathway in all species in liver microsome incubations. A small number of minor metabolites were formed at levels of less than 1% (radioactivity) in rabbit, dog and human and less than 2% in mouse and less than 5% in rat in microsomal incubations. M1 was the major metabolite in dog and human hepatocyte incubations but in rat M1 was produced additional to M9, M10 and M11. Hydroxylations of the fluorobenzl moiety were additional major reactions in rat leading to M9, M10 and M11. Hepatocyte incubations revealed minor glucuronide formation pathway conjugating both parent and M1 in humans (<2.4 %). From 20 tested isozymes, the P45 cytochrome isozymed CYP1A1, 2C8, 2J2, 3A4, 3A5 and to a much lesser extent CYP3A7, were found to be able to form M1. In human liver microsomes CYP2C8, CYP2J2 and CYP3A4 contribute to the formation of M1 to a similar extent while CYP3A4 and CYP2J2 contribute equally in microsomes from the intestine. CYP1A1 was shown to be an

important catalyst of M1 formation in liver and lung microsomes with increased metabolite formation in lung microsomes from smokers. No metabolites were restricted to humans only in the *in vitro* studies. Single oral administration of riociguat to mice, rats, dogs and humans revealed the riociguat parent as the major circulating compound in plasma and M1 the major circulating metabolite. In humans the M1-glucuronide (M4) was an additional major circulating metabolite which, although not detected in plasma of mice, rats or dogs was produced by rat and dog hepatocytes *in vitro*. One of four subjects in the human mass balance study showed significantly lower metabolic conversion to M1 compared to the other three subjects. M1 contributed between 42 and 59 % of total $AUC_{radioactivity}$ in three subjects but only 11% in the fourth. The inter-individual variability in riociguat oxidation is possibly due to variability in CYP1A1 activity in these subjects.

Excretion

Oral doses of riociguat in rat and dog were excreted mainly via the biliary/faecal route (>80%) while in humans faecal excretion (48-59%) was combined with moderate renal excretion (33 to 45%). Experiments with bile duct cannulated rats revealed significant extra biliary excretion of 24% of the administered dose. Unchanged drug was the predominant component in rat faeces accounting for 37 (male) to 41% (female) of the administered dose while in dogs the main component in faeces was M1 (35% dose) with a further 7 % of the dose accounted for by the M1 glucuronide M4. The main component in rat urine was unchanged drug from 4 to 8 % of administered does for males and females respectively while in dog urine M1 was the predominant compound (6% dose), then M4 (2%) and unchanged riociguat contributed 1.4 % of dose.

Conclusion

The pharmacokinetic profiles in the laboratory animal species were sufficiently similar to allow them to serve as appropriate models for the assessment of drug toxicity in humans. The metabolism profile of riociguat in dogs with respect to production of the M1 metabolite allowed appropriate coverage of exposure to the metabolite. The absorption and distribution patterns in the animals studied were well aligned with the disposition of riociguat in man.

Pharmacokinetic drug interactions

Riociguat inhibited the activity of CYP1A1 (IC_{50} 14.7 µmol/L) and weakly inhibited 2C19 (IC_{50} 44.4 µmol/L). Riociguat did not inhibit the activity of major isoforms *in vitro* including CYP1A2, 2A6, 2B6, 2C8, 2C9, 2D6, 2E1, 2J2, and 3A4. The K_i values for riociguat against CYP1A1 activity (0.6 µmol/L) are not substantially different from the anticipated therapeutic plasma concentrations (C_{max} approximately 200 µg/L [0.5 µmol/L]) and are therefore of potential clinical relevance.

No inhibitory potency of riociguat against human UDP-glucuronosyltransferase (UGT) isoforms or human sulfotransferases (SULT isoforms) was detected. Treatment with riociguat had no significant effect on CYP1A2 or CYP2C19 activity but did to some extent increase CYP3A4 and CYP2B6 activity at concentrations above 1111 ng/mL. The formation of the metabolite M1 in human liver microsomes was inhibited by drugs known to inhibit several CYP isozymes reflecting the contribution of CYP isoforms 2C8, 2J2, and 3A4/A5 in riociguat metabolism. In particular protease inhibitors and azole antifungals were able to inhibit the metabolism of riociguat by human liver microsomes. Several other drugs such as carvedilol, ethinylestradiol, quercetin, terfenadine and several tyrosine kinase inhibitors were able to inhibit riociguat metabolism with IC_{50} values below 20 µmol/L. Metabolism of riociguat by recombinant CYP1A1 was inhibited by amiodarone, ethinylestradiol, fenofibrate, naringenin, rosiglitazone, simvastatin, terfenadine and in particular by azole

antifungals. Of these, ketoconazole was identified as the most potent inhibitor of M1 formation (IC_{50} 0.3 and 0.5 µmol/L for recombinant CYP1A1 and human liver microsomes respectively).

Riociguat and M1 are both classified as P-gp and breast cancer resistance protein (BCRP) substrates *in vitro*. It is possible that inhibition of P-gp and/or BCRP by concomitantly administered drugs might increase plasma concentrations of riociguat and M1 via inhibition of their excretion. Studies using coadministration of drugs with riociguat *in vitro* revealed the potential for drug-drug interactions. Drugs such as atorvastatin, clarithromycin, cyclosporine A, erythromycin, ketoconazole, itraconazole, pantoprazole, quinidine, ritonavir, saquinavir, verapamil and voriconazole had the potential to inhibit riociguat excretion via BCRP transport. Due to the high bioavailability of riociguat the inhibition of BCRP or P-gp is unlikely to cause clinically relevant increases in bioavailability. However, the studies reveal that the inhibition of BCRP or P-gp by co-administered drugs could possibly lead to increased exposure to riociguat.

Riociguat was shown to be a substrate for the uptake transporter OCT2 (expressed in the kidney) but not OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT3. M1 was not transported by OCT2 or the other uptake transporters (OATP1B1, OATP1B3, OAT1, OAT3, OCT1 or OCT3). No drug-drug interactions due to inhibition of OCT2 are expected due to the significant faecal route of excretion although the possibility remains that some decrease in renal excretion might result from such inhibition.

Toxicology

Acute toxicity

Acute toxicity by the oral route was assessed in female mice and rats and by the intravenous route in female mice. The maximum non-lethal oral dose in mice and rats was 300 mg/kg. At the one higher dose tested in both species (2000 mg/kg) 3/6 mice and 3/3 rats died. No pathology was performed on the mice but in the rats which died at 2000 mg/kg gas filled stomach, dark red discolorations of lung and adrenal glands and pale discolorations of kidneys were noted. A maximum nonlethal dosage (MNLD) was not determined in the intravenous study in mice as 2/6 animals died at 30 mg/kg and 3/3 died at 200 mg/kg, the only two doses tested. There was no notable pathology in the animals which died in the intravenous study. The cause of death in the animals in these studies is unknown. There was no pharmacokinetic data relating to these doses so a direct comparison with human exposure was not possible. Extrapolation from the data available suggests that acute oral toxicity is low.

Repeat-dose toxicity

Pivotal repeat-dose toxicity studies were conducted in three species: mouse rat and dog. Studies of up to 13 weeks duration were conducted in mice, 26 weeks duration in rats and 52 weeks duration in dogs. The no-observed-adverse-effect levels (NOAEL) in the 13 week study in mice were 80 parts per million (ppm) (ER_{AUCU} 2.4) and in the 26 week study in rats were 2.5 mg/kg in males (ER_{AUCU} 0.4) and 10 mg/kg in females (ER_{AUCU} 1.7). In the 52 week toxicity study in dogs the NOAEL was not determined although the majority of the effects could be related directly or indirectly to the primary pharmacological action of riociguat. The maximum doses employed in the pivotal repeat-dose toxicity studies were 3 mg/kg/day (ER_{AUCU} 3.8) in the dog, 40 mg/kg/day (ER_{AUCU} 10.5) in the rat and 400 ppm (ER_{AUCU} 11) in the mouse.

Relative exposure

Exposure ratios have been calculated based on animal: human plasma $AUC_{0-24\,h}$ and C_{max} data. Human reference values are from population PK analysis of phase II Study 12166. The value for $AUC_{0-24\,h}$ is 4161 ng.h/mL which is equal to 3 times the AUC_t value of 1387 ng.h/mL (t = 7 to 8 h dosing interval) in this study. These values were in general agreement with summary geometric mean values of AUC (1292 ng.h/mL) and C_{max} (196 ng/mL) from combined phase 3 data (PATENT-1, PATENT-2, CHEST-1, CHEST-2 studies) which included 2028 dosing occasions and therefore appear to be adequate indicators of human exposure. Since riociguat is highly bound to plasma proteins in humans and displays low to moderate plasma protein binding in animals the exposure ratios based on the predicted amount of free drug based on *in vitro* binding characteristics in humans and test species are also presented in the table.

Table 1. Relative exposure in repeat-dose toxicity and carcinogenicity studies.

Species	Study duration / analyte	Dose (mg/kg/day)	C_{max} (ng/mL)	$AUC_{0-24\,h}$ (ng·h/mL)	Exposure ratio (total)		Exposure ratio (unbound)	
					C_{max}	AUC#	C_{max}	AUC#
Mouse (CD-1)	13 weeks / riociguat	16†	23.7	434	0.1	0.1	0.5	0.4
		80†	161.5	2529	0.8	0.6	3.2	2.4
		200†	317.5	4623	1.6	1.1	6.3	4.5
		400†£	559	11359	2.8	2.7	11.1	11.0
	13 weeks / M1	16†	3.1	57	0.0	0.0	0.1	0.1
		80†	22.2	407	0.2	0.2	0.9	0.7
		200†	53.5	943	0.5	0.4	2.3	1.7
	2 years [carcinogenicity]	50†	63.7	1070	0.3	0.3	1.3	1.0
		100†	164.5	2624	0.8	0.6	3.3	2.5
		200†	368	5465	1.8	1.3	7.3	5.3
	2 years [carcinogenicity] /M1	50†	7.3	121.5	0.1	0.0	0.3	0.2
		100†	20.3	295	0.2	0.1	0.9	0.5
		200†	59.1	754	0.5	0.3	2.5	1.4
Rat (Wistar)	3 months / riociguat	3	174	956	0.9	0.2	2.7	0.7
		10	746	3699	3.7	0.9	11.5	2.8
		30	1817	10388	9.0	2.5	28.1	7.8
	3 months / M1	3	9.3	41	0.1	0.0	0.2	0.0

Species	Study duration / analyte	Dose (mg/kg/day)	C_{max} (ng/mL)	$AUC_{0-24\,h}$ (ng·h/mL)	Exposure ratio (total)		Exposure ratio (unbound)	
					C_{max}	AUC#	C_{max}	AUC#
		10	53.4	369	0.5	0.1	1.4	0.4
		30	208	1125	1.9	0.4	5.6	1.3
	6 months / riociguat	2.5	116	594	0.6	0.1	1.8	0.4
		10	524	2283	2.6	0.5	8.1	1.7
		40	2107	13927	10.4	3.3	32.6	10.5
	6 months / M1	2.5	10.9	68	0.1	0.0	0.3	0.1
		10	53.5	300	0.5	0.1	1.4	0.3
		40	211	1784	1.9	0.7	5.6	2.0
	2 years [carcinogenicity] / riociguat	5	98.1	1746	0.5	0.4	1.5	1.3
		10	229	3905	1.1	0.9	3.5	2.9
		20	420	7511	2.1	1.8	6.5	5.7
	2 years [carcinogenicity] / M1	5	10.7	187	0.1	0.1	0.3	0.2
		10	24.9	439	0.2	0.2	0.7	0.5
		20	49.9	895	0.4	0.3	1.3	1.0
Dog (Beagle)	26 weeks / riociguat	0.3	186	1103	0.9	0.3	3.1	0.9
		1	367	3089	1.8	0.7	6.2	2.5
		3	852	4654	4.2	1.1	14.4	3.8
	26 weeks / M1	0.3	61.2	808	0.6	0.3	2.5	1.4
		1	111	1573	1.0	0.6	4.6	2.8
		3	398	4969	3.6	1.9	16.4	8.7
Dog (Beagle)	52 week / riociguat	0.3	125	828	0.6	0.2	2.1	0.7
		1	238	1205	1.2	0.3	4.0	1.0
		2	489	2980	2.4	0.7	8.2	2.4
	52 week / M1	0.3	46.2	556	0.4	0.2	1.9	1.0

Species	Study duration / analyte	Dose (mg/kg/day)	C_{max} (ng/mL)	$AUC_{0-24\,h}$ (ng·h/mL)	Exposure ratio (total)		Exposure ratio (unbound)	
					C_{max}	AUC#	C_{max}	AUC#
		1	127	1324	1.1	0.5	5.2	2.3
		2	234	2709	2.1	1.0	9.7	4.8
Human (PH patients)	steady state / riociguat	[7.5 mg]	203	4161	–		–	
	steady state / M1		111	2604				

= animal:human plasma $AUC_{0-24\,h}$; †Doses in parts per million; £Data from week 2 due to unscheduled deaths. Fraction unbound (f_u) used for the different species were: mouse, 0.201; rat, 0.157; dog, 0.171; human, 0.0497.

Major toxicities

Significant mortality was seen at high doses in the repeat dose toxicity studies in mice. A dose of 800 ppm killed all animals in this group. Clinical symptoms in these animals included high stepping gait, pallor and/or distended abdomen. Dilated and/or elongated intestines were apparent at necropsy. 400 ppm (equivalent to 85.5 mg/kg/day in males and 124.1 mg/kg/day in females) also caused deaths in both males (7/10) and females (6/10). The major pathological changes noted in these animals were dilatation and/or oedema and/or inflammation of various regions of the gastrointestinal tract and swollen spleen. The precise cause of death in these animals has however not been established. A 400 ppm dose gave an ER_{AUCU} of 11 in males and an ER_{AUCU} of 10.3 in females.

The major toxicities associated with riociguat in all species were related to the primary mode of action of the drug to stimulate sGC and to increase intracellular cGMP levels. The cardiovascular, gastrointestinal and skeletal systems were identified as target organs of toxicity. The principal toxicity seen in rodents was gastrointestinal. The gastrointestinal effects in the repeat dose toxicity studies in mice included dilatation, edema, inflammatory infiltration and prominent Paneth cells. In the carcinogenicity study in mice the most prominent non-neoplastic lesion was inflammation in the large bowel. This was accompanied by increased incidence of ulceration and erosions, mucosal hyperplasia and increased occurrence of diverticula. In repeat dose studies in rats, elongation of the intestines was seen along with prominent Paneth cells. Although the function of Paneth cells is not fully understood they are associated with the secretion of anti-microbial peptides and play a role in controlling microbial density in the intestinal lumen. An increase in the prominence of Paneth cells may indicate an increase/alteration in the intestinal microbiome. Although no inflammation of the bowel itself was reported in rats inflammatory changes in the mesenteric veins around mesenteric lymph nodes were seen in the 26 week study. The only gastrointestinal effects noted in dogs were increased vomitus and diarrhoea and no histopathological changes were observed in this species.

Evidence of toxic effects on the cardiovascular system was limited, despite the fact that a major action of riociguat is act on the smooth muscle of the vascular system to reduce blood pressure. The extent of blood pressure reduction in the toxicity studies was only evaluated in the repeat dose dog studies. Systolic and diastolic pressures were generally reduced in a roughly dose dependent manner but there was considerable individual variation in these studies. In the last week of the 52 week study, systolic pressures were reduced by about 30% in males and 20% in females and heart rates increased by 27% in males and 49% in females at 2 h after 2 mg/kg riociguat.

The pathological changes noted in the cardiovascular system in the dog were degenerative changes to the myocardium and hypertrophy of the coronary arteries in the 52 week study (ER_{AUCU} 2.4). The highest dose tested where blood pressure was monitored in the rat safety study was 3 mg/kg which produced arterial blood pressure falls of 23% and heart rate increases of 40%. In rats, overt signs of cardiovascular effects were penile erection in males and reddening of ears and extremities in both sexes at doses ≥10 mg/kg day (ER_{AUCU} 1.7 in the 26 week repeat-dose study). This latter effect was not, however, seen consistently and was not reported in 13 week repeat dose study (ER_{AUCU} 2.8). In the two year carcinogenicity study in rats, cardiac enlargement was significant at the highest dose in males and there was a positive trend for cardiomyopathy and vasculopathy in males. These effects were not seen with shorter exposures in this species.

Riociguat related effects on bone in adult mice were increased myelopoiesis (400 ppm ER_{AUCU} 11) and thickened femur growth plate (800 ppm). In adult rats thickened femur growth plates (males 15 mg/kg/day), increased haematopoiesis, bone remodelling and hyperostosis (≥ 10 mg/kg/day; ER_{AUCU} 2.8) were observed. An initial study in juvenile rats confirmed the hyperostosis at doses ≥ 10 mg/kg/day. A second study on juvenile animals which employed a maximum dose of 3 mg/kg/day did not detect any effects on bone. In the mechanistic study in older (starting age 17 weeks) male rats there were no effects on the circulating markers of bone formation or resorption and no histopathological effects on bone seen at autopsies conducted throughout and at the end of the study. Small (< 5 %) but statistically significant decreases in the cortical bone mineral density at the femur diaphysis were observed in high dose animals from Week 4. There was however no indication of progression of the effect. It should be noted that the maximum dose employed in this study was lower than the doses which produced the effects on bone morphology in the repeat-dose toxicity studies (25 mg/kg/day in the mechanistic study versus 100 mg/kg/day in the 13 week study and 40 mg/kg/day in the 26 week study).

In addition to these clearly 'on-target' adverse events a number of organ systems were affected in different repeat-dose toxicity studies. These effects on different organ systems are summarised in the table below. In all three species enlargement of the liver was seen at the highest doses tested. In mice and rats there was enlargement of the spleen with increased haematopoiesis. The adrenal gland enlargement observed in some repeat dose studies in rats and in male and female dogs (1 to 3 mg/kg/day) was secondary to renin-angiotensin-aldosterone system (RAAS) activation following blood pressure decrease and has been consistently noted with other anti-hypertensive agents. Increases in red blood cells, haemoglobin and haematocrit were also seen in rats the 4 week and longer studies. Riociguat exposure was shown to be high in these three tissues using quantitative whole body autoradiography. These findings were interpreted by the sponsor to be a consequence of the haemodynamic actions of riociguat. NO and cGMP do, however, play important roles in the growth and differentiation of erythrocytes and some of these effects may be the result of direct actions of riociguat on the haematopoietic system.

Table 2. Effects on liver spleen and adrenal glands in animal studies

	Mouse	Rat	Dog
Liver	**PH-34866** ♂♀ hypertrophy **PH-34865** ♂ weight ↑, hypertrophy **PH-34519** ♂ weight ↑	**PH-36257** ♂ weight ↑ **PH-34791** ♂♀ hypertrophy **PH-33408** ♂♀ weight ↑, cytoplasmic change	**PH-33454** ♀ weight ↑,

	Mouse	Rat	Dog
		PH-34674 ♂♀ weight ↑ **PH-34877** ♀ weight ↑, ♂♀ cytoplasmic condensation **PH-35002** ♂♀ weight ↑ enlargement, ♀ hypertrophy	
Spleen	**PH-34865** ♀ weight ↑ **PH-34866** ♂♀ weight ↑, swollen **PH-34519** ♂♀ weight ↑ swollen **PH-36818** ♂♀increased haematopoiesis	**PH-33408** ♀ weight ↑ **PH-36257** ♂ weight ↑	-
Adrenals	-	**PH-35002** ♂♀ weight ↑, zona glomerulosa hyperplasia **PH-34877** ♂ weight ↑, zona glomerulosa increased width **PH-34674** ♂♀ weight ↑„zona glomerulosa increased width **PH-33408** ♂ weight ↑ **PH-36817** ♂♀ focal cortical hyperplasia	**PH-35050** ♂weight ↑, ♂♀ zona glomerulosa hyperplasia **PH-34778** ♂♀weight ↑, ♂♀ zona glomerulosa increased width **A45725** ♂♀weight ↑,

One adult study in rats and one in dogs, both 4 weeks exposure with 2 weeks recovery examined the persistence of riociguat effects beyond the dosing period. In both studies some changes seen during the dosing period (increased liver weights in dogs, decreased haemoglobin and reticulocytes and thickened femur growth plates in rats) persisted in the recovery period. No other information on the reversibility of the effects of riociguat was submitted. Recovery groups were also examined in the study on juvenile rats which employed low doses of riociguat. In this study increases in circulating calcium and plexiform change in the mesenteric veins both persisted to the end of the recovery period (8 weeks).

A full suite of toxicology studies were performed on the metabolite M1 (BAY 60-4552). BAY 60-4552 was not acutely toxic in rats or mice by the oral route (2000 mg/kg) but doses of 30 and 200 mg/kg were toxic to mice when administered intravenously. A cause of death was not determined. In repeat dose toxicity studies with BAY 60-4552 the principal target organ was the kidney with degenerative changes seen in male rats at doses as low as 30 mg/kg for 13 weeks (ER_{AUCU} 37.7) compared to the anticipated clinical exposure following the recommended maximum riociguat dose). Thickening of femoral and tibial growth plates accompanied by a disorganization of the subjacent trabecular bone was also seen in male and female rats at 100 mg/kg for 4 or 13 weeks (ER_{AUCU} 73.3) compared to the anticipated clinical exposure following the recommended maximum riociguat dose).

Genotoxicity

Riociguat was evaluated for its potential to induce gene mutations in *S. typhimurium*, for mutagenic potential *in vitro* in a mammalian chromosome aberration assay and *in vivo* in a bone marrow micronucleus test and a bone marrow cytogenetics assay, both in mice (Option 1 in ICH S2(R1)). The genotoxic potential of the major metabolite Bay 60-4552 (M1) was evaluated in a separate series of the same tests. Riociguat and BAY 60-4552 were negative in all the tests and riociguat is unlikely to pose a mutagenic or clastogenic risk to humans.

Carcinogenicity

Two year carcinogenicity studies were conducted in mice and rats. In both studies riociguat was administered in the diet at concentrations up to 200 ppm (ER_{AUCU} 5.3) in mice and at doses up to 20 mg/kg/day (ER_{AUCU} 5.7) in rats. These doses were agreed to by the FDA in a special protocol assessment.

In the mouse study there was a slight, not statistically significant increase in the incidence of adenocarcinoma in the caecum (females 100 mg/kg) and adenoma and adenocarcinoma of the colon (males 200 mg/kg). Inflammation with ulceration and erosions and increased occurrence of diverticula occurred in both genders at doses ≥100 ppm. These neoplasms are probably treatment related but may have developed secondarily to the sustained inflammation. They do not provide any strong evidence for a direct carcinogenic effect of riociguat and taken together with the negative results in all the genotoxicity tests suggests that riociguat does not present a carcinogenic risk.

Reproductive toxicity

Reproductive toxicity was assessed in rats and rabbits in GLP compliant studies. The studies investigated potential effects on male and female fertility in rats, embryofetal toxicity (rats and rabbits) and pre/postnatal development (rats). Adequate animal numbers were used in the pivotal studies and treatment periods were appropriate. Toxicokinetic data were obtained either from animals in the studies or from similarly-treated animals in accompanying studies.

Relative exposure

The following table shows the relative exposure in these studies.

Table 3. Relative exposure in the reproductive toxicity studies

Species	Study	Dose (mg/kg/day)	C_{max} (ng/mL)	AUC_{0-24h} (ng·h/mL)	Exposure ratio (Total)		Exposure ratio (Unbound)	
					C_{max}	AUC#	C_{max}	AUC#
Rat (Wistar)	Fertility Male*	1.5	59.1	394	0.3	0.1	0.9	0.3
		5	159	1140	0.8	0.3	2.5	0.9
		15	428	3795	2.1	0.9	6.6	2.9
		30[a]	1173	9723	5.8	2.3	18.1	7.3
	Fertility Female*	1.5	80.1	370	0.4	0.1	1.2	0.3
		5	207	1244	1.0	0.3	3.2	0.9
		15	397	3035	2.0	0.7	6.1	2.3
		30[a]	1086	6766	5.3	1.6	16.8	5.1
	Embryofetal development	1[a]	100	627	0.5	0.2	1.5	0.5
		3	268	2751	1.3	0.7	4.1	2.1
		5[b]	284	2197	1.4	0.5	4.4	1.7
		25	959	10626	4.7	2.6	14.8	8.0
Rabbit (Himalayan)	Embryofetal development	0.5[a,b]	558	5064	2.7	1.2	2.3	1.0
		1.5	1775	18898	8.7	4.5	7.3	3.8
		5	4776	62467	23.5	15.0	19.6	12.5
Human (PH patients)	steady state	[7.5 mg]	203	4161	–			

= animal:human plasma AUC_{0-24h} ; [a] NOAEL for F1 generation; [b] NOAEL for offspring; * Values are taken from D29 of the rat 4 week repeat dose toxicity study PH33408.

Riociguat at doses up to 30 mg/kg /day had no effect on the fertility of either male or female rats although there was a slight increase in the time to insemination in males. Reddening of the ears (pinnae) and some reductions in weight gain during the treatment periods was seen in both genders.

Body weights in the rat embryofetal development study were significantly reduced in fetuses at maternal exposures of 25 mg/kg/day and the occurrence of ventricular septal defects and incomplete ossification was increased in this group. At the fetal NOAEL of 5 mg/kg/day the ER_{AUCU} was only 1.7. These effects on embryofetal developmental are

likely to be related to the known role of cGMP in the activation of protein kinase G (PKG). PKG has many effects including activation of transcription factors which can lead to changes in gene expression. Moreover, riociguat was shown to affect cell migration *in vitro*. Migrating cells are observed during embryonic development and in angiogenesis so any interference with this process has the potential to cause deleterious effects on the developing organism. The reduced degree of ossification in a number of locations in pups occurred at all doses although a dose response was apparent only for the fourth sacral vertebral arch.

While no increase in malformation rate was observed in the rabbit embryofetal development study, exaggerated pharmacological effects of riociguat on the F1 dams at ≥ 1.5 mg/kg/day led to an increased rate of abortion and total resorption. At the maternal and fetal NOAEL of 0.5 mg/kg/day the ER_{AUCU} was similar to that expected clinically.

Riociguat prolonged the mean gestation time and reduced maternal bodyweight gain at the high dose (HD) of 15 mg/kg/day in the pre and postnatal development studies in rats (maternal NOAEL of 5 mg/kg/day, ER_{AUCU} of about 1). A reduced number of live births were observed at doses ≥ 5 mg/kg/day but there were no notable effects on the development of the surviving pups including on their reproductive performance (NOAEL for pup development of 15 mg/kg/day, ER_{AUCU} approximately 2 to 3).

The M1 metabolite BAY 60-4552 was not well tolerated in reproductive studies and the NOAEL for maternal and fetal toxicity was 2 mg/kg/day (ER_{AUCU} <0.1). Doses of 5 mg/kg/day in rabbits resulted in increased rates of abortion. There was, however, no evidence of a direct teratogenic effect in either species.

Pregnancy classification

The sponsor has proposed Pregnancy Category D.[2] This category is appropriate given the effects on reproduction and development described above.

Local tolerance

Local tolerance was evaluated in rabbits following intravenous infusion of riociguat (10 µg/mL) into an ear vein and paravenous injection into tissue surrounding a leg vein. The only effects noted following infusion into the ear vein were local skin reddening and vessel injection at the site of the infusions. There were small decreases in blood pressure and increases in heart rate in some animals. The only effects following paravenous injection were slight pain reactions to the injection. No histopathological changes were noted at either site. The local tolerability of a clinical solution intended for intracoronary use was evaluated in anaesthetised dogs. Following infusion of 10 mL riociguat (10 µg/mL) there were no signs of local intolerability and no histopathological changes were apparent at post mortem.

Phototoxicity

Riociguat shows some absorption of light in the range 290 to 720 nm and phototoxic potential was evaluated both *in vitro* and *in vivo*. Riociguat was classified as probably phototoxic in the mouse fibroblast *in vitro* assay. In mice irradiated following oral administration of riociguat (up to 30 mg/kg) there was no evidence of any photoreactive potential and no evidence of ultraviolet (UV) activation of immune cells. The M1

[2] Category D: Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.

metabolite (BAY 60-4552) also absorbs light in the 290 to 720 nm range but was not phototoxic in the *in vitro* mouse fibroblast assay.

Impurities

Impurities detected during the synthesis of riociguat and hypothetical impurities were analysed in silico[3] using the DEREKÒ program. The only in silico structural alert was a known mutagenic alkylating agent. The known mutagenicity was adequately addressed in the drug substance specification. An unspecified/theoretical impurity was negative for point mutagenic effects in the Ames test.

All impurities specified above the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) qualification were qualified in repeat dose studies in rats and dogs as well as *in vitro* and *in vivo* genotoxicity assay at concentrations above the specified limit.

Paediatric use

Riociguat is not proposed for paediatric use but two studies were conducted on juvenile rats. No significant unexpected toxicity effects of riociguat were seen in these studies but exposure to both riociguat and M1 was higher in neonates than adult animals. The effects of riociguat on bone may be age related, with greater effects in younger animals.

Nonclinical summary and conclusions

- The overall quality of the non-clinical dossier was good with all pivotal studies conducted according to GLP. The toxicity of riociguat in repeat dose studies limited the range of doses investigated with exposure ratios in most studies for total (bound +unbound) drug similar to or below the expected clinical exposure and exposure to the unbound drug generally < 5 times the expected clinical exposure.
- The primary action of riociguat is to stimulate soluble guanylate cyclase (sGC) initiating a cascade of events linked to increases in cyclic GMP. Riociguat stimulated recombinant sGC *in vitro* with EC_{50} values of 100-200 nmol/L. *In vitro* stimulation of sGC by riociguat was enhanced in the presence of NO. Riociguat also blocked the contractions induced by phenylephrine in a variety of isolated vascular smooth muscles with IC_{50} values of 4.8 to 380 nmol/L. These results indicate that riociguat induces relaxation of vascular smooth muscle. Metabolite M1 (BAY 60-4552) had a similar effect profile *in vitro* but was approximately 10 fold less potent in all assays.
- Oral administration of riociguat to anaesthetised rats (≥ 0.03 mg/kg) and dogs and conscious spontaneously hypertensive rats (≥ 0.03 mg/kg) lowered mean arterial pressures. The reductions in pressure were accompanied by increases in heart rate. In animal models of pulmonary hypertension chronic treatment with riociguat reduced pulmonary arterial pressures and accompanying structural changes.
- Riociguat (10 µM) had no effect on radioligand binding to a wide range of enzymes and receptors. Riociguat inhibited human PDE7B (IC_{50} 2.9 µM) but had no effect on 9 other phosphodiesterases. In safety studies riociguat had profound effects on the cardiovascular system causing reductions in systolic and diastolic pressure and increases in heart rate. ECG parameters were not affected and there was no evidence for QT interval prolongation *in vitro* or *in vivo*. Riociguat did not have any notable effects on CNS or respiratory function following oral administration.

[3] In silico is an expression used to mean "performed on computer or via computer simulation."

- Riociguat was rapidly absorbed in all nonclinical species with peak plasma concentrations occurring between 0.5 and 2.88 h. Oral bioavailability was moderate (35 to 66%) in rat and higher (50 to 80%) in dog. The plasma elimination half-lives were short in the interval up to 8 h in rat (0.7 to 1.5 h) and dog (1.5 to 3.1 h). Riociguat was highly plasma protein bound in humans with a1-acidic glycoprotein the main species of binding. Plasma protein binding was moderate in nonclinical species. Studies in Long Evans rats revealed affinity for melanin containing tissues.
- The primary metabolite of riociguat in humans is the oxidation product M1 which can be produced by CYP1A1, 2C8, 2J2, 3A4, 3A5 and to a much lesser extent CYP3A7. Of these CYP1A1 was an important contributor to riociguat metabolism in liver and lung derived tissues. CYP1A1 is known to be highly inducible in the lungs of smokers. Riociguat inhibited the activity of CYP1A1 (K_i 0.6 µmol/L) and this has potential clinical relevance. The formation of the metabolite M1 in human liver microsomes was inhibited by drugs known to inhibit CYP1A1, 2C8, 2J2, and 3A4/A5. Riociguat and M1 are both classified as P-gp and BCRP substrates *in vitro*. It is possible that inhibition of P-gp and/or BCRP by concomitantly administered drugs might increase plasma concentrations of riociguat and M1 via inhibition of their excretion. Riociguat was shown to be a substrate for the uptake transporter OCT2 in kidney but due to significant biliary/faecal route of excretion this is not likely to cause drug-drug interactions.
- Pivotal repeat dose toxicity studies were performed in mice for 13 weeks, in rats for 26 weeks and in dogs for 52 weeks. The maximum doses employed in the pivotal repeat dose toxicity studies were 2 mg/kg/day (ER_{AUCU} 3.8) [4] in the dog, 40 mg/kg/day (ER_{AUCU} 10.5) in the rat and 400 ppm (ER_{AUCU} 11) in the mouse). The cardiovascular, gastrointestinal and skeletal systems were identified as target organs for toxicity. Gastrointestinal effects were generally apparent only at the highest doses and differed between species. Intestines were dilated in rodents, with evidence of inflammation in mice. In both rats and mice prominent Paneth cells were a feature of the histopathological changes. An increase in the prominence of Paneth cells may indicate an increase/alteration in the intestinal microbiome. Pathological changes in the cardiovascular system (degenerative changes to the myocardium and hypertrophy of the coronary arteries) were seen in the dog at 2 mg/kg and only after prolonged exposure (52 weeks). In rats, pathological changes in the cardiovascular system (cardiac enlargement and a positive trend for cardiomyopathy and vasculopathy in males) were seen only in the 2 year carcinogenicity study, again at the highest dose (ER_{AUCU} 5.7). Effects on bone were seen only in rodents with thickened femur growth plates in mice and rats and hyperostosis in rats. The issue of whether this effect is only apparent in developing/young animals has not been properly resolved.
- The potential genotoxicity of riociguat was investigated in a standard battery of tests. The results were negative in all tests and riociguat is unlikely to pose a mutagenic or clastogenic risk to humans.
- No significant increase in tumour incidence was observed in mice or rats in 2 year oral carcinogenicity studies. The ER_{AUCU} at the high doses in these studies was around 5 to 6 in mice and in rats.
- Riociguat (25 mg/kg/day) reduced fetal body weights in rats and caused an increase in cardiac malformations. The reduced fetal weights were associated with incomplete of ossification. Riociguat (15 mg/kg/day) caused increased abortion in rabbits and

[4] Riociguat is extensively bound to plasma proteins in animals and humans but there are some species differences. Exposure ratios quoted in this report compare the exposures to both the total (bound + unbound) ER_{AUCT} and unbound ER_{AUCU} forms of riociguat.

caused complete resorption of some litters. No significant effects on male or female fertility were seen at doses up to 30 mg/kg/day in adult animals and reproductive performance in surviving pups in the postnatal development study was not affected.

- Both riociguat and the M1 metabolite BAY 60-4552 absorb light in the 290 to 720 nm range. Riociguat was positive in an *in vitro* assay for phototoxicity but negative *in vivo*. The M1 metabolite (BAY 60-4552) was negative in the same *in vitro* assay.

Conclusions and recommendation

- The nonclinical development program was particularly extensive for an orphan drug.
- There are no major deficiencies in the nonclinical submission. Primary pharmacology studies *in vitro* confirmed that riociguat acts to stimulate sGC and to sensitize sGC to NO. The principal action in intact smooth muscle was relaxation and systemic administration of riociguat resulted in falls in blood pressure with reflex tachycardia.
- No clinically relevant hazards beyond those resulting from the primary action of riociguat-activated sGC on the circulatory system were identified.
- The primary metabolite of riociguat in humans is the oxidation product M1 which can be produced by CYP1A1, 2C8, 2J2, 3A4 and 3A5. Drugs known to inhibit these isoforms were shown to reduce riociguat metabolism *in vitro*. Induction of CYP1A1 in the lungs of smokers alters the metabolism of riociguat significantly. Riociguat is transported by P-gp and BCRP and inhibitors of these transporters may affect exposure to riociguat.
- Toxic effects seen in the gastrointestinal and cardiovascular systems were most likely the direct consequence of actions on sGC leading to smooth muscle relaxation and vasodilatation. Effects on the skeletal system are also probably the result of sGC stimulation in this system.
- Riociguat is unlikely to pose a genotoxic or carcinogenic hazard to patients.
- The reproductive toxicity of riociguat included reduced fetal weights and increased frequency of cardiac malformations in rats and abortion/total litter resorption in rabbits. These effects may be secondary to the primary pharmacodynamic action of riociguat.
- There are no nonclinical objections to the registration of riociguat.
- The evaluator also recommend changes to the draft PI but these are beyond the scope of this AusPAR.

IV. Clinical findings

A summary of the clinical findings is presented in this section. Further details of these clinical findings can be found in Attachment 2.

Introduction

Clinical rationale

Riociguat is the first member of a novel class of compounds, the soluble guanylate cyclase (sGC) stimulators and has been developed to treat patients with chronic thromboembolic pulmonary hypertension (CTEPH) and pulmonary arterial hypertension (PAH). The sponsor has stated that riociguat is a direct and specific sGC stimulator. *In vitro* and *in vivo* riociguat stimulates sGC and increases production of the second messenger cyclic

guanosine monophosphate (cGMP). It does this independent of nitric oxide (NO). In the presence of NO, it enhances the effects of NO. This mechanism of action is stated as unique in the setting of CTEPH and PAH.

Both CTEPH and PAH are rare and life threatening forms of pulmonary hypertension (PH). These conditions share similar pathological features and are characterised by pulmonary arterial micro vascular remodelling, dysregulation in vascular cell proliferation and in situ thrombosis, leading to increased pulmonary vascular resistance (PVR), abnormal pulmonary vascular tone, progressive right ventricular dysfunction/failure and ultimately, premature death. The rate of disease progression is highly variable and depends on the type and severity of the pulmonary hypertension. It is defined by a mean pulmonary artery pressure (PAP) >25 mmHg.

The classification system for PH endorsed by the World Health Organization (WHO) is shown in Table 4 (below).

Table 4. Classification of Pulmonary Hypertension.

1. Pulmonary arterial hypertension (PAH)
1.1 Idiopathic PAH (IPAH)
1.2 Heritable PAH (HPAH)
1.2.1. BMPR2
1.2.2. ALK1, endoglin (with or without hereditary haemorrhagic telangiectasia)
1.2.3. Unknown
1.3. Drug- and toxin-induced
1.4 Associated with (APAH)
1.4.1 Connective tissue disease
1.4.2 HIV infection
1.4.3 Portal hypertension
1.4.4 Congenital heart disease
1.4.5. Schistosomiasis
1.4.6. Chronic haemolytic anaemia
1.5 Persistent Pulmonary Hypertension of the Newborn (PPHN)
1' Pulmonary veno-occlusive disease (PVOD) and/or pulmonary capillary haemangiomatosis (PCH)
2. Pulmonary hypertension owing to left heart diseases
2.1 Systolic dysfunction
2.2 Diastolic dysfunction
2.3 Valvular disease
3.Pulmonary hypertension owing to respiratory disease and /or hypoxia
3.1 Chronic obstructive pulmonary disease
3.2 Interstitial lung disease
3.3 Other pulmonary diseases with mixed restrictive and obstructive pattern
3.4 Sleep disordered breathing
3.5 Alveolar hypoventilation disorders
3.6 Chronic exposure to high altitude
3.7 Developmental abnormalities
4. Chronic thromboembolic pulmonary hypertension (CTEPH)
5. Pulmonary hypertension with unclear multifactorial mechanisms
5.1. Haematological disorders: myeloproliferative disorders, splenectomy
5.2. Systemic disorders: sarcoidosis, pulmonary Langerhans cell histiocytosis, lymphangioleiomyomatosis, neurofibromatosis, vasculitis
5.3. Metabolic disorders: glycogen storage disease, Gaucher disease, thyroid disorders
5.4. Others: tumoral obstruction, fibrosing mediastinitis, chronic renal failure on dialysis

Source: (13)

For patients in Group 4 PH, pulmonary endarterectomy (PEA) surgery is the treatment of choice for patients with symptomatic, operable CTEPH. There are, however, a proportion of patients who are not suitable for surgery (30 to 40%) or who have persistent PH after surgery (approximately30%). In these patients medical therapy is warranted. There are currently no approved pharmacotherapies for CTEPH and patients are frequently treated off-label. Anticoagulation may prevent further embolism and in situ thrombosis but not necessarily disease progression.

There are no effective primary therapies for most types of Group 1 PAH that address the disease cause and as a result advanced therapy is often needed. This may include treatment with prostanoids, endothelin receptor antagonists (ERA), phosphodiesterase 5(PDE-5) inhibitors or occasionally calcium channel blockers.

Riociguat (BAY 63-2521) was discovered in-house by Bayer. The sponsor stated that a combination of nonclinical investigations in animal models, together with early signs of

efficacy studies in patients, have suggested that sGC is a valid therapeutic target for patients with PH. The submission seeks authorisation of riociguat for treatment of PH patients in Group 1 and also in Group 4. The sponsor stated that riociguat is also currently being developed in PH due to left heart disease (WHO Group 2) and due to interstitial lung disease (WHO Group 3.2).

Guidance

Overall the clinical development program was conducted in accordance with relevant The Committee for Medicinal Products for Human Use (CHMP) guidelines on the clinical investigations of medicinal products for the treatment of pulmonary arterial hypertension (EMA 2009).[5] The exception to this was that the pivotal trials were not sufficiently long for demonstrating an improvement in time to clinical worsening where a minimum of 6 months is necessary.

Contents of the clinical dossier

The clinical dossier included the following data:

- 30 clinical pharmacology studies, including 28 that provided pharmacokinetic data and 12 that provided pharmacodynamic data.
- 2 integrated analyses of pharmacology studies
- 6 population pharmacokinetic analyses.
- 2 pivotal efficacy/safety studies (11348 [CHEST-1] and 12934 [PATENT-1]).
- 2 Phase II studies, one uncontrolled (12166) and one controlled (15096).
- 3 long term extension studies (11349 [CHEST-2], 12935 [PATENT-2] and extension of 12166).
- 7 integrated analysis reports.
- 16 other clinical reports. These included 5 studies with the major metabolite (BAY 60-4552) and (2 associated reports), 4 studies (with 3 additional reports) in different patient populations to that proposed in the indication, one safety listing report and one report on QT assay sensitivity.

Paediatric data

There is a paediatric development program for riociguat in the following indications:

- Treatment of primary pulmonary arterial hypertension (PAH).
- Treatment of persistent pulmonary hypertension of the Newborn (PPHN).

The Paediatric Investigation Plan (PIP) accepted by the European Medicines Agency is for film coated tablets and oral liquid. For the film coated tablets, there is a waiver in place for ages from birth to less than 6 years of age. The current submission included paediatric pharmacokinetic data in Study 15463 (a physiologically based pharmacokinetic [PBPK] modelling study to predict the pharmacokinetic properties of riociguat in the paediatric population). There are two planned studies with completion dates in 2016 and 2017, one

[5] EMA (2009). Committee for medicinal products for human Use (CHMP). Guideline on the clinical investigation of medicinal products for the treatment of pulmonary arterial hypertension. EMEA/CHMP/EWP/356954/2008.

in children 28 days to 18 years old with PAH and one in neonates with pulmonary hypertension of the newborn.

Good clinical practice

The sponsor declared that all studies were conducted according to Good Clinical Practice guidelines as well as local ethical and regulatory requirements.

Pharmacokinetics

Studies providing pharmacokinetic data

Table 5 (below) shows the studies relating to each pharmacokinetic topic.

Table 5. Submitted pharmacokinetic studies.

PK topic	Subtopic	Study ID	*
PK in healthy adults	General PK	11910	Absolute bioavailability (BA)
		11258	BA relative to an oral solution
		14769	Bioequivalence (BE) of 0.5 mg tablet used in clinical trials and 0.5 mg tablet intended for marketing
		14845	BE of 1.0 mg tablet used in clinical trials and 1.0 mg tablet intended for marketing
		14986	Paediatric formulation - BA and food effects
		11525	Dosage forms - Routes of administration
		11259	Effect of food
		13010	Effect of food 2
		13009	Dose proportionality
		11260	Multiple doses and dose escalation
		11911	Mass Balance
PK in special populations	Target Population	11874	Patients with pulmonary arterial hypertension, chronic thromboembolic pulmonary hypertension or interstitial lung disease
	Hepatic Impairment	11916	Population which included smokers and non-smokers
		15001	In a non-smoking population

PK topic	Subtopic	Study ID	*
	Renal Impairment	11915	Population which included smokers and non-smokers
		15000	Non-smoking population
	Other population characteristics	11914	Age and Gender
		12639	Young Japanese males - single dose
		12640	Japanese males - multiple doses
		14361	Chinese males - single and multiple doses
Drug- drug Interaction Studies	With respect to absorption	11262	Omeprazole
		11890	Maalox
		13790	RaniTDSine (H2-antagonist)
	With respect to elimination and metabolism	11261	Ketoconazole
		13284	Clarithromycin
		14982	Midazolam
	Other factors	11918	Warfarin
		14204	Aspirin
PK topic	Subtopic	Study ID	*
Population PK Studies		12489	Structural PK for riociguat and metabolite M-1
		14362	PK model for riociguat and M-1 in renally and hepatically impaired patients
		15593	PK model for riociguat and M-1 in renally and hepatically impaired patients
		12653	Exploratory PPK analysis of riociguat in patients with pulmonary hypertension
		13817	PK model for riociguat and M-1 based on the data from four Phase III studies
		14851	PK properties of riociguat in adult non-smokers and smokers
		15463	PK properties of riociguat in children of

PK topic	Subtopic	Study ID	*
			various age groups.
		14678	Evaluation of possible sparse sampling designs for the planned paediatric study

PPK – population pharmacokinetic * Indicates the primary aim of the study. † Bioequivalence of different formulations. § Subjects who would be eligible to receive the drug if approved for the proposed indication.

Evaluator's conclusions on pharmacokinetics

Absorption

Riociguat was rapidly absorbed with a T_{max} of 45 min and a $t_{1/2}$ of 6.78 h. The absolute bioavailability (BA) of riociguat was 94.3% whereas the relative BA of an oral tablet to an oral solution was 84.1%. The 0.5 and 1.0 mg riociguat immediate release (IR) tablets used in clinical trials were bioequivalent with the corresponding doses of the to-be-marketed formulations. Topical release of riociguat granules via the Enterion capsule in the distal small bowel and ascending colon resulted in lower riociguat exposure than following oral administration. In general, following a high fat, high calorie meal, riociguat C_{max} was 25 to 35% lower, AUC was slightly lower (14%) or unaffected and T_{max} increased 2 to 4 fold compared with riociguat PKs in the fasted state. Following dose escalation (0.5, 1.0, 1.5, 2.0 and 2.5 mg), the riociguat T_{max} and $t_{1/2}$ ranged from 0.75 to 1.0 h and 5.4 to 7.2 h, respectively, and AUC and C_{max} were dose proportional. Riociguat steady state occurred 3 days following oral doses of 0.5 mg, 1.0 mg, 1.5 mg three times a day (TDS), 2.5 mg BID and 2.5 mg TDS riociguat IR tablets. Dose-proportional increases in AUC between 0 to 7 h steady state/AUC between 0 to 12 h steady state ($AUC_{(0\ 7)ss}/AUC_{(0\ to\ 12)ss}$) and steady state $C_{max,ss}$ were observed after 10 days. Following TDS dosing, mean accumulation ratios for AUC were between 110% and 157% and mean accumulation ratios for C_{max} between 105 and 146%.

Distribution

The apparent volume of distribution of riociguat ranged from 30.8 to 43.1 L indicating a low affinity for tissues. Plasma protein binding for riociguat in humans was approximately 95% *in vitro*, with serum albumin and α1-acidic glycoprotein being the main binding components. The protein-bound fraction determined *ex vivo* was 96 to 97% for riociguat and 97% for M-1. Approximately 20% of drug related radioactivity following a 1 mg dose of radioactively labelled [^{14}C] riociguat solution was distributed into blood.

Metabolism

In vitro CYP reaction phenotyping studies in human liver, intestinal and lung microsomes established that CYP2C8, CYP2J2, and CYP3A4 contribute to a similar extent to the formation of the major metabolite M-1 in the liver, whereas CYP3A4 and CYP2J2 almost equally catalyse M-1 formation in the intestine. CYP1A1 also significantly contributed to the N-demethylation of riociguat in microsomes from human liver and lung tissue. Biotransformation of riociguat was much more pronounced in lung microsomes of smokers. M-1 is a soluble guanylate cyclase (sGC) stimulator but has 3 to 10 fold lower potency than riociguat. Subjects with high plasma concentrations of the parent compound had lower concentrations of M-1, whereas, subjects with low plasma concentrations of riociguat had higher concentrations of M-1. Following single oral IR tablet doses of 1 mg riociguat the C_{max} and AUC of M-1 was 7.7 µg/L and 195.3 µg.h/L, respectively. M-1 T_{max} occurs later than that than that of riociguat (4 h compared to 0.75 h, respectively) and its $t_{1/2}$ is longer (13.2 h compared to 6.8 h, respectively). M-1 displayed linear PKs after single and multiple doses of riociguat IR tablets. The accumulation in AUC for M-1 following

riociguat TDS was approximately 4 to 5 fold. Thorough examination of a panel of 1069 genetic variations in 172 drug metabolising genes and transporters did not identify any genetic factors that contribute to the PK variability of riociguat.

Excretion

Riociguat is eliminated by metabolic degradation and direct excretion of unchanged active compound. The proportion of [^{14}C] riociguat associated radioactivity excreted in urine and faeces ranged from 33.4% to 45.6% and 47.9% to 60.6%, respectively, with the main portions excreted with 48 h and 96 h, respectively. The renal clearance of M-1 was approximately 0.5 L/h.

Intra- and inter-individual variability

Inter-individual variability of riociguat $t_{1/2}$, AUC/D and C_{max}/D was 76.9%, 89.7% and 42.0%, respectively, whereas, intra-individual variability for AUC/D and C_{max}/D was 18.4% and 23.9%.

Special populations

No studies examined the PKs of riociguat in either pregnant or breastfeeding mothers or children.

Target population

In patients with suspected PH the C_{max} and AUC of riociguat and M-1 increased dose-dependently. The T_{max} occurred at 0.25 to 1.5 h and the $t_{1/2}$ was between 10 h and 12 h for riociguat.

Subjects with impaired hepatic function

In non smokers, riociguat T_{max} was ≥≤ 1.5 h in patients with Child Pugh A and Child Pugh B hepatic impairment and healthy controls and the mean C_{max} and $_{Cmax,norm}$ values of total riociguat were also similar. By contrast, riociguat $t_{1/2}$ was prolonged in Child Pugh A and Child Pugh B subjects (12.7 h and 17.5 h) compared to healthy controls (9.2 h and 8.9 h). Exposure in terms of mean AUC of unbound riociguat increased by 60% in Child Pugh A subjects and by 88% in Child Pugh B subjects compared to healthy controls.

Subjects with impaired renal function

In non-smokers with renal impairment, riociguat clearance was lower, $t_{1/2}$ was longer, and mean AUC was higher (at least by 100%) than in healthy controls. Nevertheless, exposures observed in subjects with renal impairment were highly variable and the ranges of exposures observed in subjects with mild, moderate, and severe renal impairment overlapped those observed in healthy controls.

Age and gender

Riociguat AUC was approximately 40% higher in elderly compared to young subjects and this difference was in part accounted for by differences in weight. No notable age related change in C_{max} was observed.

Japanese subjects

Following single oral doses of 0.5, 1.0 and 2.5 mg riociguat riociguat T_{max} and $t_{1/2}$ ranged from 1 h to 1.5 h and 4.15 h to 7.59 h, respectively in Japanese subjects. C_{max} and AUC increased with dose but AUC increased more than dose-proportionally.

Following multiple oral doses of 1.0 and 1.5 mg 3 times a day over 7 days in Japanese males, riociguat PKs achieved steady state regardless of dose. Riociguat T_{max} at steady state ($T_{max,ss}$) was 1.5 h and $t_{1/2}$ ranged from 9.2 to 9.7 h. Riociguat AUC_{ss} and $C_{max,ss}$ were dose proportional. $C_{max,ss}$ was 1.18 to 1.25 times higher than that on Day 1, whereas, the $AUC_{(0-7)ss}$ was almost the same with AUC on Day 1.

Chinese subjects

Following single dose and multiple oral doses of 1.0 mg and 2.0 mg TDS over 6 days in Chinese subjects, riociguat T_{max} and $T_{max,ss}$ was 1 h. Mean $t_{1/2}$ after a single dose and at steady state g was 3.5 h 5 h, respectively. Mean exposure increased at steady state by 176% and 156% for the 1 mg and 2 mg doses, respectively. Smoking reduced riociguat exposure by at least 60%.

Drug-drug interactions

Omeprazole

Pre and co-treatment with omeprazole decreased riociguat C_{max} and AUC by 35% and 26%, respectively. Riociguat $t_{1/2}$ and oral clearance (CL/f) increased from 7.9 to 9.0 h and from 4.3 to 5.8 L/h, respectively. By contrast Omeprazole had no effect on M-1 exposure.

Maalox

Co-administration with Maalox decreased riociguat C_{max} and AUC by 56% and 34%, respectively, whereas $t_{1/2}$ and CL increased from 5.9 to 8.6 h and 5.3 to 8.1 L/h, respectively. Co-administration of Maalox also decreased M-1 Cmax and AUC by 44% and 33%, respectively.

Ranitidine

In non-smokers, $AUC_{(0-7)}$ of riociguat after co-administration with 150 mg ranitidine was 393 µg*h/L after the first dose compared to 439 µg*h/L in the multiple dose escalation study where riociguat was given alone.

Ketoconazole - strong CYP3A4 and P-gp inhibitor

Pre and co-treatment with ketoconazole increased riociguat C_{max} and AUC by 46% and 150%, respectively. Riociguat $t_{1/2}$ increased from 7.3 h to 9.2 h, whereas, CL decreased from 6.1 L/h to 2.4 L/h. The amount of riociguat excreted via urine increased from 7.9% to 17.1%. Renal clearance decreased slightly from 0.41 L/h to 0.38 L/h. Pre and co-treatment with ketoconazole decreased M-1 C_{max} and AUC by 49% and 24%, respectively.

Clarithromycin: strong and selective CYP3A4 and weak to moderate P-gp inhibitor.

Co-administration of clarithromycin increased the AUC of riociguat and M-1 by 41% and 19%, respectively, but had no effect on the C_{max} values.

Midazolam - sensitive CYP3A4 probe substrate

PKs of midazolam were not affected by concomitant administration with 2.5 mg riociguat.

Warfarin - CYP2C9 substrate

Steady state riociguat did not affect the AUC and C_{max} of warfarin. Single dose administration of warfarin led to a 16% decrease in riociguat $C_{max,ss}$ whereas it did not affect the $AUC_{t,ss}$ of riociguat or M-1.

Aspirin

The PKs of riociguat and M-1 were not affected by co-administration of Aspirin.

Population PK studies

The major outcomes identified in the PPK studies included:

- Smoking correlated with an increased clearance of riociguat.
- CL of riociguat in smokers showed high variability.
- The renal clearance of both riociguat and M-1 was mainly determined by the renal activity as measured by the creatinine clearance.

- In subjects with hepatic or renal impairment, the biomarkers for hepatic function (for example, albumin, bilirubin) and Child Pugh classification did not affect the total clearance of either riociguat or M-1.
- In patients with pulmonary hypertension and thromboembolic pulmonary hypertension, riociguat and M-1 PKs could be described by a one compartmental model each, parameterised in terms of apparent clearance, apparent volume of distribution and a first order absorption rate constant.

Bilirubin concentration (hepatic capacity) was identified as covariate inversely correlating with the individual apparent CL of riociguat.

The covariates effects (creatinine clearance, bilirubin, co-medication and smoking) on CL reduced the unexplained IIV of CL from 48.3% to 41.2%. The effect of the covariate body weight on the V reduced the unexplained IIV of V from 27.1% to 25%.

Patients receiving bosentan as a co-medication showed higher CL (35.6% increase in the clearance of riociguat) compared to patients without bosentan as a co-medication.

There was no evidence for time or dose dependent alterations in riociguat PKs over the time course of Phase III studies.

For M-1, a correlation between the bilirubin concentration and the apparent volume of distribution was identified. In addition, the apparent clearance and apparent volume of distribution of M-1 were linearly related to the weight of the patient.

- For non-smokers, liver clearance accounted for 93% of total clearance on average, whereas lung and intestinal clearance contributions were <1% and 2%, respectively. Unchanged riociguat excreted in faeces also was <1% of total clearance, whereas excretion in urine via glomerular filtration accounted for 15% of total clearance. Biliary secretion was 14% of hepatic clearance with CYP mediated metabolism of riociguat accounting for 86% with individual clearances split according to their relative expression profiles.
- For smokers, CLliv was reduced to 81% of total clearance on average whereas clearance in lungs, the site of highest exposure to polycyclic aromatic hydrocarbons in tobacco smoke and highest induction of CYP1A1, accounted for 4% of total clearance.

In children aged between 6 and 18 years old with PAH the plasma exposure at steady state was comparable with the exposure in adults, when riociguat was dosed on a mg/kg basis. Below 6 years, there was a tendency towards lower plasma levels in paediatric PAH patients with a minimum around 1 to 2 years of age. Below one year, the riociguat plasma exposure tended to increase again and 1 month old children had a plasma exposure comparable to that of adults.

Pharmacodynamics

Studies providing pharmacodynamic data

Table 6 (below) shows the studies relating to each pharmacodynamic topic.

Table 6. Submitted pharmacodynamic studies.

PD Topic	Subtopic	Study ID	*
Primary Pharmacology	Effect on pulmonary and systemic	11874	Impact of riociguat (1, 2.5 and 5 mg doses) in patients with suspected PH

PD Topic	Subtopic	Study ID	*
	haemodynamics		
Secondary Pharmacology	Effect on bone resorption and formation markers	13790	Effect of multiple-dose riociguat (2.5 mg TDS over 14 days)
	Effect on haemodynamics	11258	Oral doses of 0.25, 0.5, 1.0, 2.5, 5.0 riociguat administered as solution and 2.5 mg as a tablet.
		11259	Effects of a high-fat, high-calorie meal
		11260	Multiple oral doses of 0.5 mg, 1.0 mg, 1.5 mg TDS, 2.5 mg BID or 2.5 mg TDS given as IR tablet over 10 days
Gender and Age-on PD Response	Effect of age and gender	11914	PDs of riociguat, in young and elderly healthy volunteers of both genders, following a 2.5 mg oral tablet dose
PD Interactions	Nitroglycerin	14360	Effect on BP and heart rate
	Sildenafil	11917	Impact on pulmonary and systemic haemodynamics
	Omeprazole	11262	Haemodynamics
	Maalox	11890	Haemodynamics
	Warfarin	11918	Prothrombin time and factor VII
	Aspirin	14204	Bleeding time and platelet aggregation

* Indicates the primary aim of the study. § Subjects who would be eligible to receive the drug if approved for the proposed indication. ‡ And adolescents if applicable.

Evaluator's conclusions on pharmacodynamics

Summary of the PD

The sponsor provided a wide range of PD studies, which examined the mechanism of action and dose-response relationship of riociguat. In addition, the studies also addressed the effects of riociguat on haemodynamic parameters, pulmonary effects and neurohormonal function as well as other secondary effects such as bone formation and renal function.

Mode of action

Riociguat is a stimulator of the soluble guanylate cyclase (sGC), an enzyme in the cardiopulmonary system and the receptor for nitric oxide (NO).Riociguat has a dual mode of action. It sensitises sGC to endogenous NO by stabilising the NO-sGC binding. Riociguat also directly stimulates sGC via a different binding site, independently of NO.

Primary pharmacodynamic effects in the target population

Riociguat 2.5 and 1 mg induced similar and clinically relevant and statistically significant reductions in pulmonary artery pressure, systolic blood pressure, pulmonary vascular resistance and systemic vascular resistance and a clinically relevant and statistically significant increase in cardiac index (CI).

Reductions in pulmonary vascular resistance (PVR) and systemic vascular resistance (SVR) were more pronounced in the riociguat 1 mg dose group (296 versus 168 dyn*s*cm-5 and 690 versus 546 dyn*s*cm-5, respectively) while CI increased slightly more in subjects receiving riociguat 2.5 mg (0.95 versus 0.65 L/min/m^2).

Both doses of riociguat were superior in reducing SBP, PVR, and SVR and increasing CI than nitrous oxide (NO), (*P* between 0.0220 and <0.0001), whereas, the differences in PAP between riociguat for any of the 2 doses and NO did not reach statistical significance (*P* between 0.0546 and 0.0539).

Secondary pharmacodynamic effects in healthy subjects

Following administration of riociguat (2.5 mg TDS over 14 days) mean cGMP concentrations in plasma increased by 48.6% and mean excretion of cGMP into urine increased by 136%.

Riociguat induced an increase in pulse rate by 8.3 beats per minute (bpm) after the first 24 h of riociguat treatment. This effect was reduced to 3.6 bpm after 14 days of riociguat treatment.

Mean systolic blood pressure (SBP) decreased by 4.2 mmHg after the first 24 h and by 10 mmHg after 14 days.

Bone formation

Mean bone formation parameters in serum such as amino-terminal propeptide of type I procollagen (PINP), bone alkaline phosphatase (bAP), and osteocalcin decreased significantly by 5.5%, 12%, and 8.3%, respectively, during riociguat treatment compared to placebo.

Mean serum PTH during riociguat treatment was not different to mean PTH during placebo treatment.

Renal function

Directly following 2.5 mg dose of riociguat (0 to 4 h), there was an increase in urinary excretion of calcium, sodium, potassium and creatinine.

Over the 14 day treatment period riociguat increased urinary excretion of calcium by 22% (*P*<0.0001) compared to placebo.

Mean 24 h urine volume and the amount of sodium and potassium excreted in urine per 24 h were not significantly different between riociguat and placebo treatments.

Mean serum calcium decreased significantly by 1.2%, serum uric acid by7.9%, and creatinine by 5.4% (*P*=0.0007, *P*<0.0001, and *P*<0.0001, respectively); however, all individual values remained within the normal range.

After 48 to 72 h of riociguat treatment, red blood cell count, haematocrit and haemoglobin were significantly reduced by 3.17%, 3.57% and 3.56%, respectively. These changes were associated with a significant increase in reticulocyte count after 6 to 7 days.

Riociguat did not affect mean corpuscular volume (MCV), mean corpuscular haemoglobin (MCH), and mean corpuscular haemoglobin concentration (MCHC).

After normalisation of serum calcium to serum albumin, renin and cGMP significantly increased by 48.5 and 50.5%, respectively.

Dose escalation

Following single oral doses of 0.25, 0.5, 1.0, 2.5 and 5.0 mg riociguat, the mean heart rate measured over 1 min increased dose dependently from 4 bpm in the 1.0 mg dose to 11 bpm in the 5.0 mg dose and reached peak values 1 to 2 h.

Individual maximum increases in heart rate were 26 bpm (2.5 mg solution) and 28 bpm (5 mg solution) 2 h after drug administration and 38 bpm (2.5 mg solution) and 47 bpm (5 mg solution) 6 h after drug administration.

Mean changes 0.5 to 2 h post baseline DBP ranged from +2.8 mmHg (0.25 mg solution) to -7.7 mmHg (5 mg solution).

Riociguat at the doses tested had no effect on angiotensin II, aldosterone and platelet aggregation.

Effect of a meal

Following a 2.5 mg dose of riociguat IR tablets the heart rate increase ranged from 4.5 to 9.8 bpm in fasted subjects and from 4.7 to 12.8 bpm in subjects following a high-fat, high-calorie meal.

Steady-state versus single doses

Increases in heart rate and plasma renin activity were more pronounced following single doses than at steady state, whereas the effect on cGMP in plasma was more pronounced at steady-state than following a single dose.

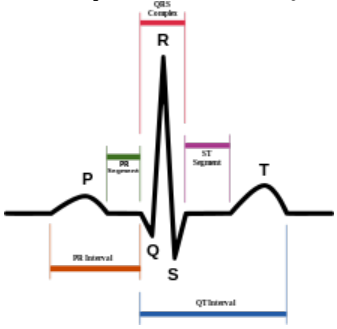
Relationship between drug concentration and pharmacodynamic effects

Riociguat plasma concentrations were significantly correlated with reductions in pulmonary arterial pressure (PAP), SBP, PVR, and SVR and increases in CI. By contrast there was no correlation between six minute walk distance (6MWD) and baseline riociguat AUC.

Gender and age

Following a 2.5 mg oral tablet dose there were no distinct trends for the subgroups (young males, young females, elderly males, and elderly females) for the change from baseline for the mean pulse rate and QRS intervals[6] when comparing riociguat to the placebo group.

[6]A graphic tracing of the variations in electrical potential caused by the excitation of the heart muscle and detected at the body surface is shown below. The normal electrocardiogram is a scalar representation that shows deflections resulting from cardiac activity as changes in the magnitude of voltage and polarity over time and comprises the P wave, QRS complex, and T and U waves.



QTcF[7] in both the young and elderly female groups and the elderly male group were prolonged by >5msec one h after dosing compared with the matching placebo groups.

Effect on QTcF

QTcF in both the young and elderly female groups and the elderly male group were prolonged by >5msec one h after dosing compared with the matching placebo groups. In the absence of qualifying data from the Phase II and III studies this finding would in general warrant the need for a Thorough QT study to be undertaken prior to drug registration. However, as discussed in sections under Safety, *Electrocardiogram* (see Attachment 2) and *Safety issues with the potential for major regulatory impact* of this report, healthy subjects do not tolerate riociguat administration; therefore, a Thorough QT study was not possible. In addition, the two pivotal clinical trials did not identify any relevant changes in QT, QTcB and QTcF duration nor were there any events reported that were linked to QT prolongation.

Pharmacodynamic interactions

Nitroglycerin

A single sublingual dose of 0.4 mg nitroglycerin administered 8 h after pre-treatment with a single oral dose of 2.5 mg riociguat resulted in a significantly more pronounced maximum decrease in seated SBP than a single nitroglycerin dose after placebo pretreatment. Such a significant difference was not detected when nitroglycerin was administered 24 h after riociguat pre-treatment.

Sildenafil

No significant postbaseline changes in the primary PD parameters PAP_{mean} and PVR were observed after riociguat administration on top of a stable Sildenafil treatment.

No significant effect on SBP was observed after riociguat administration on top of a stable sildenafil treatment, whereas, a significant decrease in mean DBP (-3.1 mmHg) and increase in mean HR (+3.4 bpm) were identified.

No clinically relevant changes in any of the blood gas parameters[8] were detected after sildenafil and riociguat administrations.

Omeprazole

Mean heart rate increased continuously until 8 h after drug administration by a maximum of 12 bpm compared to baseline when riociguat was given alone and by a maximum of 10 bpm when given in combination with omeprazole.

Mean SBP changes within 8 h postbaseline ranged between -3.2 and +1.0 mmHg when riociguat was given alone and between -3.8 and -0.8 bpm in combination with omeprazole.

Mean diastolic blood pressure (DBP) decreased by 4.3 to 8.7 mmHg within 2 and 8 h postbaseline when riociguat was given alone and by 0.8 to 4.2 mmHg when given in combination with omeprazole.

[7] QT interval: a measure of the time between the start of the Q wave and the end of the T wave in the heart's electrical cycle. A prolonged QT interval is a risk factor for ventricular tachyarrhythmias and sudden death. The QT interval is dependent on the heart rate (the faster the heart rate, the shorter the QT interval). To correct for changes in heart rate and thereby improve the detection of patients at increased risk of ventricular arrhythmia, a heart rate-corrected QT interval *QTc* is often calculated. Clinical correction use Bazett's formula or Fridericia's formula (giving QT_{cB} or QT_{cF}).

[8] PaO2, PaCO2, PvO2, SaO2, and SvO2

Maalox

Mean heart rate increased by a maximum of 12.5 bpm 6 h after drug administration compared to baseline when riociguat was given alone and by a maximum of 10.4 bpm 6 h after drug administration when given in combination with Maalox.

Mean SBP decreased by a maximum of 6.3 mmHg 4 h after drug administration compared to baseline when riociguat was given alone and by a maximum of 2.5 mmHg 6 h after drug administration when given in combination with Maalox.

Mean DBP decreased by a maximum of 3.4 mmHg 1.5 h after drug administration compared to baseline when riociguat was given alone and by a maximum of 3.2 mmHg 6 h after drug administration when given in combination with Maalox.

Warfarin

In comparison to placebo, concomitant administration of riociguat 2.5 mg TDS at steady state did not influence the prothrombin time and Factor VII % activity of warfarin. Riociguat did not induce any relevant effects on Factor II % and Factor X % activity.

Aspirin

When riociguat was co-administered with Aspirin it had no significant effect on bleeding time. When given alone, riociguat had no effect on maximal platelet aggregation or platelet function.

Dosage selection for the pivotal studies

The sponsor's justification for the dose selection was as follows:

- The dose ranging Study 11260 found that the rate of adverse events (AEs) increased with the highest dose of 2.5 mg TDS (7.5 mg) in healthy volunteers.
- Study 11258 found that 0.5 mg was the no effect dose in healthy volunteers and Study 11874 found haemodynamic effects in patients at doses of 1.0 mg and orthostatic hypotension at 5.0 mg.
- From this it was concluded that 1.0 mg was the minimum effective dose and 2.5 mg the maximum tolerated dose and this range was chosen for the Phase II Study 12166.
- Due to the high inter-individual variability in PK (C_{max} and AUC) and the parallel reduction in pulmonary vascular resistance (PVR) with systemic vascular resistance (SVR), an individual titration scheme was chosen according to peripheral systolic blood pressure (SBP).
- While the PK steady state was noted at 3 days (Study 11260), the PD steady state (in terms of BP) was noted at 10 to 14 days (Study 13790) therefore dose titration was selected to be each 2 weeks.

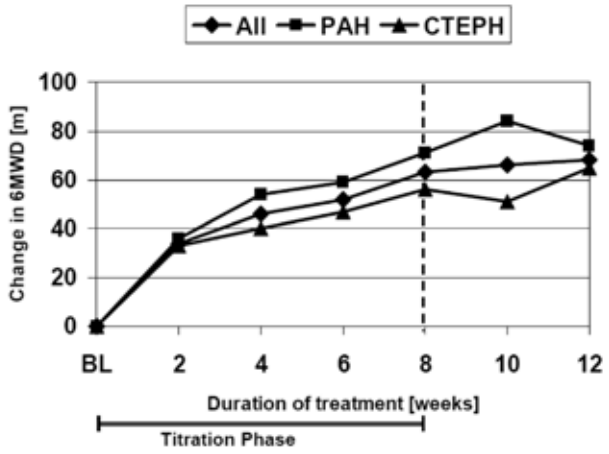
This strategy was implemented in Study 12166. This was a multicentre, not controlled, not blinded Phase II study which assessed multiple doses of riociguat in 75 subjects with either PAH (33 subjects) or CTEPH (42 subjects) after 12 weeks treatment. Individual dose titration was assessed from a starting dose of 1.0 mg TDS and within a range of 0.5 mg TDS to 2.5 mg TDS. Subjects were up-titrated (0.5 mg TDS increments) each 2 weeks if SBP was >100 mmHg, or down-titrated with SBP <90 mmHg. There were 20 subjects with PAH and 30 with CTEPH who had their right heart haemodynamics assessed at the end of the study. Titration to the highest level of 2.5 mg TDS occurred in 68% of the study population.

In the total population, data show statistically significant improvement in systolic, diastolic and mean pulmonary artery pressure (PAP) as well as systemic SBP, DBP, pulmonary and systemic vascular resistance and cardiac output. These changes were more

noted in those with WHO functional class III/IV. Significant changes were also noted on echocardiograph for the total population and the CTEPH subgroup. There was a statistically significant improvement in the 6MWD in the total population (least square (LS) mean change of 68 m) and the subgroups of PAH and CTEPH (LS mean change from baseline of 73 and 64 m, respectively) with improvement seen from Week 2 and increasing to Week 8 during dose titration (Figure 2). Treatment was tolerated within this dose range and in the 6 subjects on concomitant bosentan. Changes in mean heart rate were not clinically meaningful.

> Comment: Study 12166 demonstrated positive effects, in both the PAH and CTEPH populations, on haemodynamics and acceptable safety with the individual dose titration regimen guided by SBP within the range of 0.5 mg to 2.5 mg TDS. The study did however lack a control group so the extent of efficacy and the minimum and maximum effective dose was unable to be determined. Only 68% of subjects were able to tolerate the maximal dose of 2.5 mg TDS.

Figure 2. Study 121166 6 minute walk test mean changes in walking distance over time (population valid for PD and PK, n=72)



Efficacy

Studies providing efficacy data

Efficacy data were provided from 2 pivotal efficacy/safety studies (11348 [CHEST-1] and 12934 [PATENT-1]).

Please see Attachment 2 for further details of the efficacy studies and the data collected.

Evaluator's conclusions on efficacy

The efficacy of riociguat in PAH and CTEPH was based on two Phase III randomised, double blind, placebo-controlled, international studies, one in each indication. The PAH study (PATENT-1) included 443 patients with symptomatic PAH (WHO group 1) which was primarily idiopathic (59-67%) or due to connective tissue disease (20 to 28%). These PAH subjects could be treatment naïve (about half the subjects) or pretreated with an endothelin receptor antagonist (ERA) or prostacylin analogue. The CTEPH study (CHEST-1) included both subjects with inoperable CTEPH (70-77%) or with PH persisting after pulmonary endarterectomy (23-30%). Subjects with CTEPH received oral anticoagulation but not specific PH medication. The studies included patients with a 6MWD between 150 toc450 m, a PVR of >300 dyn*sec*cm^{-5} and a mean PAP of >25 mmHg. The vast majority of subjects were WHO FC II and III at baseline.

The trials employed an individual dose titration (IDT) regimen with a starting dose of 1.0 mg TDS and increases of 0.5 mg TDS each two weeks based on the subject's peripheral SBP. The dose range was between 0.5 mg and 2.5 mg TDS and there was a separate arm in study PATENT-1 which assessed a titration regimen capped at 1.5 mg TDS. Controlled treatment was for 16 weeks in the CHEST-1 and 12 weeks in PATENT-1. At Week 16 in CHEST-1, 77% of subjects were on riociguat 2.5 mg TDS and 12% were on 2.0 mg TDS. At Week 12 in PATENT-1, 75% of the 1.0 to 2.5 mg group were on 2.5 mg TDS and 15% on 2.0mg TDS and in the capped 1.0 to 1.5 mg group, 95% were on 1.5 mg TDS. Subjects could then enter open label long term extensions.

The primary efficacy endpoint in both studies was the mean change from baseline in the 6MWD compared to placebo in the Intention-to-Treat (ITT) population with imputation for missing values. Secondary endpoints were tested in a hierarchical procedure in the following order: PVR, N-terminal of the prohormone brain natriuretic peptide (NT-proBNP), WHO functional class, Time to clinical worsening, Borg CR 10[9], EQ-5D[10] and Living with Pulmonary Hypertension (LPH) questionnaire.

Premature treatment discontinuation was lower in the riociguat group than the placebo group (6.7% versus 12.6%) in the PAH study but this was not seen in the CTEPH study (8.0% versus 5.7%) (Table 7).

Table 7. Primary reasons for premature termination of study treatment. Main and extensions CTEPH and PAH studies (randomised subjects).

	11348 (CHEST-1)				12934 (PATENT-1)			
	Riociguat IDT		Placebo		Riociguat IDT		Placebo	
Completed treatment	160	(92.0%)	83	(94.3%)	237	(93.3%)	111	(87.4%)
Prematurely discontinued	14	(8.0%)	5	(5.7%)	17	(6.7%)	16	(12.6%)
Adverse event	4	(2.3%)	2	(2.3%)	8	(3.1%)	7	(5.5%)
Death	2	(1.1%)	2	(2.3%)	0	–	2	(1.6%)
Lack of efficacy	2	(1.1%)	1	(1.1%)	0	–	1	(0.8%)
Lost to follow-up	0	-	0	-	1	(0.4%)	0	–
Non-compliance with study drug	1	(0.6%)	0	–	1	(0.4%)	0	–
Protocol violation	3[a]	(1.7%)	0	–	1	(0.4%)	3[a]	(2.4%)
Withdrawal by subject	2	(1.1%)	0	–	6	(2.4%)	3	(2.4%)
	11349 (CHEST-2)				12935 (PATENT-2)			
	Former riociguat IDT		Former placebo		Former riociguat IDT		Former placebo	
Prematurely discontinued	7	(5.4%)	5	(7.7%)	32	(14.9%)	19	(19.8%)
Adverse event	2	(1.6%)	0	–	17	(7.9%)	8	(8.3%)
Death	3	(2.3%)	2	(3.1%)	6	(2.8%)	6	(6.2%)
Lack of efficacy	1	(0.8%)	1	(1.5%)	1	(0.5%)	1	(1.0%)
Non-compliance with study drug	0	-	0	-	0	–	2	(2.1%)
Protocol violation	0	-	0	-	2	(0.9%)	0	–
Withdrawal by subject	1	(0.8%)	2	(3.1%)	5	(2.3%)	2	(2.1%)
Other	0	-	0	-	1	(0.5%)	0	–

a Including one randomized subject who did not receive study medication.

Both studies were positive with statistically significant and clinically meaningful improvement in exercise capacity. In CHEST-1 in the CTEPH population, the LS mean improvement in the 6MWD after 16 weeks with riociguat compared to placebo was 46 m (95% CI 25,67, p<0.0001) (Table 8). In PATENT-1 in the PAH population, riociguat treatment (1.0 to 2.5 mg TDS regimen) resulted in improvement over placebo in the 6MWD after 12 week of 36 m (95% CI: 20-52, p<0.0001) (Table 9).

[9] The Borg scale measures perceived exertion. The Borg CR 10 is especially used in clinical diagnosis of breathlessness and dyspnea, chest pain, angina and musculo-skeletal pain.
[10] EQ-5D™ is a standardised instrument for use as a measure of health outcome. It generates a single index value for health status for use in health care evaluation

Table 8. Study 11348 (CHEST-1) Summary of efficacy results for predefined variables in the hierarchical testing order. ITT analysis set.

Variable	LS mean (treatment difference of riociguat IDT to placebo)	95% CI	Stratified Wilcoxon test p-value	Statistically significant	Statistically significant in hierarchical testing
6MWD (m) (primary)	46	25 to 67	<0.0001	Yes	Yes
PVR (dyn*s* cm^{-5})	-246	-303 to -190	<0.0001	Yes	Yes
NT-proBNP (pg/mL)	-444	-843 to -45	<0.0001	Yes	Yes
WHO functional class	32.9%[a] riociguat 14.9% [a] placebo	N/A	0.0026	Yes	Yes
Time to clinical worsening	2% [b] riociguat 6% [b] placebo	N/A	0.1724 [c]	No	No
Borg CR 10 score [d]	-0.8 [e] riociguat 0.2 [e] placebo	N/A	0.0035	Yes	No
EQ-5D questionnaire	0.13	0.06 to 0.21	<0.0001	Yes	No
LPH questionnaire	-5.76	- 10.45 to -1.06	0.1220	No	No

Abbreviations: LS = least square; CI = confidence interval; IDT = individual dose titration (riociguat 1.0 to 2.5 mg); 6MWD = 6 minute walking distance; PVR = pulmonary vascular resistance; EQ-5D = European quality of life 5-dimensions instrument; LPH = Living with Pulmonary Hypertension

[a] Improvement by at least 1 WHO functional class in the respective treatment group

[b] Percentage of subjects with any clinical worsening event in the respective treatment group

[c] Stratified log-rank test p-value for time to clinical worsening.

[d] Subjects enrolled before amendment 3 used the Modified Borg Dyspnoea Scale.

[e] Change from baseline to last visit in the respective treatment group

Table 9. Study 12934 (PATENT-1) Summary of efficacy results for predefined variables in the hierarchical testing order. ITT analysis set.

Variable	LS mean (treatment difference of riociguat IDT to placebo)	95% CI	Stratified Wilcoxon test p-value	Statistically significant	Statistically significant in hierarchical testing
6MWD (m) (primary)	36	20 to 52	<0.0001	Yes	Yes
PVR (dyn*s* cm^{-5})	-226	-281 to -170	<0.0001	Yes	Yes
NT-proBNP (pg/mL)	-432	-782 to -82	<0.0001	Yes	Yes
WHO functional class	20.9%[a] riociguat 14.4% [a] placebo	N/A	0.0033	Yes	Yes
Time to clinical worsening	1% [b] riociguat 6% [b] placebo	N/A	0.0046 [c]	Yes	Yes
Borg CR 10 scale [d]	-0.4 [e] riociguat 0.1 [e] placebo	N/A	0.0022	Yes	Yes
EQ-5D questionnaire	0.06	0.01 to 0.11	0.0663	No	No
LPH questionnaire	-6.17	- 9.79 to -2.54	0.0019	Yes	No

Abbreviations: LS = least square; CI = confidence interval; IDT = individual dose titration (riociguat 1.0 to 2.5 mg); 6MWD = 6 minute walking distance; PVR = pulmonary vascular resistance; EQ-5D = European quality of life 5-dimensions instrument; LPH = Living with Pulmonary Hypertension

[a] Improvement by at least 1 WHO functional class in the respective treatment group

[b] Percentage of subjects with any clinical worsening event in the respective treatment group

[c] Stratified log-rank test p-value for time to clinical worsening.

[d] Subjects enrolled before amendment 3 used the Modified Borg Dyspnoea Scale.

[e] Change from baseline to last visit in the respective treatment group

The results were robust in both studies being supported by sensitivity analyses using different imputation methods and by the PP population analysis. In addition, efficacy on the primary endpoint of 6MWD was demonstrated across subgroups. This included inoperable CTEPH (LS mean difference 54m) and postoperative CTEPH (LS mean difference27 m), therapy naïve PAH patients (LS mean difference of 38m) and pretreated PAH subjects (LS mean 26 m CHECK), WHO functional class (I/II or III/IV), gender, age group (± 65 years), baseline 6MWD (± 380 m, ± 320 m), race (White, Asian). The efficacy was noted to be greater in those with more impaired WHO FC and to have less of an effect on those PAH patients already on background PH specific medication.

Efficacy was supported by statistically significant results for secondary endpoints of PVR, NT-proBNP level and WHO functional class in both studies. While there was a trend in favour of riociguat in time to clinical worsening and the Borg CR 10 score for dyspnoea in both studies, this was only significant in the PAH study. It is noted that the duration of the pivotal trials (12 to 16 weeks) was less than the European Medicines Agency's (EMA's)

recommended 6 months for studies aiming to demonstrate improvement in time to clinical worsening (EMA 2009).[11] Improvements on the Quality of Life (QOL) questionnaires did not reach significance in either study. The efficacy data were also supported by positive effects on haemodynamic parameters of PVR, cardiac output (CO), SVR and mean PAP in both studies.

In the long term open label studies, the mean exposure was 388 and 438 days in CHEST-2 and PATENT-2, respectively. Persistence of efficacy, as measured by 6MWD and WHO functional class maintenance, was found and the addition of PH medication was low at 6.2% and 12.1% in CHEST-2 and PATENT-2, respectively. There are however no controlled data past 12 weeks PAH and 16 weeks in CTEPH on which to confirm these findings.

There were no specific withdrawal studies and no studies assessing switching between medications.

The efficacy data on the capped titration regimen (1.0 to 1.5 mg TDS) were very similar to the higher titration regimen across all parameters. The low dose group had a small sample size (n=63) and there were no formal comparisons of the two dose groups. This means it is not possible to draw conclusions on the relative efficacy of one dose compared to the other.

The interaction of riociguat with the PDE inhibitor sildenafil was assessed in a small study (15096) in PAH patients and found a negative benefit risk balance so the combination must be avoided.

Safety

Studies providing safety data

The following studies provided evaluable safety data:

Pivotal efficacy studies

There were four Phase III studies: Study 11348 (CHEST-1) and its long-term extension Study 11349 (CHEST-2); and Study 12934 (PATENT-1) and its long-term extension Study 12935 (PATENT-2). For information on the safety data collected in the pivotal efficacy studies see Attachment 2 *Safety*.

Phase II studies

There were seven Phase II studies: Study 12166 and its long term extension (LTE), Study 15096 (PATENT PLUS), Study 12915 (PH due to COPD), Study 12916 (PH due to ILD), Study 14308 (PH due to LVD) and Study 14549 (PH due to LVD). The studies included 265 subjects and the daily dose range varied from 1.0 to 9.0 mg. These studies provided data on treatment-emergent AEs (TEAEs), laboratory variables, vital signs (blood pressure (BP) and heart rate (HR)), ECGs and blood gas analysis.

Phase I studies

There were 30 Phase I studies on riociguat including 768 healthy subjects and patient volunteers. There were 5 Phase I studies on the active metabolite of riociguat BAY 60-4552. In 25 these Phase I studies riociguat was administered as a single agent. The safety

[11] EMA (2009). Committee for medicinal products for human Use (CHMP). Guideline on the clinical investigation of medicinal products for the treatment of pulmonary arterial hypertension. EMEA/CHMP/EWP/356954/2008.

analysis set included 738 subjects. Single dose studies assessed doses from 0.25 to 5 mg in 543 subjects and multi-dose studies assessed doses from 1.5 mg to 7.5 mg in 189 subjects.

Due to differing aetiologies, safety data have been presented for each indication, PAH and CTEPH, separately. In addition the sponsor pooled safety data as follows:

- Pool 1: the two Phase III placebo-controlled studies and their two non-controlled extension studies
- Pool 2: all multi-dose studies in CTEPH and PAH (the 4 Phase III studies plus studies 12166 and 15096)
- Pool 3: all Phase II and III riociguat studies (Pool 2 plus studies 12915, 12916, 14308 and 14549).

The sponsor stated that for the integrated analysis of safety *to ensure that all events which occurred in an extension study/phase are completely counted and not masked by events in the main study, all subjects in the extension study/phase were counted as additional subjects. Consequently, the number of analyzed subjects is higher than the number of enrolled subjects*.

Patient exposure

In the Phase II studies there were 265 subjects treated with riociguat with a mean treatment duration in the various studies ranging from 2 days to 36 months.

In the Phase III program where data available are for the safety analysis, there were 317 subjects with PAH and 173 with CTEPH exposed to riociguat in the primary studies and (due to the swap from placebo to active in the long term extension studies) the number rose to 363 and 194 in the respective long term extension studies (Table 10 below).

Table 10. Exposure to Riociguat and placebo in the Phase III clinical studies.

Study type/ Indication	Controlled studies		Uncontrolled studies
	Riociguat	Placebo	Riociguat
Clinical pharmacology			
Indication PAH			
Pivotal	317#	126	
Long term extension			363*
Indication CTEPH			
Pivotal	173	88	
Long term extension			194**
TOTAL	490	214	557

254 riociguat 1.0 to 2.5 mg and 63 riociguat 1.0 to 1.5 mg; *At cut off of 16 April 2012, 363 of 396 subjects in the extension were included in the safety analysis. **At cut off of 3 May 2012, 194 of the 237 subjects were included in the safety analysis

The mean treatment duration in PATENT-1 was 81.4 days (± 15.6), 80.0 days (± 18.9) and 78.2 days (± 20.5) in the riociguat 1.0 to 2.5 mg, riociguat 1.0 to 1.5 mg and placebo groups, respectively. The average total dose received was 457 mg (± 122.5) and 335.8 (± 86.1) in the 1.0 to 2.5 mg and 1.0 to 1.5 mg groups, respectively.

At Week 12, 74.6% of the riociguat 1.0 to 2.5 mg group were on the highest dose of 2.5 mg, 15.3% were on 2.0 mg, 5.9% were on 1.5 mg, 2.5% on 1.0 mg, and 1.7% on 0.5 mg. In the riociguat 1.0 to 1.5 mg group, 94.7% were on 1.5 mg.

In the long term extension study (PATENT-2), the mean treatment duration was 436.2 days (± 268.9) in the former riociguat 1.0 to 2.5 mg group, 426.1 days (± 261.7) in the former placebo group and 470.1 days (± 282.2) for the former riociguat 1.0 to 1.5 capped dose group. There were 325 subjects who received treatment for 8 weeks (titration phase), 290 subjects for 24 weeks, 221 subjects for 48 weeks, 162 subjects for 72 weeks and 52 subjects (14.3%) for 108 weeks. The total exposure was 435.7 person-years. The mean cumulative exposure was 3082.5 mg (± 1994.3).

The mean treatment duration in CHEST-1 was 108.2 days (± 21.2) and 110.2 days (± 14.8) in the riociguat 1.0 to 2.5 mg and placebo groups, respectively. The average total dose received was 645 mg (± 166.5). At Week 16, 76.9% (123/160) were on the highest dose of 2.5 mg TDS, 12.5% were on 2.0 mg TDS, 6.3% were on 1.5 mg TDS, 3.8% on 1.0 mg TDS, and 0.6% on 0.5 mg TDS.

In the extension study (CHEST-2), the mean treatment duration was 388.3 days (± 276.3). There were 187 subjects who received treatment for 8 weeks (titration phase), 97 subjects for 48 weeks and 39 subjects (20.1%) for 96 weeks. The total exposure was 206.2 person-years. The mean cumulative treatment exposure was 2732 mg (± 2015).

The demographics of patients in the two Phase III studies and in the pooled population were summarised in the submission.

Safety issues with the potential for major regulatory impact

Cardiovascular safety

In Study 11914 there was a signal of QTcF prolongation of 6 to 12 msec in females and 5 to 7 msec in males. In addition, the sponsor stated that *in vitro* studies noted minor effects of riociguat and its main metabolite on ventricular repolarisation while nonclinical studies in dogs found no adverse ECG effects.

Despite this, data from the Phase I single dose studies showed no cases with an absolute QTcF value of over 500 msec and one case of >60 msec prolongation over baseline. Similarly in the multiple dose Phase I studies there were no cases of an absolute value >500 msec and no cases of prolongation >60 msec compared to baseline.

A Thorough QT study was not conducted due to safety concerns with administering riociguat to healthy volunteers (the maximum well tolerated dose in healthy volunteers was 2.5 mg and 5 mg resulted in haemodynamic effects). As a consequence, ECG data were obtained from the subject population in the Phase III program. This included a randomised controlled study (**Study 13796**) in healthy volunteers conducted at study sites participating in PATENT-1 using the same ECG recording methods. The study was designed to validate ECG assay sensitivity for PATENT-1. Secondly there was extended ECG monitoring with centralised reading in 98 riociguat subjects (76 high dose, 22 low dose) and 35 placebo subjects in PATENT-1. Routine ECG recording was conducted on all Phase III trial participants.

Study 13796 found that using a positive control of moxifloxacin 400 mg, the study setting was sensitive to detect a LS mean difference (moxifloxacin versus placebo) in QTcF of 15 msec and in QTcB of 16 msec. In the Thorough QT subset of PATENT-1, the mean change

from baseline in QTcB was 2 msec and 4 msec in the riociguat 1.0 to 2.5 mg and placebo groups, respectively. In the overall PATENT-1 population (193, 43 and 84 subjects in the riociguat 1.0 to 2.5 mg, placebo and riociguat 1.0 to 1.5 mg groups, respectively) where single ECGs were collected, the mean QTcF was between 420 and 435 msec with no mean change from baseline of >7 msec at any visit. There were no cases of QT interval increase of 60 msec during the treatment phase (although there was one case at the safety follow up visit) and no reports of QT prolongation associated events. There was also no indication of QT prolongation in the overall Phase III population.

> Comment: The evaluator concludes that it is possible that riociguat may result in small changes to the QT interval although any prolongation appears small and from the provided data did not appear to result in any adverse clinical effects.

Bone toxicity

The exploratory biomarkers dihydroxy vitamin D, type I collagen C-telopeptides (CTX) and osteopontin as well as calcium and phosphate were evaluated to assess possible change in bone metabolism. This was due to nonclinical findings of skeletal effects, in particular at the growth plate in juvenile and adolescent rats and mice.

In the pivotal trials, there were no relevant changes in mean serum calcium or phosphate or relevant differences compared to placebo. The change from baseline to end of the primary study in 1,25-dihydroxy vitamin D was also unremarkable. There were small increases from baseline in mean CTX and mean osteopontin levels in the two pivotal Phase II trials which appeared similar to placebo.

> Comment: The clinical implication of these findings is uncertain.

The rate of musculoskeletal and connective tissue disorders was similar between riociguat and placebo in the CTEPH (19.7 versus 21.6%) and PAH patients (15.7%, 15.9% 15.9% in the riociguat 1.0 to 2.5 mg, placebo and riociguat 1.0 to 1.5 mg groups, respectively). The most frequent events were back pain, pain in extremity and arthralgia. All events were mild or moderate in severity. In the extension studies the rate of musculoskeletal disorders was 27.3% in PATENT-2 and 29.9 % in CHEST-2, and there were no SAEs in this SOC.

Postmarketing data

None listed.

Evaluator's conclusions on safety

In the Phase III clinical program there were 490 subjects treated with riociguat, 317 with PAH and 173 with CTEPH. The mean treatment duration in the PAH controlled study was 81 days, 80 days and 78 days in the riociguat 1.0 to 2.5 mg, riociguat 1.0 to 1.5 mg and placebo groups, respectively and in the CTEPH controlled study was 108 days and 110 days in the riociguat 1.0 to 2.5 mg and placebo groups, respectively. In the PAH population there were 221 subjects who received treatment for 48 weeks and 52 subjects for 108 weeks. The total exposure was 435.7 person years. In the CTEPH population, there were 97 subjects who received treatment for 48 weeks and 39 subjects for 96 weeks. The total exposure was 206.2 person years.

The rate of death in both pivotal trials was lower in the riociguat than placebo groups (PAH: 0.8%, 2.4% and 1.6% in the riociguat 1.0 to 2.5 mg, riociguat 1.0 to 1.5 mg and placebo groups, respectively. CTEPH: 1.2% versus 3.4% riociguat versus placebo). Four of the five deaths in CHEST-1 were cardiopulmonary related events. There was one death from renal failure. There were 3 deaths in PATENT-1, one right ventricular (RV) failure with PAH, one sepsis and one haemoptysis.

SAE rates were no higher with riociguat than placebo in PATENT-1 (11-18% riociguat versus 18% placebo) and slightly higher in CHEST-1 (20% riociguat versus 16% placebo). The most frequent SAEs were syncope and right ventricular failure with the addition of PAH, PH, cardiac catheterisation and pneumonia in the long term extension studies.

Discontinuation rates due to TEAEs were similar to or lower than placebo in both studies (2.9% riociguat versus 2.3% placebo in CHEST-1 and 1.6-3.1% riociguat versus 7.1% placebo in PATENT-1). Discontinuation due TEAEs was low in the extension studies (1.5% in CHEST-2 and 7.7% in PATENT-2).

Most TEAEs were mild or moderate with severe events occurring in 9 to 11% of riociguat treated subjects in both controlled studies which was similar or lower to the rate in the placebo groups. The most frequently involved System Organ Classes (SOCs) were the Gastrointestinal and Nervous systems. Events more frequent with riociguat were headache, dyspepsia, peripheral oedema, dizziness, hypotension, anaemia, diarrhoea and vomiting.

The sponsor stated that *'headache can be attributed to riociguat-induced vasodilation, whereas dyspepsia and gastro-oesophageal reflux disease can be attributed to riociguat-induced relaxation of smooth muscle cells of the lower oesophageal sphincter'*.

The rate of syncope was no greater with riociguat. Hypotension was the most notable adverse event (10.2%, 3.2%, 4.8% in the in the riociguat 1.0 to 2.5 mg, riociguat 1.0 to 1.5 mg and placebo groups, respectively in PATENT-1, and 11.5% riociguat versus 4.5% placebo in CHEST-1). There was evidence of dose response effect on hypotension as measured by rates of TEAE and proportion of subjects with low SBP (<95 mmHg) 2 to 3 h post dose. Serious hypotension was not frequent and was reported in 0.4% (versus 0% placebo) in pooled analysis of the pivotal trials. Hypotension TEAEs occurred in 8% and 6% of the subjects in the long term studies PATENT-2 and CHEST-2, respectively.

Severe bleeding events were more frequent with riociguat (1.6 to 3.2% versus 0% in PATENT-1, 3.5% versus 0% in CHEST-1). The most frequently reported serious bleeding event was haemoptysis and these SAEs occurred at a higher rate with riociguat (5 cases, 1.0% versus 0 cases in the placebo group).

Data also indicated a risk of anaemia with a higher rate of TEAEs in the PAH population (8.3%, 2.4%, 1.6% in the respective PATENT-1 groups). This was not seen in the CTEPH population. The mean change from baseline in haemoglobin was not clinically relevant.

While there were variable findings on laboratory assessment of renal function, there was a signal of renal failure with a higher rate of serious TEAEs of renal failure in pooled data (Pool 3: 1.3% versus 0.3%) with two unresolved and one fatal case.

There were no notable findings on liver function. Vital sign assessments, including arterial blood gases, were unremarkable except for the effects on blood pressure. There was an overall shift to lower mean SBP and DBP with riociguat consistent with it mechanism of action. ECG findings were unremarkable and there was no evidence of QTc prolongation in the subset of subjects assessed in PATENT-1.

Long term safety data were not controlled so definitive conclusions cannot be drawn. Nonetheless, the profile and rates of events were consistent with the primary studies.

Bone toxicity findings in nonclinical studies have been noted. While there were exploratory biomarkers (CTX and osteoponin) assessed, the clinical implications of the findings are uncertain. In assessment of TEAEs, there were no signals evident in the musculoskeletal and connective tissue SOC.

Data from Study 15096 found that efficacy was not improved by the combined use of riociguat and PDE inhibitors and that there was a high risk of treatment discontinuation

and death in the extension study. Therefore, PDE inhibitors should not be used with riociguat.

Safety findings in subgroups showed a higher rate of hypotension in females, limited number of elderly subjects and increased risk of hypotension and of SAEs with decreasing renal function.

There were no safety data in pregnant or lactating women, children or subjects with severe renal impairment (creatinine clearance < 30 mL/min), on dialysis or with significant hepatic disease. It is noted that subjects with hepatic and renal impairment have increased exposure to riociguat. Due to the reproductive toxicity and breast milk secretion riociguat must be avoided in pregnancy and lactation.

Subjects with low SBP (<95 mmHg) at baseline or with a history of atrial fibrillation or left heart failure were excluded from the pivotal trials and consequently safety data in these potentially at risk groups are unavailable in the PAH or CTEPH population. The Phase II Study 14308 in patients with PH associated with LV systolic dysfunction (ejection fraction ≤40%) found an increased risk of atrial fibrillation and cardiac failure with riociguat 2.0 mg.

Drug interactions with CYP inhibitors result in increased exposure and consequently safety risks and will need to be avoided. The severe risk of hypotension with concomitant nitroglycerine and the safety risks found in the clinical trial with sildenafil mean that nitrates must be contraindicated and PDE-5 inhibitors avoided.

First round benefit-risk assessment

First round assessment of benefits

The benefits of riociguat in the proposed usage are:

- Robust efficacy data from two pivotal trials, one in each population of PAH and CTEPH which were supported by secondary endpoints of WHO functional class and haemodynamic parameters.
- Clinically meaningful efficacy data (improvement in 6MWD of 36 m in PAH and 46 m in CTEPH) in rare, potentially fatal conditions where there are limited treatment options and an evident unmet medical need.
- Clinically meaningful efficacy was also demonstrated across subgroups (inoperable and postoperative CTEPH, therapy naïve and ERA pretreatment PAH, idiopathic PAH and connective tissue disease PAH).
- Maintenance of efficacy up to 18 months, albeit in an uncontrolled study.
- No evident negative impact on mortality in either pivotal trial.
- An acceptable safety profile where the rates of SAEs and discontinuations due to AEs were low and in line with placebo.
- Adequate long term safety data, with 376 patients treated for at least 48 weeks and 173 for at least 96 weeks (Pool 3).

First round assessment of risks

The risks of riociguat in the proposed usage are:

- Hypotension, with an increased risk in patients who are ≥65 years and those with renal impairment. The risk appeared manageable as the rate of serious or severe hypotension or that resulted in discontinuation was low.

- Serious haemoptysis and pulmonary haemorrhage which could be fatal. A risk of other bleeding events and anaemia was also seen.
- Renal failure which could be via a hypotensive effect or perhaps direct action.
- Unmasking of pulmonary venous occlusive disease with resultant pulmonary oedema.
- Common adverse events included headache, dizziness, dyspepsia, peripheral oedema, nausea, diarrhoea and vomiting.
- Gastrointestinal effects of abdominal pains, abdominal distension, constipation, dysphagia, gastroesophageal reflux, gastritis and gastroenteritis. These were generally mild or moderate in severity.
- Long term safety and efficacy data not fully characterised with controlled data.
- Populations at risk included patients with hypotension, hepatic impairment and severe renal impairment.
- Drug interactions including with nitrates, PDE-5 inhibitors and inhibitors or inducers of hepatic cytochromes.
- Reproductive toxicity with potential risks in pregnant or lactating women and the paediatric population.
- Vasodilatory action results in risks to certain patient groups such as those with hypovolaemia or left ventricular (LV) outflow obstruction.
- Lack of safety data in patients with significant cardiovascular or cerebrovascular disease.
- Potential for off-label use in other types of pulmonary hypertension.

First round assessment of benefit-risk balance

Pulmonary hypertension is group of diseases characterised by a progressive increase in PVR leading to right heart failure and premature death. Riociguat is a new chemical entity which acts by stimulating the soluble guanylate ecyclase (sGC), the enzyme that catalyses the formation of cGMP. This elevation of cGMP in smooth muscle causes relaxation and consequent pulmonary and systemic vasodilation. Riociguat has been developed in two PH patient populations: PAH (WHO Group 1) and CTEPH (Group 4). This application covers both indications which have been granted Orphan designation.

Overall, the submitted dossier was very well compiled and comprehensive. The clinical development program was based on two Phase III randomised, placebo controlled efficacy studies in which the primary endpoint was the change from baseline in the 6 minute walk distance. This improvement in exercise capacity, using the 6MWD, is the EMA recommended endpoint for PH trials provided there is no negative impact on survival (EMA 2009).[12]

These pivotal trials, PATENT-1 and CHEST-1, both met their primary endpoint with statistically significant and clinically meaningful improvement compared to placebo in the 6MWD. Exploratory responder analysis also found that approximately half the patients in both populations improved at least 40 m on the 6MWD (compared to 20 to 30% of placebo treated subjects). The trials were well conducted and the data were considered robust as results were concordant between trials, consistent across analysis populations and

[12] EMA (2009). Committee for medicinal products for human Use (CHMP). Guideline on the clinical investigation of medicinal products for the treatment of pulmonary arterial hypertension. EMEA/CHMP/EWP/356954/2008.

subgroups, there were relatively low levels of missing data and sensitivity analyses using different assumptions for dealing with missing data were also consistent with the primary analysis.

The sponsor has proposed a complex indication which included a number of subgroups of PAH and CTEPH. Efficacy was demonstrated across the PAH groups of idiopathic and connective tissue disease as well in those using riociguat as monotherapy or in combination in an ERA or PCA. For the CTEPH population, efficacy was also seen in those with inoperable CTEPH. For those with persistent postoperative disease CTEPH efficacy was as at a lower level (27 m versus 54 m) and the confidence intervals crossed zero. The sample size in this subgroup was much smaller (52 riociguat treated compared to 121 with inoperable CTEPH) which is likely to have contributed to the wide confidence interval. Given the consistency of effect across all subgroups, the evaluator believes that it is acceptable to include these specified subgroups in the indication.

ERAs and prostanoids are being recommended for inclusion in the indication but there were no PK interaction studies conducted. Nonetheless concomitant use occurred in the pivotal studies with acceptable results and the variety of products used was broad. Therefore the evaluator believes it is acceptable for their inclusion in the proposed indication.

The indication specifies that the efficacy in PAH predominantly included patients with WHO functional class II-III. This was also the case in the CTEPH study but this information has not been included in the indication. As the vast majority of patients in both studies were in WHO functional class II or III and there are minimal data from other functional classes, the evaluator recommends that the indicated population be limited to WHO functional class II and III (for example, *for the treatment of adult patients with PAH/CTEPH classified as WHO functional class II and III*...). Similar wording is used in the indications for tadalafil and sildenfil.

The primary efficacy endpoint was supported by improvement in WHO functional class in both trials and positive haemodynamic effects. The time to clinical worsening, a composite endpoint of death, not planned PH hospitalisation and PH related deterioration (as recommended in the EMA guidelines) was significantly improved in the larger trial in PAH but not in the CTEPH population.

The proposed indication also includes secondary efficacy endpoints in addition to improvement in exercise capacity. Even though the selected secondary endpoints of (WHO functional class in both populations and delay in clinical worsening in PAH) were found to be statistically significant, the evaluator does not believe the indication should be based on secondary endpoints. In addition, the EMA guidelines clearly state that while studies using improvement in exercise testing may vary between 3 and 6 months *a minimum of 6 months is usually necessary to demonstrate an improvement in time to clinical worsening*. The two pivotal studies were of shorter duration. Consequently, the indication needs to be reworded using only the primary endpoint "*to improve exercise capacity*". The effect on other endpoints has been included in the *Clinical Trials Section* of the draft PI. This recommendation is also in line with the indication of other PH treatments (for example, tadalafil). In addition, the evaluator noted in the risk management plan (RMP) the proposed indication for both conditions in the EU is only "*to improve exercise capacity*".

The dosing regimen is an individual titration regimen with a starting dose of 1.0 mg TDS and an increase each 2 weeks based on patient's peripheral SBP to a maximum of 2.5 mg TDS. A lower dose of 0.5 mg is also proposed should down titration be necessary. This regimen was used in both pivotal studies and at the end of the controlled period (12 to 16 weeks) approximately 90% of subjects were tolerating 2.5 mg or 2.0 mg. In the PAH population of PATENT-1, there were very similar results on the primary efficacy outcome for subjects treated with the proposed dosage regimen (to 2.5 mg TDS) and those treated

with a capped regimen up to 1.5 mg TDS. Also it is interesting to note that while riociguat plasma concentrations were significantly correlated with reductions in haemodynamic parameters and increases in cardiac index, there was no correlation between change in 6MWD and riociguat AUC. It was also found that the rate of hypotension, a major adverse effect of riociguat, was dose dependent. This leads to questioning whether there may be no additional benefit in titrating beyond 1.5 mg TDS. Unfortunately, the capped regimen was an exploratory arm with a small sample size and no formal statistical comparisons were undertaken between dose groups. Therefore, a definite conclusion regarding efficacy of one regimen over another is not possible. Given that the proposed dosage is based on an individual's haemodynamic response and the safety profile of the 2.5 mg regimen was acceptable, the evaluator believes it may be reasonable to allow dosage up to 2.5 mg with strong wording on hypotension risks and when not to continue dose escalation or when to down titrate. Nevertheless, the sponsor has been asked to discuss the rationale for the decision not to pursue the lower maximum dose.

A question has also been raised regarding the timing of hypotension events to assess the risk during titration compared to during maintenance therapy. Given the results of this enquiry, further wording regarding hypotension risk may need to be included in the PI. In addition, the sponsor has also been asked to justify the 1.0 mg starting dose for titration. Given the known variability in SBP measurement, it could be prudent to start all patients at lower dose of 0.5 mg TDS and then titrate slowly.

Overall, the safety profile of riociguat was acceptable. The number of subjects with long term data are sufficient particularly given the condition's rarity; 376 for at least 48 weeks which included 221 with PAH and 97 with CTEPH from the two pivotal trials. These data will still need to be supplemented by ongoing active surveillance as outlined in the RMP. There was no formal assessment of survival nonetheless it was encouraging to see lower rates of death in the riociguat treated patients in both Phase III trials. In addition, the rates of SAEs and adverse event related treatment discontinuation were low and not notably greater than in the placebo groups.

Hypotension was a significant adverse event and is a direct consequence of riociguat's mode of action. Most events were not serious, did not result in treatment discontinuation. Furthermore, there was no increased risk of syncope. Nevertheless, this major risk of hypotension needs to be made more prominent in the PI and the evaluator recommends severe hypotension (SBP <90 mmHg) is added as a contraindication. In addition, due to the lack of clinical data in patients with severe proven or suspected coronary artery disease and the contraindication nitrates due to the drug interaction, the evaluator recommends that the use of riociguat in patients with coronary artery disease who require nitrates also be specified as a contraindication.

Haemoptysis and pulmonary haemorrhage were identified major risks and the precaution in the draft PI clearly states that the treating physician *should regularly assess the benefit–risk with each individual patient*. The sponsor has also adequately outlined the risk of unmasking pulmonary venous occlusive disease with discontinuation of treatment if the diagnosis is considered.

The data also indicated a signal for renal failure, with a higher risk of SAEs of renal failure, whether it be from hypotensive effects or perhaps a direct renal effect. Monitoring of renal function is recommended and this has been requested to be included in the PI. Likewise due to the risk of bleeding events and the signal of higher anaemia rates in the riociguat treated patients, monitoring of haemoglobin is also recommended for inclusion in PI.

Patients with hepatic and renal impairment are at risk of adverse effects due to the increased exposure. The precautions in patients with severe renal impairment or on dialysis, as well as in those with severe hepatic impairment, need to be made more prominent in the PI. Furthermore, the statements regarding similar exposure between

healthy controls and subjects with mild hepatic impairment in the PI are incorrect and need altering together with dosage instructions for this population. Dosage instructions for patients with renal impairment are adequate.

Pharmacokinetic studies showed a number of drug interactions which have been adequately outlined in the proposed PI. A major interaction with nitrates was seen during the interaction study with nitroglycerine and so this combination is contraindicated. The small study assessing coadministration with the phosphodiesterase-5 inhibitors (sildenafil 20 mg TDS) found no efficacy benefit and a higher risk of treatment discontinuation and death in the extension study. Therefore, PDE inhibitors should not be used with riociguat and the evaluator recommends this be added as a contraindication.

Reproductive toxicity has been noted in nonclinical studies and riociguat is also secreted in breast milk. Currently the draft PI only contraindicates riociguat in pregnancy and the evaluator recommends that lactation should be added to the contraindications. Importantly, it is recommended to implement an active risk minimisation strategy to ensure there is no foetal exposure in women taking riociguat. This should include pregnancy testing prior to treatment initiation and at regular intervals in women of child-bearing potential.

The potential paediatric risk due to the nonclinical bone findings has been stated in the PI and the risk management plan should monitor any potential off-label paediatric use as well as any skeletal defects. The labelling is clear on the indicated population however the evaluator recommends close monitoring of off-label use in other PH populations as part of the RMP. It is noted that the RMP proposes a registry for all PH patients treated with riociguat and this should allow close safety surveillance.

In summary, pulmonary hypertension is a rare, progressive and ultimately fatal disease although rate of progression may be variable. For patients with PAH there are few treatment options, while for patients with CTEPH many may not be surgical candidates or have persistent PH postsurgery. These are conditions in which there is an evident unmet medical need. The development program for riociguat found a safety profile with some significant risks (such as haemoptysis and hypotension), nonetheless these risks were outweighed by the robust and clinically meaningful efficacy results and the high need for further treatments in this potentially fatal condition. Given this, the evaluator finds the benefit-risk balance of riociguat given the proposed usage, is favourable. This is subject to the sponsor addressing the recommended changes to the PI, the questions (see below) and adoption of the proposed changes to the indication.

First round recommendation regarding authorisation

The evaluator finds the benefit-risk balance of riociguat in the treatment of PAH and CTEPH to be positive and recommends authorisation subject to:

- Alteration of the indication (see below).
- Adoption of changes to the draft PI and Consumer Medicine Information (CMI).
- Satisfactory responses to the clinical questions (see below).
- Inclusion in the RMP of the additional risks for postmarketing surveillance.

A proposed revised indication is:

Chronic thromboembolic pulmonary hypertension (CTEPH, WHO Group 4):

Adempas is indicated for the treatment of adult patients with

- *inoperable CTEPH,*
- *persistent or recurrent CTEPH after surgical treatment*

classified as WHO functional class II and III to improve exercise capacity.

Pulmonary arterial hypertension (PAH, WHO Group 1):

Adempas is indicated for the treatment of adult patients with PAH classified as WHO functional class II and III to improve exercise capacity.

Efficacy in PAH was shown in patients on riociguat monotherapy or in combination with endothelin receptor antagonists or prostanoids.

Studies establishing effectiveness in PAH predominately included patients with aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease.

Clinical questions

Pharmacokinetics

Nil.

Pharmacodynamics

Nil.

Efficacy

1. The efficacy of the capped dose regimen (1.0 to 1.5 mg) appeared to be comparable to the proposed regimen for registration (1.0 to 2.5 mg) in the PATENT-1 study. In line with good therapeutic practice of prescribing the lowest efficacious dose, discuss why this lower dose has not been examined further and any benefits of using the higher dose over the lower dose.

Safety

2. In the Phase III program, describe when the hypotension events occur in relation to treatment commencement or titration and during maintenance therapy. Describe any risk of hypotension events in subjects who have already tolerated a given dose. Given these data, discuss if any specific warnings should be included in the product information which would alert physicians to the risk of hypotension at any time rather than just during dose titration.
3. Was there a greater risk of hypotension in patients with lower SBP at commencement of treatment? Should this be included in the product information? Discuss.
4. Given the known variability in SBP measurement, it could be prudent to start dose titration for all patients at the lower dose of 0.5 mg TDS and titrate slowly. Discuss this proposal and justify the choice of 1.0 mg over 0.5 mg as a starting dose for titration.
5. Given the results from Study 15096, discuss why concomitant use of PDE-5 inhibitors is listed as a precaution and not a contraindication. Does the sponsor believer there is a clinical place for concomitant administration of riociguat with a PDE-5 inhibitor?

Second round evaluation of clinical data submitted in response to questions

The sponsor submitted a response to the questions posed.

A summary of the sponsor's response and the evaluator's comments on the sponsor's response are shown for each question below.

Efficacy

Question 1

Sponsor's response

Based on data from CHEST and PATENT studies, riociguat is safe and efficacious using the individual dose titration (IDT) to 2.5 mg TDS. The sponsor acknowledges that the capped titration (CT) arm (to 1.5 mg TDS) was comparable to IDT on the 6MWD but *considers that no definitive judgment on the efficacy of the CT arm can be made due its exploratory nature and relatively small sample size*. The capped dose group was included at FDA request but the study was not designed to assess the benefit risk of this regimen.

With the similar results on the 6MWD in PATENT-1 between IDT and CT groups, the FDA and EMA requested post-hoc comparisons of the riociguat capped titration versus placebo. The sponsor stated that *nominally statistically significant differences favouring riociguat CT versus placebo included 6MWD (p<0.0001), PVR (p<0.0001), NT-proBNP (p<0.0001), and LPH (p<0.0001). However, nominal statistical significance was not observed for WHO functional class (p=0.0674), time to clinical worsening (p=0.3939), Borg CR 10 (p=0.1068), and EQ-5D (p=0.0914).* The mean change from baseline in PVR was -8.9, -223.3, and -167.8 dyn*second*cm-5 and for CO was -0.01, 0.93, and0.42 L/min in the placebo, riociguat IDT, and riociguat CT groups, respectively. It was concluded that these haemodynamic data on PVR and CO *suggest a benefit from the increased dose in the riociguat IDT treatment group when compared to the riociguat CT.*

The data based on a post-hoc analysis from the added exploratory CT treatment arm with limited patient numbers support that 1.5 mg TDS is already an effective and safe dose in patients with PAH. If approved, there will be patients who would benefit from this dose. However, patients who can tolerate higher doses of riociguat may have an additional clinical benefit.

The sponsor also stated that *based on the primary endpoint 6MWD, at least 5 populations of PAH patients have been identified in the PATENT-1 study who may have benefited from the IDT regimen as compared to the CT regimen within the 12 weeks of double-blinded treatment (patients with connective tissue disease associated PAH, patients pretreated with ERAs, smokers, patients with a creatinine clearance ≥80 mL/min, and patients with a baseline 6 MWD ≥380 m)* (Figure 3). The latter 4 groups were associated with lower riociguat exposure (Figure 4).

Figure 3. Subgroup analyses for 6MWD by riociguat treatment–Study 12934 (PATENT-1)

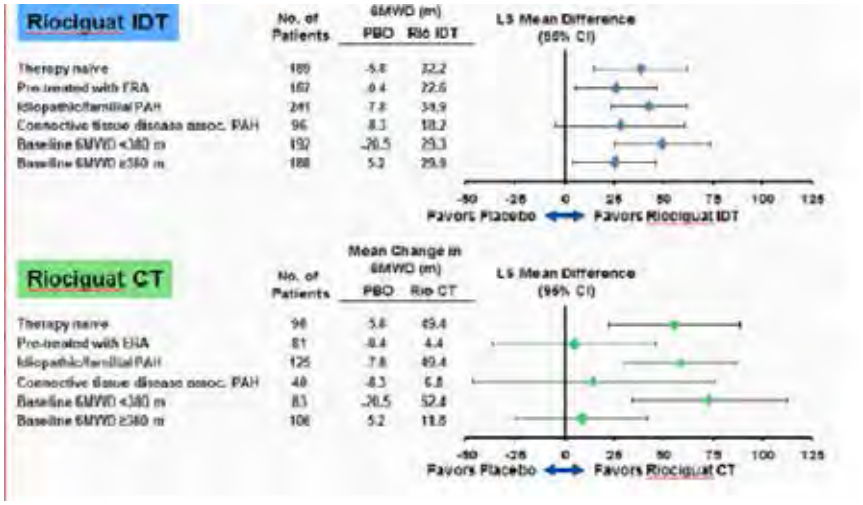
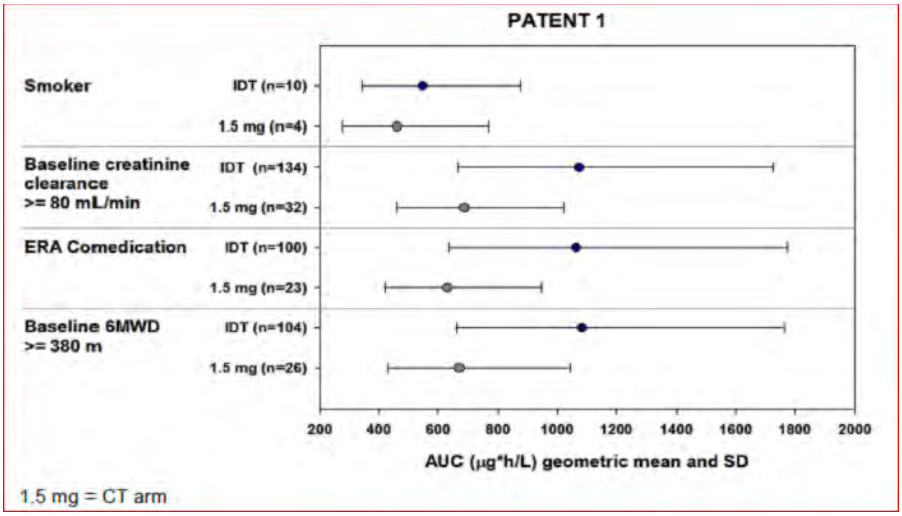


Figure 4. Comparison of riociguat exposure following CT and IDT administration in subgroups identified to have lower exposure – Study 12934 (PATENT-1)



The sponsor also states that longer term data are available with the IDT regimen while only 12 week data are available from PAH patients in PATENT-1 study with the 1.5 mg capped regimen. The dose escalation to 2.5 mg was well tolerated and *does not appear to be associated with incremental safety concerns. In the Sponsor's opinion, the robustness of the efficacy results for the CT dose arm is limited due to the small sample size and, in that light, should be seen as indicative of the riociguat 1.5 mg TDS dose being already effective.*

Evaluator's comments

The evaluator agrees that the data are *indicative of the riociguat 1.5 mg TDS dose being already effective* and acknowledges that there are possible benefits of the IDT regimen over the CT in some patient subgroups and on haemodynamic data for PVR and CO. Data on the CT regimen are limited by sample size, short treatment duration and exploratory post hoc analyses and as such cannot form the basis for dosing recommendations. Given that the proposed dosage is an individual titration regimen and is based on haemodynamic tolerability, the evaluator concludes that a regimen up to 2.5 mg is acceptable.

Safety

Question 2

Sponsor's response

Hypotension data were presented for hypotension reported as an adverse event (AE), hypotension as recorded by blood pressure measurements (that is, SBP <90 mmHg), and hypotension as combined for both.

Overall, treatment-emergent hypotension adverse events were reported in 10.0% (49/490) of patients in the riociguat group and 3.7% (8/214) in the placebo group during the double-blind phase of the phase 3 studies CHEST-1 and PATENT-1. The sponsor claims that during the double-blind phase of the Phase III studies CHEST-1 and PATENT-1, most hypotension AEs occurred during the titration phase in both treatment groups (visits 1 to 4, maintenance dose from visit 5) (Table 11).

Table 11. Number and incidences of subject with treatment emergent hypotension (documented as AE) by dose level and time interval in the main studies. All pivotal studies (safety analysis set)

Visit Interval / Dose	Visit 1 - Visit 2	Visit 2 - Visit 3	Visit 3 - Visit 4	Visit 4 - Visit 5	Visit 5 - Visit 6	Visit 6 - Visit 7
0.5 mg		0/ 9 (0.0%)	0/ 7 (0.0%)	0/ 4 (0.0%)	0/ 4 (0.0%)	0/ 1 (0.0%)
1.0 mg	17/ 490 (3.5%)	0/ 41 (0.0%)	0/ 22 (0.0%)	0/ 15 (0.0%)	1/ 16 (6.3%)	0/ 6 (0.0%)
1.5 mg		9/ 428 (2.1%)	2/ 95 (2.1%)	0/ 80 (0.0%)	0/ 78 (0.0%)	0/ 11 (0.0%)
2.0 mg			7/ 349 (2.0%)	1/ 44 (2.3%)	0/ 55 (0.0%)	0/ 20 (0.0%)
2.5 mg				4/ 323 (1.2%)	10/ 307 (3.3%)	1/ 123 (0.8%)
Placebo	2/ 214 (0.9%)	1/ 208 (0.5%)	1/ 204 (0.5%)	1/ 201 (0.5%)	0/ 200 (0.0%)	3/ 84 (3.6%)
Total Verum	17/ 490 (3.5%)	9/ 478 (1.9%)	9/ 473 (1.9%)	5/ 466 (1.1%)	11/ 460 (2.4%)	1/ 161 (0.6%)

Note: Events were identified by Project Bayer MedDRA Query 'Hypotension'.
Note: The time of the first dose of the new visit was relevant for the assignment of adverse events to the visit interval and dose group
Note: Interval visit 6 - visit 7 exists in study chest 1 only
/by-sasp/patdb/ia/632521/stat/2013/04_ae_dose_time/pgms/t-adae-visit.sas ae01 evzrx 08MAY2013 14:30
End of table

Comment: The evaluator has noted that the rate of hypotension AEs in all riociguat treated patients during the titration periods ranged from 3.5% at Visit 1 to 2 to 1.1% at Visit 4 to 5. At the Visit 5-6 period (post-titration), the hypotension rate was still 2.4% overall and the rates by dose level were 3.3% in the 2.5 mg, 6.3% in the 1.0 mg and 0% in the other groups.

In the double blind part of the CHEST-1 and PATENT-1 studies, the rate of treatment emergent hypotension was 42.7 versus 14.9 per 100 person-years in the riociguat and placebo groups, respectively and decreased to 7.1 events in the long term extension studies.

The rate of SBP <90 mmHg was 17.8% (87/490) and 9.8% (21/214) in the riociguat and placebo groups, respectively, in the Phase III studies CHEST-1 and PATENT-1. It was more frequent between Visit 1 and 2 (7.3%) but still occurred at subsequent periods (2.9% to 6.3%) (Table 12). The rate during double blind treatment (124.0 versus 71.0 events per 100 p-y) decreased during the long term extension studies (49.5 events per 100 p-y). The combined rate of hypotension AEs and low SBP was 138 versus 80 events per 100 patient-years (p-y) in the riociguat and placebo groups respectively and 53.5 events per 100 p-y in the long term studies.

Table 12. Number and incidences of subject with treatment emergent hypotension (SBP <90 mmHg) by dose level and time interval in the main studies. All pivotal studies (safety analysis set)

Visit Interval / Dose	Visit 1 - Visit 2	Visit 2 - Visit 3	Visit 3 - Visit 4	Visit 4 - Visit 5	Visit 5 - Visit 6	Visit 6 - Visit 7
0.5 mg		0/ 9 (0.0%)	0/ 7 (0.0%)	0/ 4 (0.0%)	0/ 4 (0.0%)	0/ 1 (0.0%)
1.0 mg	36/ 490 (7.3%)	3/ 41 (7.3%)	7/ 22 (31.8%)	2/ 15 (13.3%)	3/ 16 (18.8%)	1/ 6 (16.7%)
1.5 mg		11/ 428 (2.6%)	3/ 95 (3.2%)	1/ 80 (1.3%)	3/ 78 (3.8%)	1/ 11 (9.1%)
2.0 mg			12/ 349 (3.4%)	4/ 44 (9.1%)	5/ 55 (9.1%)	1/ 20 (5.0%)
2.5 mg				12/ 323 (3.7%)	18/ 307 (5.9%)	4/ 123 (3.3%)
Placebo	8/ 214 (3.7%)	4/ 208 (1.9%)	4/ 204 (2.0%)	8/ 201 (4.0%)	5/ 200 (2.5%)	2/ 84 (2.4%)
Total Verum	36/ 490 (7.3%)	14/ 478 (2.9%)	22/ 473 (4.7%)	19/ 466 (4.1%)	29/ 460 (6.3%)	7/ 161 (4.3%)

Note: Events were identified by low systolic blood pressure (<90 mmHg).
Note: The time of the first dose of the new visit was relevant for the assignment of adverse events to the visit interval and dose group
Note: Interval visit 6 - visit 7 exists in study chest 1 only

Kaplan Meier plots for the time to first hypotension event (AE or SBP <90 mmHg) in the pivotal studies show fewer events in the maintenance period (Figures 5 and 6).

Figure 5. Kaplan Meier plot for time to first hypotension after start of study drug (Adverse event or systolic blood pressure <90 mmHg) in pooled CHEST-1 and PATENT-1 (Main phase, Safety analysis set)

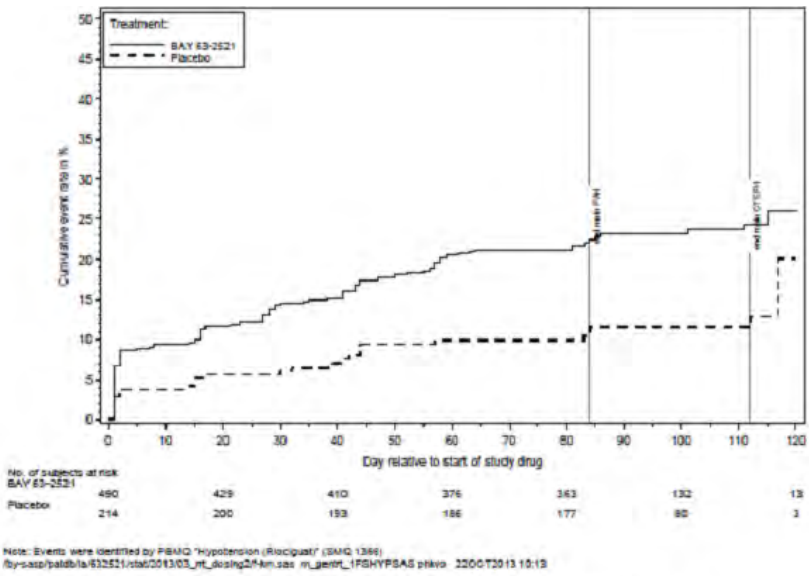


Figure Note: The end of double blind treatment is indicated by the vertical lines.

Figure 6. Kaplan Meier plot for time to first hypotension after start of study drug (Adverse event or systolic blood pressure <90 mmHg) in pooled CHEST-1 and PATENT-1 (Main and Extension phases, Safety analysis set)

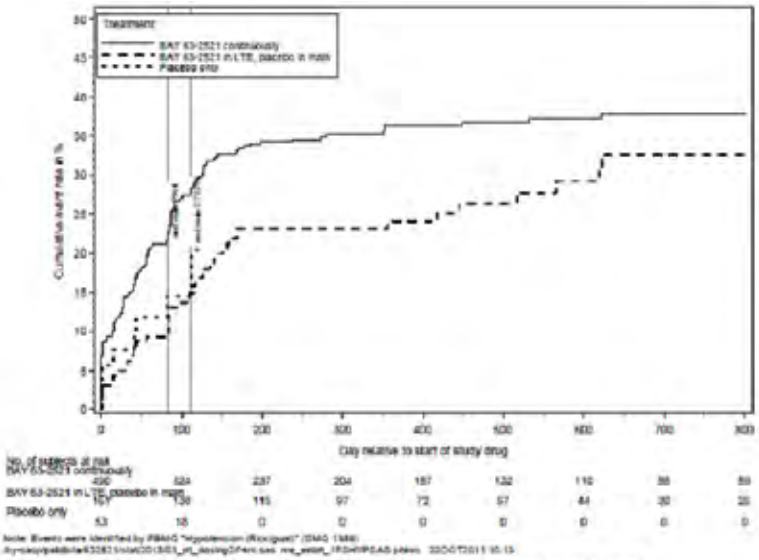


Figure Note: The end of double blind treatment is indicated by the vertical lines.

The sponsor concludes that the *low incidence of hypotension after the titration period (including the blinded sham titration of 8 weeks in PATENT-2 and CHEST-2) demonstrates the good long term tolerability that has been also observed in patients in phase 2 (Study 12166) covering treatment periods of more than 4 years. Based on the study data no other specific warnings for hypotension need to be included at any time other than just during dose titration*.

Evaluator's comments

The evaluator agrees that the risk of hypotension is greater during titration than during maintenance therapy but does not agree that the risk is such that it does not warrant warning physicians. It is recommended that specific wording is included in the *Precaution*

section relating to hypotension to state that while the risk of hypotension is greater during titration it may occur during maintenance therapy. It should also state that physicians should consider a dose reduction if patient develops signs or symptoms of hypotension.

Question 3

Sponsor's response

The analysis of hypotension events by baseline systolic blood pressure showed an increased risk of hypotension with lower levels of baseline systolic blood pressure. Patients with a systolic blood pressure of <95 mmHg at baseline should have been excluded from the study according to the protocol (Table 13). The sponsor states that *the design of the study led to an increased rate of reported events of hypotension. The vast majority of hypotension events were not assessed as SAEs, did not lead to discontinuation of treatment, were transient and most events occurred at initiation of therapy or at titration. Thus, the Applicant is of the opinion that this information does not need to be included in the product information.*

Table 13. Number of subjects with treatment emergent hypotension (documented as AE or SBP <90 mmHg) by systolic blood pressure at baseline (categories) by primary system organ class. All pivotal studies (safety analysis set)

MedDRA primary system organ class	All riociguat (double-blind studies) n (%)	All placebo (double-blind studies) n (%)	All riociguat (long-term extension treatment) n (%)
	Systolic blood pressure at baseline: <95 mmHg		
	N=2 (100%)	N=0 (100%)	N=2 (100%)
Any Event	2 (100%)	0	1 (50%)
Investigations	2 (100%)	0	1 (50%)
Vascular	0	0	0
	Systolic blood pressure at baseline: 95 to < 105 mmHg		
	N=113 (100%)	N=42 (100%)	N=127 (100%)
Any Event	43 (38.1%)	12 (28.6%)	54 (42.5%)
Investigations	32 (28.3%)	11 (26.2%)	49 (38.6%)
Vascular	14 (12.4%)	1 (2.4%)	12 (9.4%)
	Systolic blood pressure at baseline: 105 to < 115 mmHg		
	N=145 (100%)	N=63 (100%)	N=171 (100%)
Any Event	30 (20.7%)	7 (11.1%)	53 (31.0%)
Investigations	22 (15.2%)	5 (7.9%)	44 (25.7%)
Vascular	9 (6.2%)	3 (4.8%)	13 (7.6%)
	Systolic blood pressure at baseline: 115 to < 125 mmHg		
	N=102 (100%)	N=42 (100%)	N=114 (100%)
Any Event	15 (14.7%)	6 (14.3%)	18 (15.8%)
Investigations	7 (6.9%)	4 (9.5%)	16 (14.0%)
Vascular	9 (7.8%)	2 (4.8%)	3 (2.6%)
	Systolic blood pressure at baseline: ≥125 mmHg		
	N=128 (100%)	N=67 (100%)	N=143 (100%)
Any Event	24 (18.8%)	1 (1.5%)	14 (9.8%)
Investigations	13 (10.2%)	1 (1.5%)	4 (2.8%)
Vascular	13 (10.2%)	0	11 (7.7%)

Evaluator's comment

Hypotension risk is greater in those with low SBP (95-115 mmHg) at baseline (Table 13). For this reason the evaluator recommends including wording in the *Dosage and Administration* section of the PI along the lines of that included in the US label: *For patients who may not tolerate the hypotensive effect of Adempas, consider a starting dose of 0.5 mg taken three times a day.*

Question 4

Sponsor's response

The sponsor stated *that the clinical study program did not test the 0.5 mg TDS dose of riociguat. In the phase 3 studies, only four patients received a reduced the dose to 0.5 mg riociguat TDS after starting with 1.0 mg riociguat TDS…. Data from the phase 3 studies by titration step show that most events of hypotension (reported as AE) are more linked to onset of new treatment and dose change rather than to the actual received dose. As the Applicant has no data using a starting dose of 0.5 mg riociguat TDS in patients with CTEPH or PAH, the*

Applicant cannot make a recommendation for the lower dose and there are only hypothetical reasons that might suggest to start with a lower dose.

Evaluator's comments

The evaluator accepts the development program was structured around a starting dose of 1.0 mg. Nevertheless, as a safety precaution it is recommended that a lower starting dose is considered for those who may be at risk of hypotension. The following wording is suggested for inclusion in the *Dosage and Administration* section of the PI (as per the US label):

For patients who may not tolerate the hypotensive effect of Adempas, consider a starting dose of 0.5 mg taken three times a day.

Question 5

Sponsor's response

The sponsor proposed to change the PI and contraindicate concomitant use with PDE-5 inhibitors. The details of these changes are beyond the scope of this AusPAR.

Evaluator's comments

These changes are acceptable.

Second round benefit-risk assessment

Second round assessment of benefits

After evaluation of the data provided in response to the first round of evaluation, the assessment of benefits of riociguat in the proposed usage remain unchanged.

Second round assessment of risks

After evaluation of the data provided in response to the first round of evaluation, the assessment of risks of riociguat in the proposed usage remain unchanged.

Second round assessment of benefit-risk balance

In the second round evaluation, clinical data in relation to dosage and hypotensive effects were reviewed. In particular, assessment of the capped titration regimen (to 1.5 mg TDS) over the individual dose titration regimen (to 2.5 mg TDS) was undertaken. These data on the capped regimen indicated an efficacy effect, however were limited by the small sample size and exploratory nature of the assessment which resulted in an inability to formally draw conclusions. As the dosage regimen proposed is tailored to the individual's response, the evaluator concludes that it is acceptable for this regimen up to 2.5 mg TDS to be used.

Data on hypotension risks during maintenance therapy, while less prominent than during dose titration, demonstrated an ongoing risk. Therefore, it is recommended specific wording on this is added to the *Precaution* section of the PI relating to hypotension. The risk of hypotension was higher in those with lower SBP at baseline and a lower starting dose could be considered in this group or any patient the physician may feel is at risk of hypotension. Relevant changes to the *Dosage and Administration* section have been proposed which are along the lines of that approved in the US.

The sponsor did not provide any situations where it believed there would be a clinical place for concomitant use of riociguat with a PDE-5 inhibitor and given the notable safety risks has agreed to make such concomitant use a contraindication rather than a precaution.

In summary, after the second round of evaluation of data submitted in response to questions, the evaluator finds that the benefit-risk balance of riociguat given the proposed usage remains favourable. This is subject to the sponsor addressing the recommended changes to the PI and adoption of the proposed changes to the indication.

Second round recommendation regarding authorisation

The evaluator finds the benefit-risk balance of riociguat in the treatment of PAH and CTEPH to be positive and recommends authorisation subject to:

- Alteration of the indication (see below).
- Adoption of changes to the draft PI and CMI.
- Inclusion in the RMP of the additional risks for postmarketing surveillance.
- A proposed revised indication is:

  Chronic thromboembolic pulmonary hypertension (CTEPH, WHO Group 4):

  Adempas is indicated for the treatment of adult patients with

  – *inoperable CTEPH,*

  – *persistent or recurrent CTEPH after surgical treatment*

  classified as WHO functional class II and III to improve exercise capacity.

  Pulmonary arterial hypertension (PAH, WHO Group 1):

  Adempas is indicated for the treatment of adult patients with PAH classified as WHO functional class II and III to improve exercise capacity.

  Efficacy in PAH was shown in patients on riociguat monotherapy or in combination with endothelin receptor antagonists or prostanoids.

  Studies establishing effectiveness in PAH predominately included patients with aetiologies of idiopathic or heritable PAH or PAH associated with connective tissue disease.

V. Pharmacovigilance findings

Risk management plan

The sponsor submitted a Risk Management Plan (RMP) Adempas EU-RMP version 1.0 dated 18 January 2013 (data lock point 2 November 2012) with an Australian specific Annex version 1.0 dated 20 March 2013 which was reviewed by the TGA's Office of Product Review (OPR).

Safety specification

The sponsor provided a summary of ongoing safety concerns which are shown at Table 14.

Table 14. Summary of ongoing safety concerns

Summary of safety concerns	
Important identified risks	Hypotension Upper gastrointestinal motility disorders Unmasking of pulmonary venous occlusive disease
Important potential risks	Serious haemoptysis/pulmonary haemorrhage Embryo–fetal toxicity
Important drug interactions	Concomitant treatment with organic nitrates Concomitant treatment with a phosphodiesterase-5 inhibitor Concomitant treatment with strong multi-pathway cytochrome P450 (CYP) and P-glycoprotein (P-gp)/ breast cancer resistance protein (BCRP) inhibitors Concomitant treatment with strong CYP1A1 inhibitors and strong P-gp/BCRP inhibitors
Important missing information	Patients with systolic blood pressure < 95 mmHg at baseline Patients with severe hepatic impairment (Child–Pugh C) Patients with creatinine clearance < 15 mL/min or on dialysis Pregnancy and lactation Patients aged < 18 years Long-term safety in clinical practice

Pharmacovigilance plan

The following is a summary of the pharmacovigilance activities proposed in the EU RMP and Australian Specific Annex (ASA).

For the identified risks (hypotension, upper gastrointestinal motility disorders and unmasking of pulmonary venous occlusive disease) the sponsor proposes routine pharmacovigilance.

For the important potential risks, important drug interactions, important missing information the sponsor proposes routine pharmacovigilance as well as **EXP**osur**E** Registry **R**iocigua**T** in patients with pulmonary hypertension (EXPERT).

Risk minimisation activities

The sponsor proposes routine risk minimisation activities for all the safety concerns identified. The ASA proposes no additional risk minimisation activities for Australia. The sponsor also stated '*References to specific sections of the European Summary of Product Characteristics do not apply but equivalent label wording pertaining to important identified and potential risks, important drug interactions and important missing information are included in appropriate sections of the proposed Australian Product Information'*.

Reconciliation of issues outlined in the RMP report

The text below summarises the OPR's first round evaluation of the RMP (*Recommendation*), the sponsor's responses to recommendations raised by the OPR and the OPR's evaluation of the sponsor's responses.

Recommendation 1

It was recommended that the common adverse reaction of 'peripheral oedema' is listed as 'important identified risk' as the sponsor stated that it occurs in 'above 10% of patients on Adempas'.

Sponsor's response

The rationale for not including 'peripheral oedema' as an 'important identified risk' in the Risk Management Plan (RMP) is based on relevant EU Guidelines and riociguat clinical data.

The riociguat EU RMP is written according to guidance given in module V of the EMA Guideline on good pharmacovigilance practices: Module V - Risk management systems (EMA/838713/2011, June 2012). This document includes guidance on when an identified risk should be considered as an 'important' risk. The sponsor specifically referred to the following relevant sections of this guideline; *GVP Module V section B.B. 1 and GVP Module V V.B.8.7.3. RMP module SVII section "Details of important identified and potential risks from clinical development and post-authorisation experience*".

As observed by the TGA, peripheral oedema was one of the most frequently observed adverse events in the riociguat clinical trials. This is to be expected in a pulmonary hypertension population, in which oedema also belongs to the physical signs of the clinical presentation of the underlying disease. In the pooled placebo controlled data from the PATENT and CHEST trials, peripheral oedema was observed in 17.3% of patients treated with riociguat compared to 15.0% of patients on placebo (PH-37089). Notably, none of the observed peripheral oedema events was serious or led to treatment discontinuation (PH-37089, A62508, A62510). As peripheral oedema was more frequently seen under treatment compared to placebo, the sponsor decided to include peripheral oedema in the Product Information (PI) as an adverse drug reaction in the Adverse Effects section but not in the Precaution section. Due to the relatively small difference compared to placebo and the non-serious nature of the observations, both the public health impact as well as the impact on individual patients is considered to be low. Therefore the sponsor does not consider this as an 'important identified risk' in the context of the EU RMP, although it is a common listed reaction in the proposed PI.

Although the TGA has not formally adopted the EU Guideline on good pharmacovigilance practices: Module V - Risk management systems (EMA/838713/2011, June 2012), they have indicated that an RMP submitted in this format is acceptable. In addition, there are no local or regional considerations that necessitate altering the Safety Specification specifically for Australia. For these reasons, the sponsor respectfully requests that the TGA approve the riociguat RMP with the Safety Specification remaining harmonised with the EU RMP.

OPR evaluator's comment

The TGA accepts and encourages submission of EU-RMPs accompanied by the Australian Specific Annex.

However, the rationale provided for not including 'peripheral oedema' in the RMP is not satisfactory. The sponsor pointed out in their response that '*oedema also belongs to the physical signs of the clinical presentation of the underlying disease'.* This does not mean oedema associated with treatment is less important and could be dismissed. On the contrary, increased chance of peripheral oedema in the treatment group (as identified through clinical trials) is more concerning as this could be potentially seen as a sign of worsening condition. Although the sponsor has decided not to include 'peripheral oedema' under 'precaution' or 'contraindication', it is a clinically important risk especially for patients with the proposed indications.

The OPR evaluator is aware that the EU-RMP submitted was prepared primarily for the EU regulators. Therefore, it is recommended that 'peripheral oedema' be included as an 'important risk' in the ASA until sufficient clinical evidence can prove otherwise.

Recommendation 2

The summary table of proposed pharmacovigilance plan does not include any ongoing or completed studies. It is noted that there are six ongoing additional pharmacovigilance activities including PATENT-2, CHEST-2, study 12166, Study 14308, Study 12916 and Study 16097. The sponsor should include these studies in the summary table of the pharmacovigilance plan.

Sponsor's response

The submitted EU Risk Management Plan (RMP) was prepared in accordance with the Guideline on good pharmacovigilance practices: Module V – Risk management systems (EMA/838713/2011, June 2012). Compared with the original EU guideline on RMP, guidance on pharmacovigilance activities is now given in greater detail. As per the requirement stated in the current version of the EU guideline on RMP, section V.B.9.4 RMP part III section "Summary table of additional pharmacovigilance activities", pharmacovigilance activity should be categorised into the following areas:

1. Imposed obligations in the meaning of Art. 10/10a and 21a/22a included as a condition of the MA
2. Specific Obligations in the framework of a MA under exceptional circumstances. These studies will also be reflected in Annex II to the marketing authorisation (or national equivalent)
3. Required to investigate a safety concern in the RMP or to evaluate the effectiveness of risk minimisation activities
4. Other studies conducted by the marketing authorisation holder (MAH) which may provide safety information but are not considered to be of significant importance in investigating a safety concern or the effectiveness of risk minimisation activities

The six ongoing additional pharmacovigilance activities as cited by the evaluator are listed in section 4.4 of the riociguat EU RMP Details of Outstanding Additional Pharmacovigilance Activities.

These activities include long-term extensions to PAH and CTEPH clinical trials (Nos 1-3), studies in other indications (Nos 4-5) and an expanded access program (No 6). They were not designed to observe a specific risk or a new (for example, broader 'real life') population within the indications CTEPH and PAH. It is therefore considered to be unlikely, that important new information beyond the knowledge already described in the safety specification regarding identified/potential risks or missing populations will be identified from these activities.

Based on the categorisation outlined in the EU RMP guideline, the sponsor considers Category 4 is the most appropriate in describing the nature of these activities. As recommended in the EU RMP guideline, an RMP template provided by the EU regulatory Agency should be utilised for the preparation of RMP. The relevant template for this section of the RMP is 'Guidance on format of risk-management plan in the European Union part III: Pharmacovigilance plan'. The guidance given for *Summary of the Pharmacovigilance Plan* states that the table of ongoing and planned additional PhV studies/activities in the Pharmacovigilance plan should be a complete overview of all on-going and planned studies in Categories 1 to 3. Thus Table 5.1 in the section Summary of the Pharmacovigilance Plan of the EU RMP does not include the six on-going additional pharmacovigilance activities which are classified as Category 4.

Although the TGA has not formally adopted the EU Guideline on good pharmacovigilance practices: Module V - Risk management systems (EMA/838713/2011, June 2012), they have indicated that an RMP submitted in this format is acceptable. In addition, there are no local or regional considerations that necessitate altering the Pharmacovigilance plan specifically for Australia. For these reasons, the sponsor respectfully requests that the TGA approve the riociguat RMP with the Pharmacovigilance plan remaining harmonised with the EU-RMP.

OPR evaluator's comment

The sponsor's response is acceptable. It is noted that Table 5.3 setting out all the forthcoming studies and the anticipated dates for their submission in Australia has been included in the ASA version 2.

Recommendation 3

The sponsor states that the EXPERT registry will be a 'global' registry and 'the data collected... will be applicable to Australia'. The sponsor should confirm that pending the approval by the TGA, Australian patients will be included in the registry. The sponsor should also clarify what it plans to do in case its applications to overseas regulatory agencies such as the ones in the EU, the US are rejected or deferred.

Sponsor's response

The EXPERT registry is an international, multi center, prospective, uncontrolled, non-interventional study of patients who have been prescribed riociguat according to the approved product label. Patients will be followed up for an observation period of 1 up to 4 years (recruitment period 3 years) or until 30 days after end of riociguat treatment. Patient data will be collected every three to six months according to local clinical practice. Serious adverse events will be followed up adequately until they are resolved.

The current planned timing for the EXPERT registry is presented in Section 4.3 of the EU Risk Management Plan. Since this is a non-interventional study, commencement is dependent on product approval. Consequently, if applications to overseas regulatory agencies such as the ones in the EU or the US are rejected or deferred, this could have a significant impact on feasibility and or timing of the EXPERT registry. However, applications for registration of riociguat tablets in the US and Canada have already been approved and rejection or significant deferral of currently on-going evaluations are not foreseen at this time.

The EXPERT registry will enrol up to 900 patients worldwide. Since enrolling and completing the study in a timely manner is a priority, enrollment will be managed on a 'first come first served' basis. However, significant commercial use of riociguat in Australia will be limited until reimbursement on the Pharmaceutical Benefits Scheme (PBS), which could affect the feasibility of including Australian patients in the EXPERT registry.

The sponsor has an intention to include Australian patients in the EXPERT registry although it is not possible to give a definite commitment at this time.

OPR evaluator's comment

The evaluator noted the sponsor's plan for the EXPERT registry. It is recommended that if the submission to register riociguat is rejected or deferred in the EU, an alternative Australian registry be implemented.

In addition, the sponsor should ensure that the EXPERT registry includes off-label use of the product including use in patients less than 18 years old and concomitant use with PDE5 inhibitors.

The planned sample size of 900 patients for the EXPERT registry may not be sufficiently powered to detect rare and very rare serious adverse events. The sponsor should

undertake to follow up and report serious adverse events in the Periodic Safety update Reports (PSURs).

Recommendation 4

It is noted that the EXPERT registry is not included as an additional pharmacovigilance activity for the 'identified risks'. The evaluator recommends that adverse event reports on the identified risks to be recorded and reported in the same way as other safety concerns through the registry.

Sponsor's response

Bayer provides an assurance that all adverse event reports from the EXPERT registry will be recorded, reported and evaluated, including adverse events associated with identified risks.

The rationale not to explicitly mention EXPERT in the context of the pharmacovigilance plan for hypotension, upper GI motility disorders and unmasking of pulmonary veno-occlusive disease (PVOD) was that there seem to be no areas requiring confirmation regarding these typical vasodilatory effects, so routine pharmacovigilance was considered an appropriate measure. No 'additional' pharmacovigilance (that is, EXPERT registry) activity was therefore formally implemented for these risks besides routine pharmacovigilance.

OPR evaluator's comment

The sponsor's response is satisfactory. It should be noted that additional pharmacovigilance activities are often employed for 'identified risks' including class effects to further characterise, rather than 'confirming', the scale and severity of safety risks for using a new product in a new patient population at a new dosage.

Recommendation 5

The evaluator recommends that the sponsor uses a free-call number for the EXPERT registry to encourage reporting of adverse events and include it in the PI and Consumer Medicine Information (CMI).

Sponsor's response

Bayer agrees to include a free-call number in the PI and CMI to encourage the reporting of adverse events.

If Australia participates in the EXPERT registry, assurance is provided that a free-call number will be available to encourage reporting of adverse events.

OPR evaluator's comment

The sponsor's response is satisfactory.

Recommendation 6

As embryo-foetal toxicity is an important potential risk and pregnancy is a contraindication, the sponsor should provide details on how it plans to record, follow up, assess and report cases of exposure (intentional or unintentional) to riociguat during pregnancy.

Sponsor's response

According to standard procedure, if any employee of Bayer becomes aware that a patient has been exposed to a Bayer product during pregnancy, they must contact local Bayer Pharmacovigilance (PV) to report the case. The internal pharmacovigilance database is used for capturing all data for transmission of pregnancy cases to Global PV. Pregnancy Report Forms A and B (see attached) are sent out as soon as possible and are used to capture all relevant information for inclusion in the internal pharmacovigilance database.

Pregnancy Report Form A is used to capture the details of the pregnancy. Pregnancy Report Form B is used to capture the details of the foetal and maternal outcome.

Follow-up requests for pregnancy reports related to drugs with embryo-fetal toxicity potential, such as riociguat, must be sent 3, 6 and 9 months after the initial receipt date, preferably to the treating gynaecologist. Follow-up will be stopped after delivery, when sufficient data on the whole period of pregnancy and on the fetus /infant are available. Follow-up may also be stopped if sufficient information on outcome of pregnancy is available earlier (for example, due to interruption or premature delivery), or no relevant additional data can be obtained despite request. The Global Case Evaluator is responsible for initiating the follow-up process with Local Pharmacovigilance (PV) and to track the resolution of the follow-up request.

Global PV assess all pregnancy cases and provide a comprehensive evaluation as part of the PBRER (Periodic Benefit Risk Evaluation Report). Reporting to the TGA will be conducted in accordance with the applicable TGA guidelines.

OPR evaluator's comment

The sponsor's response is satisfactory.

Recommendation 7

The sponsor should provide a table summarising the safety specification, pharmacovigilance plan and planned risk minimisation measures in Australian context in the ASA. Wording pertaining to important safety concerns in the proposed Australian PI and CMI should be included in the table.

Sponsor's response

The sponsor agrees to include a table summarising the safety specification, pharmacovigilance plan and planned risk minimisation measures in Australian context in the ASA. Wording pertaining to important safety concerns in the proposed Australian PI and CMI will be included in the table.

OPR evaluator's comment

The sponsor's response is satisfactory. It is noted that the summary tables have been included in the updated ASA version 2.

Recommendation 8

Five patients were reported for taking overdose erroneously and received total daily dose 9 to 25 mg (maximum planned total daily dose was 7.5 mg) for periods of 2 to 32 days in Study 12166. Analysis of causes of the errors revealed confusion about the dose regimen. Considering the planned number of patients to be treated in this Phase II study is expected to be 75 and the treatment duration is 12 weeks, the scale of the error is notable. The sponsor should provide programs to educate patients, prescribers and pharmacists to minimise occurrence of medication errors.

Sponsor's response

Bayer agrees with the TGA that the number of medication errors in Study 12166 is notable and deserving of due consideration when assessing risk minimisation for potential medication errors with riociguat tablets. However, the sponsor considers that the issues related to medication errors in Study 12166 are unlikely to be encountered in the commercial setting because:

- There are significant differences in the test product used in Study 12166 compared with the final product proposed for commercial use

- Commercial product presentation and packaging for riociguat is designed to reduce the number of options the patient has in taking their medication, thus increasing the likelihood of them taking the correct action
- In Australia, the likelihood of medication errors with agents like riociguat is further reduced as a result of restrictions on prescribing mandated by reimbursement criteria imposed under Section 100 of the National Health Act 1953.

Consequently, Bayer does not anticipate that additional education beyond what would be undertaken with any new product will be required in order to prevent medication errors with riociguat. Nevertheless, the sponsor will monitor the situation and, if necessary, revise this position should this be warranted due to experience in the post-marketing period, or based on feedback from the Australian Adempas Advisory Board of specialist physicians assembled by Bayer to provide the sponsor with local expert advice in relation to pulmonary hypertension.

OPR evaluator's comment

The sponsor has provided practical measures in reducing the risk of medication errors.

However, there is a risk of providing the 2 week titration pack as a sample pack by specialists directly. This could undermine its intended purpose and result in missed opportunities for effective patient education by pharmacists. It is recommended that additional patient education material be used to raise patient awareness of potential adverse events.

Recommendation 9

The proposed CMI contains the following advice: *'Do not stop taking your medicine or lower the dose without checking with your doctor. If you stop taking it suddenly, your condition may worsen.'* It is recommended to the Delegate that the draft product information document be revised to include advice on how dosage should be gradually reduced before stopping treatment.

The sponsor's response to this recommendation was considered to be satisfactory.

It is recommended to the Delegate that relevant text in the CMI should be changed to: *'Do not stop taking your medicine or lower the dose without checking with your doctor. If you stop taking it, your condition may worsen.'*

Summary of recommendations

It is considered that the sponsor's response to the TGA request for further information has adequately addressed most of the issues identified in the RMP evaluation report. Outstanding issues are detailed below.

Outstanding issues

Issues in relation to the RMP

Details on the following outstanding issues are detailed above under '*Reconciliation of issues outlined in the RMP report*'.

Recommendation 1:

The TGA accepts and encourages submission of EU RMPs accompanied by the Australian Specific Annex.

However, the rationale provided for not including 'peripheral oedema' in the RMP is not satisfactory. The sponsor pointed out that '*oedema also belongs to the physical signs of the clinical presentation of the underlying disease'.* This does not mean oedema associated with treatment is less important and could be dismissed. On the contrary, increased chance of

peripheral oedema in the treatment group (as identified through clinical trials) is more concerning as this could be potentially seen as a sign of worsening condition. Although the sponsor has decided not to include 'peripheral oedema' under '*Precaution'* or '*Contraindication'*, it is still a clinically important risk especially for patients with the proposed indications.

The OPR evaluator is aware that the EU RMP submitted was prepared primarily for the EU regulators. Therefore, it is recommended that 'peripheral oedema' be added as an 'important risk' in the ASA until sufficient clinical evidence can prove otherwise.

Recommendation 3:

The evaluator noted the sponsor's plan for the EXPERT registry. It is recommended that if the submission to register riociguat is rejected or deferred in the EU, an alternative Australian registry be implemented.

In addition, the sponsor should ensure that the EXPERT registry includes off-label use of the product including use in patients less than 18 years old and concomitant use with phosphodiesterase 5 (PDE5) inhibitors.

The planned sample size of 900 patients for the EXPERT registry may not be sufficiently powered to detect rare and very rare serious adverse events. The sponsor should undertake to follow up and report serious adverse events in the Periodic Safety update Reports (PSURs).

Recommendation 8:

The sponsor has provided practical measures in reducing the risk of medication errors. However, there is a risk in providing the 2 week titration pack as a sample pack by specialists directly to patients. This could undermine its intended purpose and result in missed opportunities for effective patient education by pharmacists. It is recommended that additional patient education material be used to raise patient awareness of potential adverse events.

Recommendation 9:

The sponsor's response is satisfactory.

It is recommended to the Delegate that relevant text in the CMI should be changed to: *'Do not stop taking your medicine or lower the dose without checking with your doctor. If you stop taking it, your condition may worsen.'*

It is noted that the indication of CTEPH is for use in a poorly defined population where a large number of patients, especially elderly, could potentially use riociguat with other drugs such as anticoagulants. It is recommended that the Delegate considers whether it would be necessary to more clearly define the treatment criteria in the PI for CTEPH.

Further, the dosage advice in the PI referring to 'TDS' should be changed to 'TDS' to align with Australian practice.

Advice from the Advisory Committee on the Safety of Medicines (ACSOM)

A copy of the advice from the ACSOM is to be provided in a separate document when it becomes available.

Suggested wording for conditions of registration

RMP

Implement RMP version1.0, dated 18 January 2013 (data lock point 2 November 2012), with Australian-specific Annex version 2, dated 25 October 2013, any future updates as a condition of registration.

VI. Overall conclusion and risk/benefit assessment

The submission was summarised in the following Delegate's overview and recommendations:

Quality

The quality evaluator has recommended approval for riociguat.

The proposed tablets are immediate release, non-scored and film coated. The tablets remained unchanged throughout the clinical development program except for tablet colour. The proposed shelf life is 36 months.

The absolute bioavailability is high at 94% and no relevant differences were found between the tablet and an oral solution. A high fat meal decreased C_{max} by 25% and AUC by 15% in one study and in another food effect study it showed a delay in T_{max} from 1 h fasted to 4 h fed and a reduction in C_{max} of 35% with bioequivalence not maintained (lower limit at 57.8% which is below the standard 80% limit) but bioequivalence was seen for AUC (82 to 95%). A reduction in the metabolite was also seen. The sponsor has claimed in the PI that food does not affect the AUC or C_{max} to a clinically relevant extent and that riociguat can be taken with or without food. This is probably reasonable given that the effect of riociguat is probably related more to the AUC which maintained bioequivalence when taken with food and that pulmonary hypertension requires daily dosing and is not an acute condition.

Nonclinical

The nonclinical evaluator has no objections to the registration of riociguat. The quality of the dossier was good and the program extensive for an orphan drug. Overall exposure to the drug in the repeat dose studies was low due to the toxicity of riociguat.

Riociguat relaxes vascular smooth muscle, lowers arterial blood pressure, increases heart rate and reduces pulmonary arterial pressures. There were no effects on ECG parameters, no QT interval prolongation, no notable effects on CNS or respiratory function. It has an active metabolite that is 10 fold less potent and produced by CYP 1A1, 2C8, 2J2, 3A4, 3A5 and 3A7 with CYP 1A1 (highly inducible in the lungs of smokers) being an important contributor in the lungs and liver. Riociguat inhibits CYP 1A1. Riociguat inhibits human phosphodiesterase 7B but has no effect on nine other phosphodiesterases. Both riociguat and its metabolite are substrates for PgP and BCRP and therefore inhibition of these substrates might increase riociguat's exposure.

Target organs for toxicity are cardiovascular, gastrointestinal and skeletal systems. Riociguat is unlikely to be mutagenic, clastogenic or carcinogenic. Reproductive toxicity was seen with reduced fetal body weight (incomplete ossification) and increased cardiac malformations in rats whilst in rabbits it caused increased abortion and complete resorption of some litters.

The proposed pregnancy classification is Category D which is supported by the nonclinical assessment. No significant effects on male or female fertility were seen in animals. It was positive for phototoxicity *in vitro* but negative *in vivo*.

Clinical

The clinical evaluator has recommended approval for riociguat with a revised indication to add specific WHO functional classes II-III for CTEPH, remove endpoint claims on improving WHO functional class and delaying clinical worsening and only allow the claim

of improving exercise capacity, for both CTEPH and PAH, as this was the primary endpoint of the studies.

Pharmacology

The pharmacology studies noted the following findings:

T_{max} is 45 min, the half-life ($t_{1/2}$) is 6.8 h in healthy subjects and 10 to 12 h in patients, absolute bioavailability is 94%, clearance (Cl) is 3 to 6L/hr.

Pharmacokinetics are linear, volume of distribution (Vd) is 31 to 43 L, 20% of drug is distributed into blood, 95% plasma protein bound, CYP 1A1, 2C8, 2J2, 3A4 were mainly involved in metabolism with 1A1 (inducible in smokers) involved in the liver and lung, the major active metabolite is a 1/3 to 1/10 less potent.

Excretion is via metabolism and unchanged active drug with 33 to 46% in urine and 48 to 61% in faeces.

Inter individual variability is high, for example, $t_{1/2}$ is 77% and AUC is 90%.

Impaired hepatic function: AUC unbound exposure increased 60% in Child Pugh A and 88% in Child Pugh B subjects.

Impaired renal function: total AUC exposure increased for riociguat and metabolite by 98% in mild, 129% in moderate and 72% in severe renal impairment but results were highly variable and often overlapped with controls.

There was a 40% increase in AUC in elderly subjects.

Drug interaction studies showed: omeprazole decreased riociguat AUC by 26%, antacids decreased riociguat AUC by 34%, ketoconazole increased riociguat AUC by 150%, clarithromycin increased riociguat AUC by 41%, aspirin did not affect riociguat and midazolam and warfarin were not significantly affected by riociguat.

The population pharmacokinetic studies showed smoking increased clearance of riociguat, bosentan led to a decrease in riociguat concentrations by 27%, in non-smokers liver clearance accounted for 95% of total clearance whereas in smokers it was 81%, subjects 6 to 18 years old had comparable exposure to adults but below it varied depending on age.

Riociguat reduces pulmonary artery pressure, systolic blood pressure (-10mmHg at 14 days), pulmonary vascular resistance and systemic vascular resistance and increases heart rate (4 beats per minute (bpm) on 1mg with some large individual increases, for example 26 bpm on 2.5mg solution) and cardiac index. Reductions in systolic blood pressure (SBP), pulmonary vascular resistance and systemic vascular resistance (SVR) and increase in cardiac index were greater than with nitrous oxide.

Bone formation parameters were decreased and increases in urinary excretion of calcium, sodium, potassium and creatinine were seen.

Healthy subjects didn't tolerate riociguat and therefore a Thorough QT study[13] was not performed. QTcF in young and elderly females and elderly males was prolonged by >5 ms compared with placebo but the two pivotal trials did not identify any relevant changes in QT, QTcB and QTcF nor any events related to QT prolongation.

Glyceryl trinitrate given 8 h after riociguat still resulted in a greater reduction in systolic blood pressure than in a placebo group but not at 24 h.

[13] Since 2005, the FDA and European regulators have required that nearly all new molecular entities be evaluated in a Thorough QT (TQT) study to determine a drug's effect on the QT interval.[24] The TQT study serves to assess the potential arrhythmia liability of a drug.
<http://www.fda.gov/downloads/RegulatoryInformation/Guidances/UCM129357.pdf>

Patients on stable sildenafil showed a decrease in diastolic blood pressure (not systolic) and increased heart rate.

Warfarin's effect on prothrombin time and aspirin's effect on bleeding time were not affected by riociguat.

The minimum effective dose was 1 mg and the maximum tolerated dose was 2.5 mg with PK steady state at 3 days and pharmacodynamic (PD) steady state at 10 to 14 days thus leading to a 2 week titration period for the clinical studies.

Efficacy

Pulmonary arterial hypertension

Study 12934 (PATENT-1):

This was a Phase III, multi-centre, multi-national, randomised, double blind, placebo controlled, parallel group study of 1, 1.5, 2 or 2.5mg three times a day (TDS) riociguat versus placebo in 445 subjects (91% completion, 14% major protocol violations) with symptomatic PAH for 12 weeks. Patients were either treatment naive (48%) or pre-treated with ERAs (44.5%) or prostacyclin analogues (7.9%) and remained at stable doses throughout but intravenous prostacyclin analogues (for example, epoprostenol), phosphodiesterase inhibitors and nitric oxide donors (for example, nitrates) were not allowed. Patients were up-titrated every 2 weeks based on systolic blood pressure from the starting dose of 1mg TDS in steps of 0.5mg TDS to a maximum 2.5mg TDS if tolerated. There was also an exploratory group in which the dose was capped at 1.5mg TDS. Patients from PAH WHO Group 1 (1.1 to 1.3.3 and 1.3.5) of the Venice classification (Table 15), that is, idiopathic, familial, collagen vascular disease, corrected congenital heart disease, portal hypertension, anorexigen or amphetamine use but not patients with other PAH types. Baseline demographic characteristics and concomitant medications were comparable between groups (80% female, 63% White, mean age 51 years) as to was haemodynamics (mean PVR 791 versus 834dyn*s*cm^{-5}, mean PAP 47 versus 49 mmHg) but there were some slight imbalances in disease characteristics for riociguat versus placebo (idiopathic PAH (59 versus 67%), familial PAH (2.8 versus 0.8%), collagen vascular disease (28 versus 20%), congenital heart disease (5.9 versus 9.5%), portal hypertension (4.3 versus 1.6%) and anorexigens/amphetamines (0.4 versus 1.6%), WHO FC II (43 versus 48%), WHO FC III (55 versus 46%), WHO FC IV (0.4 versus 2.4%)). At the end of treatment, 75% of subjects were on the maximum dose of 2.5mg TDS (95% on 1.5mg TDS in the capped dose group). The study had 90% power to detect a 25m difference in the 6 minute walk distance (6MWD) and the secondary endpoints were assessed in sequential order. The capped dosing regimen was only analysed descriptively. The mean baseline 6MWD was 361m on riociguat versus 368m on placebo.

Table 15. Venice classification (2003) for Pulmonary Hypertension: Simonneau G et al: Clinical Classification of Pulmonary Hypertension; JACC Vol 43, No. 12 Suppl S, June 16, 2004:5S-12S

1. Pulmonary arterial hypertension (PAH)
   1.1. **Idiopathic** (IPAH)
   1.2. Familial (FPAH)
   1.3. Associated with (APAH):
      1.3.1. Collagen vascular disease
      1.3.2. Congenital systemic-to-pulmonary shunts**
      1.3.3. Portal hypertension
      1.3.4. HIV infection
      1.3.5. Drugs and toxins
      1.3.6. **Other** (thyroid disorders, glycogen storage disease, Gaucher disease, hereditary hemorrhagic telangiectasia, hemoglobinopathies, myeloproliferative disorders, splenectomy)
   1.4. **Associated with significant venous or capillary involvement**
      1.4.1. Pulmonary veno-occlusive disease (PVOD)
      1.4.2. Pulmonary capillary hemangiomatosis (PCH)
   1.5. Persistent pulmonary hypertension of the newborn
2. Pulmonary hypertension with left heart disease
   2.1. Left-sided atrial or ventricular heart disease
   2.2. Left-sided valvular heart disease
3. Pulmonary hypertension associated with lung diseases and/or hypoxemia
   3.1. Chronic obstructive pulmonary disease
   3.2. Interstitial lung disease
   3.3. Sleep-disordered breathing
   3.4. Alveolar hypoventilation disorders
   3.5. Chronic exposure to high altitude
   3.6. Developmental abnormalities
4. Pulmonary hypertension due to chronic thrombotic and/or embolic disease
   4.1. Thromboembolic obstruction of proximal pulmonary arteries
   4.2. Thromboembolic obstruction of distal pulmonary arteries
   4.3. Non-thrombotic pulmonary embolism (tumor, parasites, foreign material)
5. **Miscellaneous**
   Sarcoidosis, histiocytosis X, lymphangiomatosis, compression of pulmonary vessels (adenopathy, tumor, fibrosing mediastinitis)

The primary efficacy endpoint of change in 6MWD at 12 weeks, using an Intention-to-Treat (ITT) analysis, showed a change of +29.6m on riociguat versus -5.6m on placebo (+31.1m on the capped dose group), difference of 35.8m, 95% CI 20.1-51.5, p<0.0001. The per protocol results were consistent with the above ITT population. Subgroup analyses showed consistency with the overall population for treatment naive and pretreated subjects (38 versus 36m) and female versus male (37 versus 31m) but differences for other parameters such as idiopathic/familial versus connective tissue versus other PAH (43 versus 28 versus 18m), baseline WHO functional Class I/II versus III/IV (12 versus 60m), <65 year olds (yo) versus ≥65 yo (27 versus 55m) and North America versus Europe versus Asia Pacific (4 versus 46 versus 41m). Secondary efficacy endpoints for riociguat versus placebo showed statistically significant results for changes in pulmonary vascular resistance (-223 versus -8.9dyn*s*cm^{-5}), NT-proBNP (-198 versus +232pg/mL), WHO functional class (minus one class in 21 versus 14%), any clinical worsening (1.2 versus 6.3%) and Borg scale[14] but not for EQ-5D[15] and Living with Pulmonary Hypertension questionaries.

[14] In medicine this is used to document the patient's exertion during a test.
[15] EQ-5D™ is a standardised instrument for use as a measure of health outcome. Applicable to a wide range of health conditions and treatments, the EQ-5D health questionnaire provides a descriptive profile and a single index value for health status.

Study 15096:

This was a Phase IIb, multicentre, randomised, double blind, placebo controlled 12 week study of riociguat (1 to 2.5 mg TDS) on stable sildenafil (20 mg TDS) in 18 symptomatic PAH patients for 12 weeks. The primary endpoint was the effect on blood pressure. The study was imbalanced at baseline but did not appear to indicate an additive effect of riociguat in decreasing systolic blood pressure, however in the extension study there were some deaths with one possibly related and discontinuations due to AEs that led the sponsor to not recommend the combination.

Study 12935 (PATENT-2):

This was an open label, long term uncontrolled extension study in which all patients were titrated up on riociguat. There were 363 patients in the interim analysis with discontinuations due to adverse events (7.2%) and deaths (3.9%). The mean change in 6MWD from the start of PATENT-1 to the end of PATENT-2 (that is, 24 weeks) was 52.5m on riociguat full dose. The unadjusted mean change from baseline was 48.4m at 12 months and 47.3m at 18 months. An improvement in WHO functional class at Week 12 was reported in 30.4% and deterioration in 4.4% whereas at 18 months it was 38% and 9% respectively.

Study 12166 extension:

This extension study of the dose finding study 12166, in 68 patients with PAH or CTEPH and WHO functional class II-IV for a mean 36.5 months suggested a maintenance of the 6MWD seen from the primary study but meaningful conclusions could not be confirmed due to differing subject numbers and discontinuations.

Chronic thromboembolic pulmonary hypertension

Study 11348 (CHEST-1):

This was a Phase III, multi-centre, multi-national, randomised, double blind, placebo controlled, parallel group study of 1, 1.5, 2 or 2.5mg TDS riociguat versus placebo in 262 subjects (93% completion, 17% major protocol violations) with CTEPH (inoperable or recurrent or persistent pulmonary hypertension after surgical treatment) for 16 weeks. Patients were either treatment naive or ceased PH treatments >30 days prior to right heart catheterisation. Prostacyclin analogues, phosphodiesterase inhibitors, endothelin receptor antagonist (ERAs) and nitric oxide donors were not allowed during the study. Patients were up-titrated every 2 weeks based on systolic blood pressure from the starting dose of 1 mg TDS in steps of 0.5 mg TDS to a maximum 2.5 mg TDS if tolerated. Patients from CTEPH subgroups 4.1 and 4.2 were included. Non-specific PH treatments were allowed but anticoagulants had to have started at least 90 days beforehand. Baseline demographic characteristics were comparable between groups (68% female, 69% White, mean age 59 years) as to was haemodynamics (mean PVR 790 versus 779dyn*s*cm^{-5}) and disease characteristics for riociguat versus placebo: inoperable CTEPH (70 versus 77%), postoperative CTEPH (30 versus 23%), WHO FC II (32 versus 28%), WHO FC III (62 versus 68%), WHO FC IV (4.6 versus 2.3%). Drugs for acid disorders were higher on riociguat (24 versus 15%) and antithrombotics higher on placebo (51 versus 60%). New oral anticoagulant use was also higher on placebo (25 versus 38%). At the end of treatment, 77% of subjects were on the maximum dose of 2.5mg TDS. The study had 90% power to detect a 30m difference in the 6 minute walk distance (6MWD) and the secondary endpoints were assessed in sequential order. The mean baseline 6MWD was 342m on riociguat versus 356m on placebo.

The primary efficacy endpoint of change in 6MWD at 16 weeks, using an ITT analysis, showed a change of +38.9m on riociguat versus -5.5m on placebo, difference of 45.7m, 95% CI 24.7-66.6, p<0.0001. The per-protocol results were consistent with the above ITT population. Subgroup analyses showed some differences with the overall population for

female versus male (54 versus 40m), inoperable versus postoperative (54 versus 27m), baseline WHO functional class I/II versus III/IV (25 versus 53m), <65 yo versus ≥65 yo (44 versus 49m) and North America versus Europe versus China versus Asia Pacific (19 versus 47 versus 102 versus 15m). Secondary efficacy endpoints for riociguat versus placebo showed statistically significant results for changes in pulmonary vascular resistance (-226 versus +23.1dyn*s*cm^{-5}), NT-proBNP (-291 versus +76pg/mL) and WHO functional class (minus one class in 31 versus 15%) but any clinical worsening, Borg scale, EQ-5D and Living with Pulmonary Hypertension questionaries were not significant.

Study 11349 (CHEST-2):

This was an open label, long term uncontrolled extension study in which all patients were titrated up on riociguat. There were 194 patients in the interim analysis with 6.2% prematurely discontinuing, mainly due to deaths (2.3% of original riociguat group and 3.2% of the original placebo group). The mean change in 6MWD from the start of CHEST-1 to the end of CHEST-2 (that is, 28 weeks) was 63.3m on original riociguat group. The unadjusted mean change from baseline for the total group was 47.6m at 12 months and 60.7m at 18 months. An improvement in WHO functional class at week 12 was reported in 39.9% and deterioration in 3.3% whereas at 18 months it was 50% and 3.1% respectively.

Other studies in different patient populations are discussed in the clinical evaluation (See Attachment 2).

Safety

In the PAH pivotal study, there were 317 subjects exposed to riociguat for a mean 81 days whilst in the long term extension study there were 363 subjects in total for a mean exposure of 436 days (221 for 48 weeks and 52 for 108 weeks). In the CTEPH pivotal study, there were 173 subjects exposed to riociguat for a mean 108 days whilst in the long term extension study there were 194 subjects in total for a mean exposure of 388 days (97 for 48 weeks and 39 for 96 weeks).

In PAH pivotal study, treatment emergent adverse events occurred on riociguat compared to placebo in 89.4% versus 85.7%, with most being mild or moderate and severe TEAEs highest on placebo (11 versus 15.1%). The most common were gastrointestinal (55.1% versus 37.3%), headache (27.2 versus 19.8%), dyspepsia (18.9 versus 7.9%), peripheral oedema (17.3 versus 11.1%), dizziness (15.7 versus 11.9%), hypotension (9.8 versus 2.4%), anaemia (8.3 versus 2.4%), pyrexia (3.1 versus 3.2%) and gastritis (1.6 versus 0%). In the extension study, dizziness occurred in 18.5%, peripheral oedema in 17.9%, headache 16.5%, cough 14.3%, diarrhoea 13.8%, nausea 12.4% and dyspepsia 10.5%. In CTEPH pivotal study, TEAEs occurred in 91.9 versus 86.4%, the rate of severe TEAEs were similar between groups, nervous system (49.1 versus 30.7%) and gastrointestinal (48 versus 30.7%) were the most common and the most common TEAEs were similar to the PAH study except for peripheral oedema which occurred in 15.6 versus 20.5%. In the extension study, severe TEAEs occurred in 17% with a similar profile to the PAH extension study. Adverse drug reactions had a similar profile to TEAEs except with the addition of palpitations.

Specific adverse events of interest for riociguat versus placebo are as follows:

1. Syncope: In PAH it was lower on riociguat (3.1 versus 5.6%) and 7.2% in the extension study. In CTEPH it was similar to placebo (3.5 versus 3.4%) and 6.2% in the extension.
2. Hypotension: In PAH it was highest on riociguat (10.2 versus 3.2%) with one withdrawal and 8% in the extension study with no withdrawals. In CTEPH it was also highest on riociguat (11.5 versus 4.5%) and 6.2% in the extension with no withdrawals. Serious hypotension occurred in 0.4 versus 0% in the pooled analysis of

pivotal trials. Hypotension was more frequent in those ≥ 65 years (16.4 versus 5.2%) and women versus men (10.3 versus 4.2%) and in the pooled extension studies systolic BP <90 mmHg was in 49.5 per 100 person-years. Hypotension also increased with decreased renal function.

3. Bleeding events (haemorrhage and anaemia): In PAH it was slightly higher on riociguat (12.2 versus 10.3%) with treatment emergent serious adverse events (TEAEs) occurring in 1.6%. In the extension study bleeding events occurred in 24.5% with most being epistaxis and haemoptysis. Half the subjects were on anticoagulants in the pivotal study and 62% were in the extension. In CTEPH, with 95% on anticoagulants, TEAEs due to bleeding occurred in 13.3 versus 11.4%, mostly haemoptysis and epistaxis. In the extension study the rate was 17.5% with 3 patients having gastrointestinal bleeding. The evaluator notes that the difference in bleeding events was driven by a higher rate of anaemia in the pooled analysis.
4. Gastrointestinal disorders: These were more common on riociguat (52 versus 33.6%) in the pooled pivotal studies and in the extension study, although remaining high, the discontinuation rate was very low (0.4%).
5. Renal function: In PAH, the rate of an increase in creatinine and low creatinine clearance were higher on riociguat but the rate for eGFR was not higher (7.9 versus 9.6%). In CTEPH, the rate of an increase in creatinine was similar to placebo and low creatinine clearance was also similar. Acute renal failure occurred in two riociguat patients in the pivotal PAH study and in four patients in the pivotal CTEPH study (one on placebo). Serious TEAEs of renal failure occurred in 1.3% of the pooled riociguat subjects compared to 0.3% of the pooled placebo subjects.

Deaths occurred in 1% on riociguat compared to 3.3% on placebo in the pooled analysis of the pivotal studies. In the pooled extension studies it was 4.1%. Frequent serious adverse events in the pooled pivotal studies were syncope (1.4 versus 3.7%), right ventricular failure (2.2 versus 1.9%) and haemoptysis (1 versus 0%). Atrial fibrillation appeared to be more frequent (1.64 versus 0 events per 100 person-years). The drug interaction study with sildenafil raised safety concerns (deaths and discontinuations) that concluded the combination should be avoided. Discontinuations due to adverse events occurred in the pooled pivotal analysis in 2.9% on riociguat versus 5.1% on placebo. Liver function tests showed changes more frequently on placebo in PAH or unremarkable in CTEPH with no Hy's law cases in either pivotal study. Low calcium was higher on riociguat (PAH: 20.5 versus 0%, CTEPH: 11.1 versus 0%). Anaemia was more frequent in the pivotal PAH study at 8.3% versus 2.4% (7.4% in the extension) and CTEPH study at 3.5% versus 1.1% (4.1% in the extension). Blood pressure reductions were higher on the higher dose range of riociguat in PAH than the capped dose range (mean 6.2-10.3 versus 1.5-6.4mmHg) with a mean decrease over the extension study at 5.6-9.5mmHg at each visit. Low systolic blood pressure was also seen in CTEPH patients.

Nonclinical findings regarding bone changes at the growth plate were examined in the pivotal studies using exploratory biomarkers, calcium and phosphate and showed no clinically significant changes except small increases in type I collagen C-telopeptides. Low calcium was reported in the pivotal studies. Musculoskeletal adverse events were similar to placebo.

Risk management plan

The Office of Product Review (OPR) has accepted the EU Risk Management Plan for Adempas (riociguat), version 1, dated 18 January 2013 (data lock point 2 November 2012), with the Australian Specific Annex (ASA), version 2, dated 25 October 2013.

The following were outstanding matters and should be followed up with OPR and in the Pre-ACPM Response:

- Peripheral oedema be added as an important potential risk in the RMP-ASA given that it is observed at a higher frequency on riociguat than placebo (PAH: 17.3 versus 11.1%).
- The EXPERT registry, or an alternative Australian registry if the EXPERT registry doesn't proceed, should be implemented and will analyse potential off-label use and patients less than 18 years old due to the non-clinical bone findings, and concomitant use with PDE5 inhibitors. The sponsor should confirm that the registry will include Australian patients.
- The following matters should be added to the list of important potential safety concerns in the RMP and updated in the pharmacovigilance plan and risk minimisation plan:
  - Renal failure, off-label use, anaemia and other bleeding risks apart from pulmonary haemorrhage / haemoptysis, skeletal effects and safety in patients with other cardiovascular disease.

The sponsor's response is acceptable in relation to the nonclinical evaluator's comments about the safety specification of the RMP.

Risk-benefit analysis

Efficacy

The efficacy of riociguat is based on two pivotal studies with two extension studies in PAH and CTEPH. The clinical development program for riociguat was broadly consistent with the adopted EU guidelines on pulmonary arterial hypertension except that the duration of studies were not sufficient to demonstrate an improvement in time to clinical worsening which usually requires a minimum of 6 months. There is no specific guideline for CTEPH but the sponsor discussed the development program with the EMA and FDA and agreed that the 6 minute walk distance would be acceptable as the primary endpoint (and in combination with clinical endpoints for PAH). The 6MWD result for PAH was statistically significant at a mean placebo subtracted treatment difference of 35.8m compared to placebo from a baseline of 361m which is about a 10% improvement; although small, this was not inconsistent with other treatments for PAH. The same endpoint for CTEPH patients showed a better result with a mean placebo subtracted treatment difference of 45.7m compared to placebo from a baseline of 342m. Subgroup analyses for PAH showed the result was consistent in treatment naive and pretreated subjects but better in older rather than younger patients, idiopathic PAH rather than other PAH types, WHO functional class III rather than II and those from Europe or Asia/Pacific rather than North America. Subgroup analyses for CTEPH showed a better result for inoperable patients than post-operative, WHO functional class III than II and Europe or China than North America. It is unclear why the result in North America was seen in both pivotal studies however this may be due to insufficient numbers. Secondary endpoints were mostly supportive in both PAH and CTEPH for pulmonary vascular resistance, WHO functional class change and NT-proBNP but only in PAH for time to clinical worsening. Improvements in quality of life were not significant in either pivotal study. The long term extension studies had a mean exposure greater than a year which appeared to indicate a maintenance of effect within the limitations of the data.

Dose

The pivotal PAH study showed an improvement in the 6MWD on the full dose regimen up to 2.5 mg TDS to be similar to the exploratory group on the capped dose regimen up to 1.5 mg TDS however this was an exploratory endpoint with no formal assessment. Patient numbers in this group were about a quarter of the full dose group and the pivotal study showed that at the end of treatment, 75% of subjects were on the maximum dose of 2.5 mg TDS. In CTEPH, 77% of patients were on the maximum dose of 2.5 mg TDS by study end. Although the capped dose regimen suggested a comparable result to the full dose regimen over 12 weeks, the majority of patients ended up on the maximum dose and longer term data on the full dose regimen is available. The higher dose regimen is however associated with a higher risk of hypotension but this has been addressed through the dosing instructions in the PI depending on the systolic blood pressure. At this stage, the capped dose regimen appears to require further investigation. Overall, the proposed dosage regimen appears reasonable given it is based on hemodynamic response and patients will be managed by a specialist.

Endpoint claims

The sponsor proposed an initial indication that has been modified by the clinical evaluator. The sponsor has requested endpoint claims in the indication for CTEPH (improve exercise capacity and improve WHO functional class) and PAH (improve exercise capacity, improve WHO functional class and delay clinical worsening) which the clinical evaluator disagreed except for the claim for exercise capacity. A delay in clinical worsening usually requires longer term data to confirm than in the pivotal studies. These other claims were secondary endpoints of the studies and therefore not appropriate for the indication. Exercise capacity was a primary endpoint and therefore supported by the evaluator for inclusion in the indication. However, it is recommended that the indication align with the format of the ERAs which are simpler and place all endpoint claims in the Clinical Trials section of the PI where they are better suited. ACPMs advice is requested on this matter.

Combination treatment for PAH

For PAH, the indication also includes which combination treatments can be used. No pharmacokinetic interaction studies were conducted but the pivotal study showed consistency with the overall population for treatment naive and pre-treated subjects (38 versus 36m) thus supporting the inclusion of ERAs and prostacyclin analogues into the indication. But given that intravenous prostacyclin analogues, that is, epoprostenol, were not allowed then the indication may need to exclude this subgroup. The safety profile from combination use versus therapy naive was similar except for combination ERA use versus therapy naive for anaemia, palpitations and gastrointestinal disorders. Combination use with PDE inhibitors should be avoided given the risks of death and discontinuations and the sponsor will contraindicate this combination. Use with nitrates or nitric oxide donors was not allowed in the studies and is also contraindicated.

WHO Group 1 (PAH) subgroups

For WHO Group 1, the sponsor has identified those subgroups who were represented in the pivotal study, as part of the indication. The wording approved in USA captures similar subtypes of PAH. The primary endpoint subgroup analysis showed a significant result for idiopathic/familial (42.8m placebo subtracted difference) and a borderline result for connective tissue disease (28.1m with the confidence interval crossing zero, 95% CI -4.4 to +60.62). Given the smaller population (28%), wide confidence interval and broadly consistent result with the overall primary endpoint (35.8m) then it would appear

reasonable to include this subgroup. Other subgroups were too small and combined had a result of 18m, 95% CI -32.5 to +69, which is unclear. It is recommended that the indication be re-presented to a similar style as per the format of the ERAs and list the subgroups that have sufficient data to support them. This would approve idiopathic (61%), heritable PAH (2%) and PAH associated with connective tissue diseases (25%). PAH associated with drugs and toxins (1%) and congenital heart disease (8%) and portal hypertension (3%) were small groups and the sponsor has not applied to include these in the indication but they will be listed in the Clinical Trials section of the PI. ACPMs advice is requested on the inclusion of certain subgroups.

CTEPH subgroups

For CTEPH, the sponsor has identified inoperable and postoperative subgroups in the indication. The inoperable subgroup (placebo subtracted treatment difference of 54m) was consistent with the primary endpoint result (placebo subtracted treatment difference of 45.7m) however the postoperative subgroup's result was 27m, 95% CI -9.7 to +63m. Although the confidence interval crossed zero, given the smaller population (30%), wide confidence interval and probably consistent result with the overall primary endpoint then it would appear reasonable to include this subgroup.

WHO functional class

This issue concerns those patients in WHO functional class IV for both CTEPH and PAH and for WHO functional classes II-III for CTEPH (the sponsor has already requested WHO functional classes II-III for PAH which represented 97.6% of patients). For CTEPH, the majority of patients had WHO functional classes II-III (93.6%) and the clinical evaluator has recommended this be added to the indication which is supported and consistent with PAH. For WHO functional class IV, the submitted data only included eight patients on riociguat in class IV with CTEPH and one patient on riociguat in class IV with PAH. Some other PAH treatments have been approved with classes II-IV. Despite the few patients in class IV in the dossier, this may be best left to clinical judgement on whether continuing treatment in this group is appropriate given that patients would be worsening if they reached class IV. ACPMs advice is requested on this matter.

Adults/paediatrics

The sponsor has only applied for adults in the indications and the pivotal trial only included adult patients. Nonclinical studies raised concerns about bone formation in adult rats and changes have been recommended for the RMP to look at off-label use, paediatric use and any safety signals in the proposed registry. The PI also includes a warning under *Paediatric Use*.

Safety and RMP

Riociguat had good exposure from the pivotal and extension studies with adverse events being mostly mild to moderate and severe events at a similar rate to placebo. TEAEs most frequent on riociguat were: headache, dyspepsia, peripheral oedema, dizziness, hypotension, anaemia, diarrhoea and vomiting. Bleeding was slightly higher, including serious bleeding events (mostly haemoptysis). Anaemia was also observed and monitoring of haemoglobin is supported. Hypotension remains a concern, especially in the elderly (16.4%, exposure is 40% higher) and in renal impairment and the sponsor has proposed dose adjustments during the up-titration phase based on systolic blood pressure. Hypotension occurred during titration (visit 1-2 was 3.5%) and also the pos-titration period (2.4%) and therefore warnings and a possible dose reduction are still required during maintenance treatment. Hypotension risk was greatest in those with a low systolic

BP at baseline (95-115 mmHg) therefore consideration should be given to a lower starting dose of 0.5 mg TDS. There appeared to be a signal for renal failure and renal monitoring is recommended. Potential bone findings are unclear. Use in pregnancy is a contraindication due to reproductive toxicity. Deaths were lower on riociguat, serious adverse events were similar to placebo in PAH and slightly higher in CTEPH and discontinuations due to adverse events were similar or lower than placebo. Patients with left ventricular systolic dysfunction had an increased risk of atrial fibrillation and cardiac failure. The changes discussed in the RMP section are supported given the safety findings from the clinical studies.

QT interval

There was a signal of QTcF prolongation (females 6-12 ms; males 5-6 ms) in a PK/PD study examining age with *in vitro* studies noting a minor effect on ventricular repolarisation. In dogs there were no adverse ECG findings. Healthy subjects did not tolerate riociguat and therefore a Thorough QT study was not performed. In a QT subset of the pivotal PAH study, the mean change from baseline in QTcB was 2 ms. In the overall PAH study there was no change from baseline >7 ms at any visit, no cases of QT interval increase of 60 ms and no QT prolongation associated events. Overall there may be a small change in QT interval but this did not appear to be associated with clinical effects.

Use in pregnancy

Riociguat demonstrated reproductive toxicity with reduced fetal body weight (incomplete ossification) and teratogenicity (cardiac malformations at 7 times clinical exposure) in rats with a no effect level of two times clinical exposure. In rabbits there was no teratogenicity observed however there was an increased rate of abortion and complete resorption of some litters. The proposed pregnancy classification is Category D with a contraindication which is supported by the nonclinical evaluation. In the US, riociguat is classified as Category X and has a boxed warning, along with additional statements throughout their PI that include negative pregnancy testing at commencement, monthly pregnancy testing, a one month washout period, risk to the fetus and use of types of contraception. The clinical evaluator has supported pregnancy testing prior to initiation of treatment and at regular intervals and also recommends use during lactation be contraindicated. The classification system for medicines in pregnancy is different between the US and Australia as indicated below and Category D medicines do not usually have a boxed warning in Australia. Given these differences then it is recommended that additional PI statements be considered but without a boxed warning. ACPMs advice is requested on this matter.

Descriptions of the pregnancy categories are as follows:

- Category D (Australia): Drugs which have caused, are suspected to have caused or may be expected to cause, an increased incidence of human fetal malformations or irreversible damage. These drugs may also have adverse pharmacological effects. Accompanying texts should be consulted for further details.
- Category X (Australia): Drugs which have such a high risk of causing permanent damage to the fetus that they should not be used in pregnancy or when there is the possibility of pregnancy.
- Category X (FDA): Studies in animals or humans have demonstrated fetal abnormalities and/or there is a positive evidence of human fetal risk based on adverse reaction data from investigational or marketing experience, and the risks involved in the use of the drug in pregnant women clearly outweigh the benefits.

Data deficiencies

There were very few patients with WHO Functional Class I or IV in both the CTEPH and PAH studies. There were few patients with PAH associated with drugs and toxins (1%) and congenital heart disease (8%) and portal hypertension (3%). There is also a lack of data in those <18 years of age, severe renal impairment or dialysis, significant hepatic disease and in combination with epoprostenol. There is a lack of data showing a reduction in mortality or to confirm an improvement in time to clinical worsening. No Thorough QT study was conducted. Patients with low blood pressure (<95 mmHg) at baseline were excluded from the pivotal studies.

Conditions of registration

The following are proposed as conditions of registration:

1. The implementation in Australia of the EU Risk Management Plan for Adempas (riociguat), version 1, dated 18 January 2013 (data lock point 2 November 2012), with the Australian Specific Annex, version 2, dated 25 October 2013 and Pre-ACPM Response, included with submission PM-2013-00307-1-3, and any subsequent revisions, as agreed with the TGA.

Questions for the sponsor

The sponsor is requested to address the following issues in the Pre-ACPM Response:

1. Please provide a breakdown of which combination prostanoids were used with riociguat for the PAH trial by route of administration, for example, inhaled?
2. Are further studies planned or underway for PAH associated with congenital heart disease?
3. Please address all the outstanding RMP matters as discussed above under Risk Management Plan.
4. Please comment on the explanation for the differences seen for the primary endpoint in PATENT-1 which showed a mean treatment difference from placebo of only 4m for patients in North America compared to Europe (46m) and Asia/Pacific (41m). Please also comment on the explanation for the differences seen in the primary endpoint in the different geographic regions for CHEST-1.

Discuss the clinical significance of the low calcium findings in the PAH and CTEPH studies with riociguat compared to no reports on placebo.

Delegate's considerations

The primary issues with this submission are as follows:

1. The wording of the indication and inclusion or not of endpoint claims for PAH and CTEPH.
2. Whether riociguat should be approved for WHO Functional Class II-III or II-IV for PAH and CTEPH.
3. The adequacy of the data for various subgroups of PAH (WHO Group 1).

Proposed action

The Delegate had no reason to say, at this time, that the application for Adempas should not be approved for registration.

The Delegate's suggested indication is as follows:

Pulmonary arterial hypertension

Adempas, as monotherapy or in combination with approved PAH treatments (endothelin receptor antagonists or inhaled or subcutaneous prostanoids), is indicated for the treatment of:

- *idiopathic pulmonary arterial hypertension*
- *heritable pulmonary arterial hypertension or*
- *pulmonary arterial hypertension associated with connective tissue diseases*

in adult patients with WHO functional class II, III or IV symptoms.

Chronic thromboembolic pulmonary hypertension

Adempas is indicated for the treatment of:

- *Persistent or recurrent chronic thromboembolic pulmonary hypertension (CTEPH, WHO Group 4) after surgical treatment or*
- *inoperable CTEPH*

in adult patients with WHO functional class II, III or IV symptoms

Delegate's request for ACPM advice

The committee is requested to provide advice on the following specific issues:

1. Whether the data is sufficient to support monotherapy and combination therapy with endothelin receptor antagonists (ERAs) or prostanoids (inhaled and subcutaneous and if it should include intravenous)?
2. Whether the indications for both PAH and CTEPH should include WHO Functional class IV and whether CTEPH should include classes II-III? For CTEPH, eight patients on riociguat were in class IV and for PAH, one patient on riociguat was in class IV.
3. Whether the wording of the indications for PAH and CTEPH should be modified in relation to endpoint claims (that is, improve exercise capacity, improve WHO functional class and delay clinical worsening [only for PAH]) and place this information in the Clinical Trials section of the PI instead?
4. Whether the indication for PAH should specify subgroups of WHO Group 1 similar to the format for the ERAs, whether it should include the connective tissue disease subgroup and whether CTEPH supports the inclusion of postoperative patients?
5. Whether the Use in Pregnancy section of the PI should include additional advice, similar to the US PI, given the Category D classification in pregnancy?

The committee is also requested to provide advice on any other issues that it thinks may be relevant to a decision on whether or not to approve this application.

Response from sponsor

Bayer Australia Ltd (the sponsor) responded to the Delegate's Request for ACPM Advice (dated 7 January 2013) concerning our Category 1 application to register Adempas (riociguat) as a new chemical entity for the treatment of Pulmonary Arterial Hypertension (PAH) and Chronic Thromboembolic Pulmonary Hypertension (CTEPH).

The clinical and nonclinical evaluators support the registration of riociguat 0.5, 1.0, 1.5, 2.0 and 2.5 mg film coated tablets for both indications proposed by the sponsor. The recommendation from the Delegate is supportive of the proposed indication which is suggested to be consistent with Endothelin Receptor Antagonists (ERAs) indications with

respect to format, based on the data presented. Taking into account the recommendation from the Delegate and clinical evidence generated thus far, the sponsor proposes the following indication wording for consideration:

Pulmonary arterial hypertension

Adempas, as monotherapy or in combination with approved PAH treatments (endothelin receptor antagonists or inhaled or subcutaneous prostanoids), is indicated for the treatment of:

- *idiopathic pulmonary arterial hypertension*
- *heritable pulmonary arterial hypertension*
- *pulmonary arterial hypertension associated with connective tissue diseases or*
- *pulmonary arterial hypertension associated with congenital heart disease*

in adult patients with WHO functional class II, lll or IV symptoms (see CLINICAL TRIALS, PRECAUTIONS)

Chronic thromboembolic pulmonary hypertension

Adempas is indicated for the treatment of:

- *Persistent or recurrent chronic thromboembolic pulmonary hypertension after surgical treatment or*
- *inoperable CTEPH*

in adult patients with WHO functional class II, lll or IV symptoms (see CLINICAL TRIALS, PRECAUTIONS)

Background

PAH is a disease of the small pulmonary arteries characterised by vascular narrowing, remodelling and increased pulmonary vascular resistance, which eventually leads to right ventricular failure and death. PAH can be classified into subgroups according to aetiology. The most common type of PAH are idiopathic/heritable PAH and PAH associated with connective tissue disease and congenital heart disease. They are grouped together as they share comparable clinical and haemodynamic profiles and virtually identical pathological changes of the lung microcirculation. Despite advances in medical therapy, patients with PAH still suffer from progression of their disease and have a limited life expectancy. Adempas demonstrated efficacy in PAH in both treatment naïve-patients and in patients pre-treated with PAH-specific therapies.

CTEPH is a disease characterised by mechanical obstruction of pulmonary arteries. The most important pathobiological process in CTEPH stems from non-resolution of acute embolic masses which later undergo fibrosis. The treatment of choice is surgical removal of thrombi by Pulmonary Endarterectomy (PEA). There is an unmet medical need for patients who are deemed inoperable and patients with persistent or recurrent CTEPH after surgical treatment. Clinical efficacy of PAH specific drugs has not yet been demonstrated in patients with CTEPH to date. Adempas is the first treatment to demonstrate efficacy in CTEPH with the ability to address the unmet needs in patients with inoperable CTEPH or CTEPH in patients with persistent or recurrent CTEPH after PEA/surgical treatment.

Both PAH and CTEPH are rare diseases. The estimated prevalence of PAH and CTEPH combined was less than 2000 cases in Australia. Due to the rarity of these diseases, an orphan designation was granted in 2012.

Upon submission of the draft PI at the presubmission phase, a question was raised whether the sponsor was applying for registration for all types of PAH, that is, all types of

WHO Group I or only the following types of PAH, that is, idiopathic or heritable PAH or PAH associated with connective tissue disease. The sponsor clarified that the proposed wording was not intended to limit the Indication by aetiology. Sub-group analysis of efficacy was conducted for the largest subgroups: idiopathic/heritable PAH and PAH due to connective tissue diseases (CTD). Since sub-group analysis was not conducted on PAH of other aetiology, it was thought appropriate to include a statement about PAH sub-groups in the Indication.

Comments from the delegate

1. Inclusion of WHO Functional Class IV in the indication wording

Assessment of functional and haemodynamic impairment is an important evaluation process of a patient with suspected pulmonary hypertension. WHO Functional Class (FC) is recognised as a predictor of survival in PAH where WHO FC IV marks the most severe stage of disease in the spectrum. Patients in this class are unable to carry out any physical activity without symptoms. These patients manifest signs of right heart failure. Dyspnoea and/or fatigue may even be present at rest. Discomfort is increased by any physical activity.

Although there are approved treatments for class IV patients with PAH, treatments are usually used in combination. Withdrawal of drugs in these fragile patients is usually avoided. Moreover, there is no approved medical treatment for patients with CTEPH.

Similar to ERAs which are approved to treat PAH class IV patients in Australia, there are limited data in patients treated with Adempas who present with WHO FC IV symptoms at baseline. In the riociguat studies, it was intended to treat patients in this class and to continue treating the patients who worsened to FC IV. The sponsor is fully supportive of the Delegate's view that it is best left to clinical judgement on continuing treatment in this group. The sponsor acknowledges the limited data there are in patients with WHO FC IV, thus the sponsor agrees to include a precautionary statement as proposed by the Delegate. In addition, reference to the *Clinical Trial* and *Precautions* sections is proposed for both indications to draw attention to the limited evidence in this patient group.

2. Endpoint claims

The intention for the inclusion of endpoint claims was to present the efficacy measures demonstrated unequivocally and to illustrate the effect of Adempas in patients with these diseases. However considering assessment from the Delegate, the sponsor accepts that exclusion of endpoint claims may improve simplicity and consequently, readability of the indication. The indication wording has been updated to remove endpoint claims.

3. Pulmonary Arterial Hypertension

As explained above, the proposed wording was not intended to limit the Indication by aetiology. The sponsor acknowledges the limited data there are on certain subgroups, however it was not the intention to limit treatment of PAH patients based on certain aetiology. As outlined in the study protocol, idiopathic and familial PAH, associated PAH due to connective tissue disease, congenital heart disease, portal hypertension with liver cirrhosis and anorexigen or amphetamine use were eligible PAH subgroups in PATENT, the pivotal study.

PAH is a rare disease and for that reason a large number of patients representing each distinct subgroup could not be included in the development program. The number of enrolled patients was sufficient to consistently demonstrate the benefits in therapy-naïve and pre-treated patients but sample sizes in some of the subgroups limits the robustness of single findings. The robustness of the analysed subgroups is based on the consistent beneficial outcomes in the Adempas treatment groups.

   a. PAH associated with congenital heart disease

CHD formed the third largest subgroup in the clinical study. Of the limited number of patients with PAH associated with congenital heart disease (7.9%), a placebo corrected treatment response of 41.1 m (95% CI -0.5 to 82.6) in the 6MWD was observed in a post-hoc analysis. Based on this observation, the sponsor is of the opinion that this is clinically relevant and, therefore, this subgroup should also be included in the indication section. There are currently no further studies planned for PAH associated with congenital heart disease.

b. Data sufficiency in supporting monotherapy and combination therapy

Based principally on the data from the PATENT-1 study, as well as taking into account the PATENT-2 study and the pooled analysis of the pivotal studies, together with the risk factors associated with these life threatening conditions, the sponsor is of the opinion that the benefit-risk ratio in patients with PAH treated with Adempas is positive in monotherapy as well as on combination therapy with ERAs or prostanoids.

Adempas is the first member of a novel class of compounds, the soluble guanylate cyclase stimulators. Efficacy is demonstrated over a broad range of efficacy variables (6MWD, PVR, WHO FC, NT-proBNP, TTCW, Borg) and in monotherapy and on background therapy with ERAs and prostanoids. This broad range of efficacy parameters was not yet seen with other compounds. The analysis of time to clinical worsening was statistically significant for the whole PAH population and consistently positive for patients receiving Adempas in monotherapy and combination therapy, further corroborating the use in both populations. This is further supported by the survival data of the study population, which is favourable, in light of recently published register data taking into account current drug treatment options.

The overall safety aspects do not suggest a particular safety concern; in monotherapy nor in combination therapy with ERAs or Prostanoids.

The profile of adverse events seen with Adempas as a drug with a different mode of action compared to currently approved drugs for treatment of pulmonary hypertension (ERAs, PDE5-inhibitors and prostacyclin analogues) does not present new unknown risks or risks treating physicians are not familiar with. The identified/potential important risks are known from other approved drugs. They are linked to the mode of action, are predictable and clinically manageable (with Adempas for example, by individual dose adaptation):

- Hypotension (known from the disease and from other PAH drugs like bosentan, ambrisentan, sildenafil, tadalafil and prostanoids)
- Upper gastrointestinal motility disorders (known from bosentan, sildenafil, tadalafil)
- Serious haemoptysis/pulmonary haemorrhage
- Bleeding events [mostly epistaxis and haemoptysis] were common for prostanoids
  - Sildenafil has a special warning for the potential for increased risk of bleeding when sildenafil is initiated in subjects already using VKAs, particularly for CTD
  - For tadalafil, epistaxis is a common adverse reaction
  - Embryo-fetal toxicity (bosentan and ambrisentan have been shown to be teratogenic)

With respect to drug-interactions, Adempas has a comparable profile to approved drugs: less CYP interaction compared to other approved compounds and no clinically meaningful interaction with bosentan.

c. Combination therapy with prostanoids

The PATENT-1 study was a multinational global study in a rare disease. Due to the global enrolment in PATENT-1, the use of prostanoids was not restricted to specific drugs.

Patients were allowed to be treated with prostanoids in accordance with local practices, which was especially true for use of beraprost in Japan.

Table 16 presents the data by type of administration and by treatment group. A total of 10 patients received oral beraprost sodium (in patients from Japan only, where the drug is approved for PAH), 14 patients received iloprost (all but 2 patients inhalation, one each oral and intravenous administration) and 7 patients received subcutaneous administration of treprostinol.

Table 16. Baseline prostanoid for subjects pretreated with PCA (Safety Analysis Set)

	Adempas 1-2.5 mg (Individual Titration)	Placebo	Adempas 1-1.5 mg (fixed dose)	Total
n	20 (100.0%)	7 (100.0%)	4 (100.0%)	31 (100.0%)
Type of PCA				
BERAPROST SODIUM	8 (40.0%)	2 (28.6%)	0	10 (32.3%)
ILOPROST	9 (45.0%)	3 (42.9%)	2 (50.0%)	14 (45.2%)
TREPROSTINOL	3 (15.0%)	2 (28.6%)	2 (50.0%)	7 (22.6%)

Despite the limitation of being a small subpopulation of the total study population, it could be shown that patients receiving prostanoid therapy benefitted from additional Adempas administration. The study PATENT-1 demonstrated that in patients pretreated with prostanoids, the addition of Adempas resulted in a consistent improvement over a wide range of efficacy variables. Moreover, the safety profile in this small patient group was no different from the group pre-treated with endothelin receptor antagonists in which Adempas was added.

4. Chronic Thromboembolic Pulmonary Hypertension

    a. Postoperative patient group

By definition, the postoperative patient group has distinct characteristics compared to the inoperable patient group due to the selection criteria. In the one group the CHEST study included all inoperable patients who have different characteristics compared to a population of operable patients. In the next group from all surgical patients a postoperative patient group was selected, that can be regarded as a group of patients with insufficient response to the primary therapy (surgery), the group of patients with persistent or recurrent CTEPH after surgical treatment. Thus, some difference between the 2 subpopulations was expected. Despite these differences positive results were seen in both sub-populations. The increase of the 6MWD of 27 m seen in the post-operative group ("non-responders" to the primary therapy) as well as the consistent benefit seen in the secondary endpoints in this group is clinically relevant based on extrapolation from PAH data and also when seen in conjunction with the consistency of the secondary efficacy parameters. Thus, the Sponsor is of the opinion that patients with postoperative CTEPH should not be excluded from the overall indication in patients with CTEPH.

5. Regional differences for the primary endpoint

The sponsor has analysed the data thoroughly to investigate possible reasons for regional effects (for example, small treatment effect in North America and Latin America for 6MWD). Small sample sizes, especially in the placebo group and the impact of imputation and outliers were the main factors identified. No issues with potential to impact study results were identified in study conduct or compliance to procedures. Mainly due to low numbers it was not possible to identify a specific patient group that may not have had a treatment benefit. When considering the Adempas treated patients only, the increase of 6MWD in the regions North America and Latin America was consistent with the overall results. The results of the 6MWD were corroborated by the results of secondary efficacy parameters. Thus, the sponsor regards the overall study results as applicable for patients originating from North America and Latin America as well.

6. Safety of riociguat

    a. Clinical significance of the low calcium findings compared to no reports on placebo

Calcium was not measured in all patients in the CHEST-1 and PATENT-1 studies. However, in those patients where calcium was measured, data from the pooled analysis (CHEST-1 and PATENT-1) showed that from baseline to Week 12 to 13 (which is the last common visit from both studies) there was a very small decrease for mean calcium of 0.057 mg/dL (± 0.322; n=78) in riociguat-treated patients, compared to a small increase for mean calcium of 0.116 mg/dL (± 0.421; n=34) in the placebo group.

Analysis of changes from baseline with respect to reference ranges for calcium showed that within the riociguat treated group, out of the a total of 78 patients 2 patients with low baseline values remained on the low range and 4 patients with normal baseline values had lower than normal values at the end of Week 12 to 13. The respective numbers for placebo (N=34) were 3 patients with low baseline values remained on the low range and no patient with normal baseline values had lower than normal values at the end of Week 12 to 13. In the riociguat group 3 patients with low values at baseline had normal values at weeks 12-13 compared to 6 in the placebo group.

In the sponsor's assessment of these findings, the changes in calcium observed in the Phase III clinical program were small and considered not clinically relevant. This assessment is in accordance with preclinical observations by the sponsor that indicated no marked effect with riociguat on calciuresis.

    b. Use in Pregnancy

Due to reproductive toxicity seen in animal models, Adempas is contraindicated during pregnancy. Advice is clearly stated in the PI that women of childbearing potential should use effective contraception during treatment with Adempas. Considering the concern raised by the TGA regarding pregnancy, the sponsor proposes to adopt Category X for the pregnancy classification and inclusion of a boxed warning to alert healthcare professionals of the risk in this population (see updated PI). In conjunction with routine education provided to healthcare professionals about Adempas, the sponsor considers risk for pregnancy is sufficiently communicated. Thus additional risk minimisation activity is not necessary.

7. Risk Management Plan

In the clinical trials peripheral oedema was a common adverse reaction. This event is not included in the EU RMP as an 'important identified risk' as frequency is not the sole criterion to designate an observed risk as an 'important identified risk' in the RMP based on the understanding of the EMA RMP guidance. However, the RMP evaluator has a different view and has requested that peripheral oedema be added in the Australian Specific Annex (ASA) until sufficient clinical evidence can prove otherwise. In light of this, the sponsor will include 'peripheral oedema' in the ASA as an 'important identified risk' in accordance with request from the RMP evaluator.

Hypotension is designated as an 'important identified risk' in the EU RMP. The sponsor has proposed a drug registry known as the EXPERT registry as an additional pharmacovigilance activity in order to conduct further investigation on several safety aspects in the post-authorisation setting. This registry will allow for documentation and evaluation of riociguat use in off-label indications and populations. The documentation in the registry will not be restricted to the product label, which is reflected in the inclusion criterion 'female and male patients who start or are on treatment with riociguat'. Despite the constraint with number of patients allowed in the registry (n = 900), together with the lack of clarity of reimbursement timeframe for Adempas in Australia effectively limiting commercial availability of the product in the country, the sponsor confirms that every

effort is being made to include Australian patients in the EXPERT registry. If the submission to register riociguat is rejected or deferred in EU, an alternative Australian registry will be implemented.

The list of safety concerns as proposed by the RMP evaluator have been captured in the updated EU RMP which is applicable to Australia, except for cardiovascular disease. The sponsor is of the view that patients with other cardiovascular disease treated with riociguat is not a safety concern based on data collected thus far in an ongoing Phase II Study LEPHT in patients with symptomatic Pulmonary Hypertension due to systolic left ventricular dysfunction (LVD) (PH-sLVD). In the total study population of 201 patients included in the LEPHT study 45% (90/201) had an underlying coronary artery disease. This study population received riociguat in doses up to 2.0 mg TDS for a study period of 16 weeks. The study drug was well tolerated and in the absence of nitrates, only 1 patient had treatment-emergent angina pectoris.

Conclusion

Despite currently available treatments for PAH, both PAH and CTEPH remain progressive diseases with limited life expectancy. Pulmonary arterial hypertension (PAH) is a progressive disorder, characterised by sustained elevations of pulmonary arterial pressure, progressive dyspnoea and profound functional limitations that may eventually progress to right heart failure and death. Riociguat is a stimulator of soluble guanylate cyclase (sGC) which has a dual mode of action and leads to increased generation of cGMP. It is a first in class therapy suitable for treatment of patients with either CTEPH or PAH with a positive benefit-risk profile. Most importantly, this is the first medical treatment proven efficacious in CTEPH.

Bayer thanks the OMA and ACPM for the opportunity to respond to the issues in the Delegate's Overview for discussion at the ACPM meeting on 13 February 2014 and looks forward to ACPM's advice and the finalisation of this application to enable an effective PAH treatment alternative and the first medical treatment for CTEPH in Australia.

Advisory committee considerations

The Advisory Committee on Prescription Medicines (ACPM), having considered the evaluations and the Delegate's overview, as well as the sponsor's response to these documents, advised the following:

The submission seeks to register a new chemical entity.

The ACPM, taking into account the submitted evidence of efficacy, safety and quality, agreed with the Delegate and considered Adempas film coated tablet containing 0.5 mg, 1 mg, 1.5 mg, 2 mg and 2.5 mg of riociguat to have an overall positive benefit–risk profile for the amended indication;

1. *Pulmonary Arterial Hypertension:*

   Adempas, as monotherapy or in combination with approved PAH treatments (endothelin receptor antagonists or inhaled or subcutaneous prostanoids), is indicated for the treatment of:

   - *idiopathic pulmonary arterial hypertension*
   - *heritable pulmonary arterial hypertension or*
   - *pulmonary arterial hypertension associated with connective tissue diseases*
   - *pulmonary arterial hypertension associated with congenital heart disease*

   in adult patients with WHO functional class II, III or IV symptoms.

2. *Chronic Thromboembolic Pulmonary Hypertension:*

ADEMPAS is indicated for the treatment of:

- *Persistent or recurrent chronic thromboembolic pulmonary hypertension (CTEPH) after surgical treatment or*
- *inoperable CTEPH in adult patients with WHO functional class II, III or IV symptoms*

In making this recommendation the ACPM noted

- the small numbers of patients recruited in some subpopulations and the ad hoc nature of the analysis and advised these numbers should be clearly stated in the PI.
- a concern about the rate of erroneous dosing and agreed with ACSOM's recommendation that an education program needs to accompany prescription of the drug.

Proposed conditions of registration

The ACPM agreed with the Delegate on the proposed conditions of registration and specifically advised on the inclusion of the following:

- The submission to the TGA of the final reports on the paediatric studies being undertaken as soon as completed.

Proposed Product Information (PI)/Consumer Medicine Information (CMI) amendments:

The ACPM agreed with the Delegate to the proposed amendments to the Product Information (PI) and Consumer Medicine Information (CMI) and also provided further advice on the PI and CMI but details of these are beyond the scope of this AusPAR.

Specific advice

1. Whether the data is sufficient to support monotherapy and combination therapy with endothelin receptor antagonists (ERAs) or prostanoids (inhaled and subcutaneous and if it should include intravenous)?

The ACPM advised it would be reasonable to use this medication as monotherapy and combination therapy with endothelin receptor antagonists (ERAs) or prostanoids (inhaled and subcutaneous) but no data has been presented with intravenous prostanoids to support its use.). These patients are usually extremely unwell and will be managed by experts in this condition.

2. Whether the indications for both PAH and CTEPH should include WHO Functional class IV and whether CTEPH should include classes II-III? For CTEPH, eight patients on riociguat were in class IV and for PAH, one patient on riociguat was in class IV.

The ACPM advised that it would be reasonable to include WHO functional class IV for both indications since this is best left to clinical judgment and supported CTEPH including classes II-III. The *Clinical trials* section of the PI should state very *few patients were in FC IV and use in this population is a clinical decision.*

3. Whether the wording of the indications for PAH and CTEPH should be modified in relation to endpoint claims (that is, improve exercise capacity, improve WHO functional class and delay clinical worsening [only for PAH]) and place this information in the *Clinical Trials* section of the PI instead?

The ACPM agreed with the Delegate that endpoint claims should not, in general, be included in the indications. These are better placed in the Clinical trials section of the PI.

4. Whether the indication for PAH should specify subgroups of WHO Group 1 similar to the format for the ERAs, whether it should include the connective tissue disease subgroup and whether CTEPH supports the inclusion of postoperative patients?

The ACPM was of the view that it would be reasonable to include the subgroups proposed and to also include PAH patients with congenital heart disease. The details of numbers and percentages of subgroups should be included in the *Clinical trials* section.

5. Whether the Use in Pregnancy section of the PI should include additional advice, similar to the US PI, given the Category D classification in pregnancy?

The ACPM noted the sponsor has decided to re-classify riociguat to Category X and therefore the *Pregnancy* section of PI requires additional information consistent with this category.

The ACPM advised that the implementation by the sponsor of the recommendations outlined above to the satisfaction of the TGA, in addition to the evidence of efficacy and safety provided would support the safe and effective use of these products.

Outcome

Based on a review of quality, safety and efficacy, TGA approved the registration Adempas riociguat 0.5 mg film-coated tablet blister pack, Adempas riociguat 2.5 mg film-coated tablet blister pack, Adempas riociguat 1.5 mg film-coated tablet blister pack, Adempas riociguat 2 mg film-coated tablet blister pack, Adempas riociguat 1 mg film-coated tablet blister pack, indicated for:

Pulmonary arterial hypertension

Adempas, as monotherapy or in combination with approved PAH treatments (endothelin receptor antagonists or inhaled or subcutaneous prostanoids), is indicated for the treatment of:

- *idiopathic pulmonary arterial hypertension*
- *heritable pulmonary arterial hypertension*
- *pulmonary arterial hypertension associated with connective tissue diseases or*
- *pulmonary arterial hypertension associated with congenital heart disease*

in adult patients with WHO functional class II, III or IV symptoms

Chronic thromboembolic pulmonary hypertension

Adempas is indicated for the treatment of

- *Persistent or recurrent chronic thromboembolic pulmonary hypertension (CTEPH) after surgical treatment or*
- *inoperable CTEPH*

in adult patients with WHO functional class II, III or IV symptoms

Specific conditions of registration applying to these goods

1. The Adempas (riociguat) EU Risk Management Plan (RMP), version I, dated 18 January 2013 data locked point 2 November 2012), with the Australian Specific Annex, version 2, dated 25 October 2013 and Pre-ACPM Response of 271anuary 2014, included with submission PM-201.3-00307-I. -3, and any subsequent revisions, as agreed with the TGA will be implemented in Australia.

   An obligatory component of Risk Management Plans is Routine Pharmacovigilance. Routine Pharmacovigilance includes the submission of Periodic Safety Update Reports IPSURs). Reports are to be provided annually until the period covered by

such reports is not less than three years from the date of this approval letter. No fewer than three annual reports are required.

2. The following studies must be submitted to the TGA, as soon as possible after completion, as Category I submissions:

    a. The final study reports for the two paediatric studies for riociguat in PAH and pulmonary hypertension of the newborn

Attachment 1. Product Information

The Product Information approved for main Adempas at the time this AusPAR was published is at Attachment 1. For the most recent Product Information please refer to the TGA website at <http://www.tga.gov.au/hp/information-medicines-pi.htm>.

Attachment 2. Extract from the Clinical Evaluation Report

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