EU RISK MANAGEMENT PLAN FOR JERAYGO® (APROCITENTAN)

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The content of this RMP has been reviewed and approved by the marketing authorisation holder's QPPV. The electronic signature is available on file.

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LIST OF ABBREVIATIONS AND ACRONYMS

ADR	Adverse drug reaction
AE	Adverse event
ALT	Alanine aminotransferase
aRHT	'Apparent' resistant hypertension
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
BP	Blood pressure
BP-CARE	Blood Pressure rate control and Cardiovascular Risk profile
CI	Confidence interval
CHD	Coronary heart disease
CKD	Chronic kidney disease
COVID-19	Coronavirus disease 2019
CV	Cardiovascular
CYP	Cytochrome P450
DB	Double-blind
DB-WD	Double-blind withdrawal
DBP	Diastolic blood pressure
DM	Diabetes mellitus
ECG	Electrocardiogram/graphy
eGFR	Estimated glomerular filtration rate
EEA	European Economic Area
EMA	European Medicines Agency
EOT	End-of-Treatment
EPAR	European Public Assessment Report
ERA	Endothelin receptor antagonist
ET	Endothelin
ET-1	Endothelin-1

ET_A	Endothelin A receptor
ET_B	Endothelin B receptor
EU	European Union
GI	Gastrointestinal
Hb	Haemoglobin
hERG	Human ether-a-go-go-related gene
IC_{20}	Concentration that causes 20% inhibition
INVEST	INternational VErapamil-Trandolapril Study
MACE	Major adverse cardiac event(s)
MedDRA	Medical Dictionary for Regulatory Activities
MRHD	Maximum recommended human dose
mRNA	Messenger ribonucleic acid
NOAEL	No-observed-adverse-effect level
NOEL	No-observed-effect level
NT-proBNP	N-terminal pro-B type natriuretic peptide
NYHA	New York Heart Association
PAH	Pulmonary arterial hypertension
PASS	Post-authorisation safety study
PBRER	Periodic benefit-risk evaluation report
PDCO	Paediatric Committee (European Medicines Agency)
PK	Pharmacokinetic(s)
PL	Package leaflet
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic safety update report
QPPV	Qualified Person for Pharmacovigilance
REGARDS	Reasons for Geographic And Racial Difference in Stroke
RHT	Resistant hypertension
RI	Run-in
RMP	Risk Management Plan

RR	Risk ratio
SAE	Serious adverse event
SB	Single-blind
SBAT	Standardized background antihypertensive therapy
SBP	Systolic blood pressure
SiDBP	Sitting diastolic blood pressure
SiSBP	Sitting systolic blood pressure
SmPC	Summary of Product Characteristics
SPCCD	Swedish Primary Care Cardiovascular Database
T3	Triiodothyronine
T4	Thyroxine
TEAE	Treatment-emergent adverse event
TIA	Transient ischaemic attack
tRHT	'True' resistant hypertension
TSH	Thyroid-stimulating hormone
UGT	Uridine 5'-diphospho-glucuronosyltransferase
ULN	Upper limit of normal range
US	United States
WISE	Women's Ischemia Syndrome Evaluation
WTH	St. James Women Take Heart
WOCBP	Women of childbearing potential

PART I: PRODUCT OVERVIEW

Table 1 Product overview

Active substance(s) (INN or common name)	Aprocitentan
Pharmacotherapeutic group(s) (ATC Code)	C02KN01
Marketing Authorisation Applicant	Idorsia Pharmaceuticals Deutschland GmbH
Medicinal products to which this RMP refers	Aprocitentan
Invented name(s) in the European Economic Area (EEA)	JERAYGO
Marketing authorisation procedure	Centralised procedure
Brief description of the product	Chemical class: endothelin receptor antagonist
	Aprocitentan is a potent, orally active, dual ERA that inhibits the binding of ET-1 to ET_A and ET_B receptors. ET-1, via its receptors (ET_A and ET_B), mediates a variety of deleterious effects such as vasoconstriction, fibrosis, cell proliferation, and inflammation. In hypertension, ET-1 can cause vascular hypertrophy and remodelling, endothelial dysfunction, sympathetic activation, and increased aldosterone synthesis. ET-1 is upregulated in hypertension and especially in low-renin salt-dependent conditions in which some pharmacological classes, such as blockers of the renin-angiotensin system, are less effective.
Hyperlink to the Product Information	JERAYGO Product Information
Indication(s) in the EEA	Current: JERAYGO is indicated for the treatment of resistant hypertension in adult patients in combination with at least 3 antihypertensive medicinal products.

Dosage in the EEA	Current: The recommended dose is 12.5 mg orally once daily. The dose can be increased to 25 mg once daily for patients tolerating the 12.5 mg dose and in need of tighter BP control.
Pharmaceutical form(s) and strengths	Current: 12.5 and 25 mg film-coated tablets
Is/will the product be subject to additional monitoring in the EU?	Yes

PART II: SAFETY SPECIFICATION

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

Resistant hypertension (RHT)

Aprocitentan is indicated for the treatment of RHT in adult patients in combination with at least 3 antihypertensive medicinal products.

RHT is a classification of hypertension defined by the European Society of Cardiology/ European Society of Hypertension guidelines as office BP ≥ 140/90 mmHg in patients receiving at least 3 antihypertensive drugs, one of which is a diuretic, at optimal or best-tolerated doses [Williams 2018].

The classification of RHT requires screening for secondary causes of hypertension and to rule out pseudo-RHT due to inaccurate BP measurement, white coat effect, undertreatment, poor medication adherence, and medical inertia.

When pseudo-RHT has not been ruled out, the term 'apparent' resistant hypertension (aRHT) is used. When all causes of pseudo-RHT have been ruled out, the term 'true' resistant hypertension (tRHT) can be used.

Incidence

Incidence of RHT is largely unknown.

The incidence of aRHT in the United Kingdom in 2015 was measured using a BP threshold of SBP ≥ 140 mmHg or DBP ≥ 90 mmHg within 12 months of starting the third drug. This study found that the age-standardised aRHT incidence was 0.43 cases per 100 person-years [Sinnott 2017]. In the US the incidence of aRHT between 2002 and 2006 was estimated as 0.7 cases per 100 person-years [Daugherty 2012].

Prevalence

Reported prevalence of RHT varies based on the definition used and the underlying study populations (e.g., general treated hypertensive population vs diabetic or CKD study populations).

The prevalence rates summarised in Table 2 below represent the reported prevalence rates for RHT in the treated hypertensive population in the published literature. The reported prevalence of aRHT ranged from 6.8–16.9% and the reported prevalence of tRHT ranged from 7.6–19.4%.

Data on RHT prevalence among the total hypertensive population are limited as most studies restricted inclusion to treated hypertensive study populations.

In the German Health and Examination survey, the prevalence of aRHT among the total hypertensive population was 2.2% [Sarganas 2016]. The prevalence of RHT among the total European population is unknown.

In the US, the prevalence of aRHT in the adult hypertensive population was estimated to be 10.3%, representing approximately 9.2 million adults (BP ≥ 140/90 mmHg; ≥ 130/80 mmHg for those with diabetes mellitus or CKD) [Carey 2019].

Table 2 Reported prevalence of apparent and true resistant hypertension (BP ≥ 140/90 mmHg) in treated hypertensive populations

Study/ Country	Study design	Prevalence aRHT	Prevalence tRHT
[Noubiap 2019] Global	Meta-analyses 91 cross-sectional and cohort studies	Pooled 14.7%	Pooled 10.3%
[Noubiap 2019] WHO European region (53 countries)	Meta-analyses of studies in the WHO European region	Pooled 14.3%	NR
[Achelrod 2015] Global	Meta-analyses 20 observational studies	Pooled 13.7%	NR
[Achelrod 2015] Global	Meta-analyses 4 RCTs	Pooled 16.3%	NR
German Health and Examination Survey [Sarganas 2016] Germany	Nationwide survey	6.8%	NR
SPCCD [Holmqvist 2018] Sweden	Primary health care database linked to Swedish National registers	12%	NR
Spanish Ambulatory Blood Pressure Registry [de la Sierra 2011] Spain	Registry of patients with ambulatory BP measures	12.2%	7.6%
Spanish Ambulatory Blood Pressure Registry [Armario 2017]	Spanish Ambulatory Registry using office BP measures	16.9%	NR
BP-Care [Brambilla 2013] Albania, Belarus, Bosnia, Czech Republic, Lithuania, Romania, Serbia, Slovakia and Ukraine	Cross-sectional survey	12.8%	19.4%

Study/ Country	Study design	Prevalence aRHT	Prevalence tRHT
EURIKA [Borghi 2016] Austria, Belgium, France, Germany, Greece, Norway, Russia, Spain, Sweden, Switzerland, Turkey, and the UK	Cross-sectional cohort study	14.3%	NR

aRHT = 'Apparent' resistant hypertension; BP = blood pressure; BP-Care = Blood Pressure rate control and Cardiovascular Risk profile; EURIKA = European Study on Cardiovascular Risk Prevention and Management in Usual Daily Practice; NR = not recorded; RCT = randomised controlled trial; SPCCD = Swedish Primary Care Cardiovascular Database; tRHT = 'True' resistant hypertension; UK = United Kingdom; WHO = World Health Organization.

Demographics of RHT population and risk factors for the disease

Age

In the Noubiap et al. meta-analysis, the mean age of RHT (both aRHT and tRHT) study populations ranged from 51–72 years [Noubiap 2019]. The mean age of aRHT study populations in the Achelrod et al. meta-analysis ranged from 51–68 years [Achelrod 2015].

In the BP-CARE study, the mean age of the tRHT population was 58.4 years [Brambilla 2013] and in the SPCCD the mean age of patients with aRHT was 70 years [Holmqvist 2018]. In the Spanish Ambulatory Blood Pressure Registry, the mean age of the RHT population was 64 years [de la Sierra 2011] and 64.9 years [Armario 2017].

In a retrospective cohort study conducted in the United Kingdom, persons over 70 years of age were more likely than those aged 65–69 years to develop incident aRHT during the study period [Sinnott 2017].

Sex

In the 2015 meta-analysis conducted by Achelrod et al., the authors reported that sex differences in aRHT prevalence were negligible: 15.3% (95% CI: 12.5–18.1%) in men and 15.6% (95% CI: 13.7–17.6%) in women [Achelrod 2015].

In Germany, the prevalence of aRHT in women was 6.5% (95% CI: 4.8–8.7%) compared to 7.2% in men (95% CI: 5.4–9.6%) [Sarganas 2016].

In the pooled analysis of the 2009–2014 cycles of the nationally representative National Health and Nutrition Examination Survey conducted in the US, there was no sex difference in the prevalence of aRHT (17.5% in men vs 17.9% in women) [Carey 2019].

Age and sex are relevant for the assessment of safety and risk management in WOCBP as aprocitentan is contraindicated for use in pregnant women. The only publication identified to date that reported age-specific prevalence of RHT in women was reported by Smith 2016. Smith et al. conducted a post-hoc analysis of three prospective observational

cohort studies totalling 15,108 women from the St. James Women Take Heart (WTH), the Women's Ischemia Syndrome Evaluation (WISE), and the INternational VErapamil-Trandolapril Study (INVEST) studies [Smith 2016]. Among the 1078 women with aRHT, 1% (N = 9) were below the age of 50, 27% (N = 293) were aged 50–60, and 72% (N = 776) were aged 60 and above.

Race/ethnicity

None of the studies summarised in Table 2 provided baseline characteristics for race/ethnicity and no study provided race/ethnicity-specific RHT prevalence rates.

Studies from the US have reported differences in the prevalence of aRHT by race/ethnicity [Carey 2019, Sim 2013]. The pooled analysis of the 2009–2014 National Health and Nutrition Examination Survey cycles reported that 15% of non-Hispanic Black, 10% of non-Hispanic White, 7% of Hispanic, and 6% of 'other' race/ethnicity participants had aRHT (BP ≥ 140/90 mmHg; or BP ≥ 130/80 mmHg in adults with diabetes or CKD [Carey 2019]).

Prevalence of aRHT (BP ≥ 140/90 mmHg) in the Kaiser Permanente Southern California hypertension cohort was 12% in non-Hispanic White, 18% in Hispanic, 19% in African American, and 6% in Asian/Pacific Islander participants [Sim 2013].

Risk factors for the disease

Risk factors associated with RHT include older age, obesity, CKD, Black African race, DM, and left ventricular hypertrophy [Calhoun 2008, Myat 2012, Williams 2018].

Standard of care

Hypertension guidelines from the US and Europe [Carey 2018, Williams 2018] recommend to first optimise a 3-drug antihypertensive regimen: a long-acting calcium channel blocker, a blocker of the renin-angiotensin system (angiotensin converting enzyme inhibitor or angiotensin receptor blocker), and a diuretic. All 3 drugs must be prescribed at optimal doses (or best-tolerated doses) and at the appropriate dosing interval.

If hypertension is still not controlled, mineralocorticoid receptor antagonists are recommended as a fourth drug. Although there is no consensus on which drug should be used, the EU guidelines recommend the use of spironolactone; if the use of spironolactone is not recommended (e.g., in patients with significant renal impairment) or not tolerated (e.g., due to antiandrogenic side effects), additional diuretics such as amiloride or higher doses of thiazide/thiazide-like diuretics, or a loop diuretic, should be used.

Optimal diuretic therapy is critically important in RHT because most patients have extracellular fluid volume expansion. Therefore, thiazide-like diuretics with long half-lives such as chlorthalidone or indapamide are recommended, especially for effect on nocturnal BP. For specific populations such as CKD grade 3b-5, loop diuretics are the preferred option.

Beta-blockers are not recommended for initial therapy of hypertension (i.e., uncomplicated hypertension) but they can be used in complicated hypertension or in the presence of CHD, heart failure with reduced ejection fraction, or cardiac arrhythmia.

Natural history of resistant hypertension

Elevated uncontrolled BP is the leading global risk factor for death (attributable for 10.8 million deaths in 2019) and nonfatal CV events primarily stroke, myocardial infarction, and end-stage renal disease, as described below.

Mortality and morbidity

Patients with RHT are more likely to be older, Black, and have comorbidities including obesity, albuminuria, CKD, DM, CHD, heart failure, stroke, and/or sleep apnoea [Sim 2013].

These characteristic and complex medical conditions lead to a higher risk of CV events in RHT patients than in the essential hypertensive population. This has been consistently shown in different settings (i.e., clinical trials, observational studies, and international registries) comparing patients with RHT vs patients without RHT with adjustment for patient characteristics (e.g., age, sex, etc.) and clinical characteristics (e.g., level of BP, heart or kidney disease, diabetes, etc.).

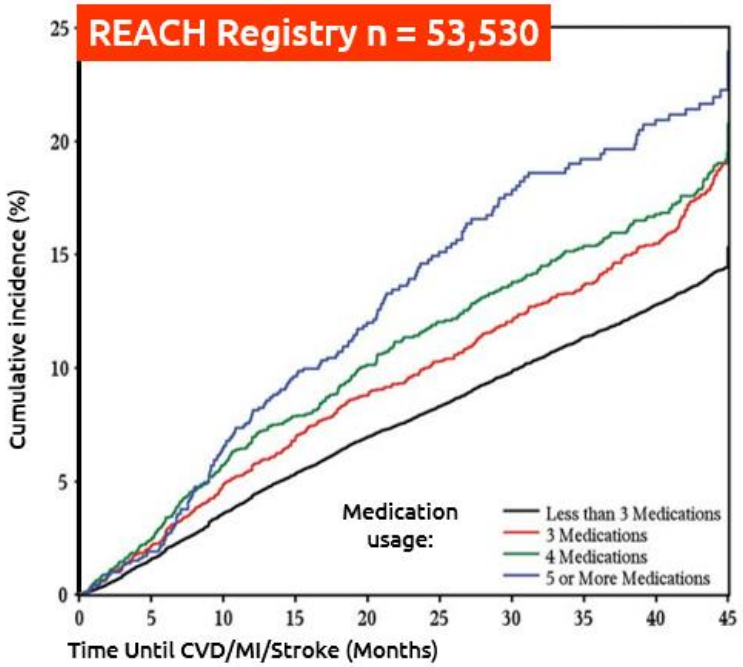
From the 2002–2006 Kaiser Permanente Colorado and Kaiser Permanente Northern California registries, 205,750 patients with incident hypertension were identified and followed to measure the incidence of RHT and to measure CV events. Over 3.8 years of median follow-up, CV event rates were significantly higher in those with RHT (unadjusted 18.0% vs 13.5%, $P < 0.001$). After adjustment for patient and clinical characteristics, RHT was associated with a higher risk of CV events (hazard ratio, 1.47; 95% CI: 1.33–1.62) [Daugherty 2012].

The CV risk associated with RHT was confirmed by a population-based observational cohort (i.e., Reasons for Geographic And Racial Difference in Stroke [REGARDS] study [n = 30,239]) treated for hypertension with RHT (n = 2043) and without RHT (n = 12,479). Over a median of 5.9, 4.4, and 6.0 years of follow-up, the multivariable adjusted Hazard Ratio for stroke, CHD, and all-cause mortality associated with RHT vs without RHT was 1.25 (95% CI: 0.94–1.65), 1.69 (95% CI: 1.27–2.24), and 1.29 (95% CI: 1.14–1.46), respectively. Compared to controlled BP, RHT with uncontrolled BP was associated with increased risk of CHD (Hazard Ratio: 2.33 [95% CI; 1.21–4.48]), but not for stroke or for mortality [Irvin 2014].

The prevalence of RHT in individuals with and without a history of stroke or TIA was 24.9% and 17.0%, respectively. After adjustment for age, race, and sex, the RHT prevalence ratio was 1.31 (95% CI: 1.12–1.52) for those with a history of TIA and 1.36 (95% CI: 1.22–1.52) for those with a history of stroke, compared to those without a history of TIA or stroke, respectively [Howard 2015].

The increased CV risk of RHT vs uncomplicated hypertension was also confirmed in a population enrolled in an outpatient hypertension unit with a median follow-up of 42 months [Tsioufis 2014], in CKD patients [de Nicola 2013], in patients with type 2 diabetes [Solini 2014] as well as in the Antihypertensive and Lipid-Lowering treatment to prevent Heart Attack Trial (ALLHAT) in which an active process for BP control was included as well as a large number of Black participants [Muntner 2014]. From the largest CV database (REACH registry), it can be concluded that the higher the number of antihypertensive medications required to control BP, the higher the CV risk for those patients, as depicted in Figure 1 [Kumbhani 2013].

Figure 1 Cumulative hazard curve for the primary endpoint of CVD/MI/stroke in patients with non-RHT (< 3 agents), RHT on 3 agents, RHT on 4 agents, and RHT on ≥ 5 agents



CVD =cardiovascular death; MI = myocardial infarction; REACH = REduction of Atherothrombosis for Continued Health; RHT = resistant hypertension.

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

Key safety findings from nonclinical studies and relevance to human usage

The general toxicity profile of aprocitentan was characterised in oral rat and dog safety pharmacology and toxicity studies with treatment durations of up to 26 weeks in the rat

and 39 weeks in the dog. In addition, male and female fertility studies, in vitro and in vivo genotoxicity studies, and embryo-foetal development studies were conducted.

Aprocitentan is a compound with the same chemical structure as the major metabolite of macitentan with the same pharmacological mode of action. Pre- and post-natal development, carcinogenicity, and phototoxicity were examined in studies conducted with macitentan in rats and mice. In these studies, the major metabolite of macitentan represented approximately 50% of the total exposure.

The main results from the nonclinical toxicity studies are reflected in the SmPC for aprocitentan.

The following Table 3 lists the key safety findings observed in the nonclinical studies and their potential relevance to human usage:

Table 3 Nonclinical key safety findings

Key safety findings from nonclinical studies	Relevance to human usage
Toxicity	
Repeated-dose toxicity In the rat and dog repeated-dose toxicity studies with aprocitentan, the heart (dog), testes (rat, dog), liver (rat, dog), thyroid (rat), and nasal cavity (dog) were identified as the main target organs.	
Heart In the heart, periarteritis/arteritis of coronary arteries, mainly in the right atrium/coronary groove, was observed in dogs treated with aprocitentan at all dose levels tested in the 4-week dog toxicity study. Periarteritis/arteritis and intimal thickening in the right and left coronary arteries in the atrium or coronary groove were observed in the 13-week dog study at doses ≥ 25 mg/kg/day. The NOEL for heart findings in the 13-week toxicity study was 5 mg/kg/day. After the recovery period, neither periarteritis/arteritis, nor intimal thickening was observed in the 4- and 13-week dog toxicity studies. No such heart findings were observed in the 39-week dog study up to the highest	According to literature, it is well-recognised that small-molecule drugs that cause vascular lesions in experimental animals, particularly in dogs, are not associated with vascular injury in humans with long records of safe clinical administration [Bendjama 2014, Dogterom 1992, Joseph 2000, Mikaelian 2014, Zabka 2016]. Therefore, the findings are not relevant for human use.

Key safety findings from nonclinical studies	Relevance to human usage
tested dose of 75/50 mg/kg/day. No heart findings were observed in rats.	
Testes Dilation of seminiferous tubules was seen in the 4-week, supplemental 26-week, and male fertility studies in rat and in the 4-, 13-, and 39-week toxicity studies in dog. The severity of this change was generally minimal, and all findings were fully reversible. The NOAEL after 26 weeks of treatment in rats was 50 mg/kg/day, and after 39 weeks of treatment in dogs it was 5 mg/kg/day. The dilation of seminiferous tubules is likely caused by direct action of aprocitentan on peritubular smooth muscle cells. Peritubular cells in the rat testis have been shown to express ET receptors and to contract upon ET-1 binding [Tripiciano 1997, Romano 2005]. This pathway is thought to play a role in propulsion of sperm and fluid out of the testis and into the epididymis. Since seminiferous tubule fluid is continuously secreted into the tubular lumen, weakening of tubule contraction likely leads to retention of fluid and dilation of the tubular lumen. In more markedly dilated tubules, the change can be accompanied by germ cell degeneration of the seminiferous epithelium.	The NOAELs provide a safety margin of 8.0 (20.6) (rodents) and 4.9 (16.6) (dogs)-fold the total (free) exposure at maximum recommended human dose (25 mg). As the findings were only minimal, reversible, and did not lead to effects on male fertility, they are regarded to be of low (if any) relevance for the clinical use of aprocitentan in humans.
Liver Increased liver weight and centrilobular hepatocellular hypertrophy were seen in rats and dogs after treatment with aprocitentan. Only in rats, hepatocellular hypertrophy was in some animals accompanied with fatty change. Liver weight increase and hepatocellular hypertrophy were reversible in both species. Induction of xenobiotic metabolism was shown by an increase in mRNAs for several CYPs and UGTs [B-17.046]. In the rat, the enzyme induction correlated with reduced aprocitentan	The liver findings in rats are considered a non-adverse adaptation of the liver to increased metabolic demand at high doses in animal studies and are not considered relevant for humans. Centrilobular hypertrophy and degenerative changes at high doses are not considered relevant for the clinical use of aprocitentan in humans.

Key safety findings from nonclinical studies	Relevance to human usage
exposure after repeated dosing. The findings are considered a non-adverse adaptation of the liver to increased metabolic demand. At doses ≥ 250 mg/kg/day in rats, the histopathologic examination revealed minimal degenerative changes in the liver. Metabolic overload of the rat liver after oral administration of aprocitentan was causing the changes. A NOEL was identified at 100 mg/kg/day in the chronic rat study.	The NOEL for degenerative findings provides a safety margin of 16 (42) in male and 27 (69) in female rats.
Thyroid In the 26-week rat study thyroid follicular hypertrophy was seen at all dose levels and correlated with increased thyroid weight [T-14.036]. Thyroid follicular hyperplasia was detected at doses ≥ 50 mg/kg/day and follicular adenoma at doses ≥ 100 mg/kg/day. In order to further characterise the findings in terms of time- and rat strain-dependency, a supplemental 26-week male rat toxicity study in two strains (Wistar and Sprague Dawley) [T-16.021] and an extended male fertility study with 14 weeks of treatment in Wistar rats [T-16.001] were conducted. The doses and the consequent exposure ranges were comparable to the first 26-week rat toxicity study. In the supplemental 26-week rat toxicity study, thyroid follicular hypertrophy was seen at all dose levels in both strains and correlated with increased thyroid weights. TSH levels were increased in Wistar rats at 250 mg/kg/day and at all dose levels in Sprague Dawley rats. T3 / T4 levels were largely unchanged. Thyroid follicular hyperplasia was detected in two Sprague Dawley rats treated at 250 mg/kg/day. No thyroid adenoma was detected. In the extended male Wistar rat fertility study, follicular hypertrophy was also seen at all dose levels and was consistent with increased thyroid weights. TSH levels were increased in rats at	The thyroid hypertrophy seen in the 26-week studies is considered secondary to hepatic microsomal enzyme induction (UGTs) leading to increased metabolism and excretion of thyroid hormones. These findings are considered adaptive, reversible, non-adverse, and rodent specific. Thyroid hormone levels (T3, T4, and TSH) were measured in the Phase 2 clinical trial AC-080A201, and no changes in thyroid hormones were observed. The findings are not considered relevant for the use of aprocitentan in humans.

Key safety findings from nonclinical studies	Relevance to human usage
dose levels ≥ 50 mg/kg/day. T3 and T4 levels were comparable between all dose groups. There are important differences in thyroid hormone homeostasis between rats and humans leading to a significantly higher sensitivity of rats to developing thyroid pathologies [Alison 1994]. This is due to the lack of thyroxin-binding-globulin in rodents. T3 and T4 in rodents are more prone to enzymatic degradation in case of enzyme induction compared to thyroid hormones in humans which are bound to thyroxine-binding globulin and thereby better protected from degradation. No thyroid findings were observed in the dog toxicity studies with aprocitentan.	
Haematology A dose-related, reversible decrease in the number of red blood cells, Hb concentration, and packed cell volume was observed in dog toxicity studies. Reticulocytes were not affected, and there was no evidence of haemolysis, or bone marrow toxicity. The changes were fully reversible	This finding in dogs is not considered relevant for humans as the exposure at the NOEL in dogs provides a safety margin of 26 (90). In rats, this finding was not observed, providing safety margins of 25 (63) and 44 (114) in males and females.
Nasal cavity Changes in the nasal cavity were seen in dogs at doses ≥ 25 mg/kg/day in the 13- and 39-week studies [T-14.072, T-15.053]. Effects on the nasal cavity were not present in the preceding 4-week study [T-14.022]. The changes consisted of enlarged turbinates characterised by submucosal hyperostosis and/or hyperchondrosis associated with congestion, vascular dilation, oedema, and goblet cell proliferation. These histological findings might be related to the clinical observation of noisy respiration in several	The findings are considered secondary to the expected pharmacodynamics of aprocitentan and adaptive. As the NOEL for this finding provides a safety margin of 4.9 (16.6) for the clinical dose of 25 mg, it is considered of low (if any) human relevance.

Key safety findings from nonclinical studies	Relevance to human usage
treated dogs. All changes were fully reversible after the recovery period. Drug-related vascular dilation might lead to congestion in the parenchyma of nasal turbinates and may have caused a secondary adaptive change of cartilage and bone cells. The nasal cavity findings are therefore considered to be secondary to the expected pharmacodynamics of aprocitentan and adaptive. Full reversibility was proven after 9 weeks of recovery.	
Genotoxicity	
Aprocitentan was not genotoxic in in vitro and in vivo studies.	Aprocitentan is not genotoxic.
Carcinogenicity	
Two carcinogenicity studies in rats and mice were conducted with macitentan. The animals were dosed for 2 years. No oncogenic potential was evident after 104 weeks of treatment with macitentan up to 250 mg/kg/day in male and 250/50 mg/kg/day in female rat or after 104 weeks of treatment with macitentan up to 400 mg/kg/day in male and 100 mg/kg/day in female mice.	Based on studies that were conducted with macitentan, macitentan as well as aprocitentan are considered not oncogenic.
Fertility	
There was no effect on fertility of male rats in a fertility study.	Aprocitentan did not affect male fertility in rats.
In females, evidence of an effect of aprocitentan on pre-implantation variables (lower number of corpora lutea, implantation sites and live embryos) was noted at the dose levels of 50 and 250 mg/kg/day. Corpora lutea findings at 50 mg/kg/day were in the historical control range and therefore not deemed toxicologically relevant. The post-implantation variables were not affected by treatment at any dose level	The findings in female rats are not considered to be relevant for humans as they provide a safety margin of 2.3 (8.6).

Key safety findings from nonclinical studies	Relevance to human usage
tested. The NOEL was 10 mg/kg/day and provides a safety margin of 2.3.	
Embryo-foetal development	
Embryo-foetal development toxicity (Segment II) studies using aprocitentan in pregnant rats and rabbits were performed [T-22.027, T-22.028, T-22.029, T-22.030]. Aprocitentan did not induce teratogenicity in studies with pregnant rats and rabbits with safety margins of 2 (6)- and 14 (3)-fold the total (free) exposure at MRHD, respectively.	Teratogenicity is considered an important identified risk based on class (ERA) considerations. However, based on the results of embryo-foetal development studies in rats and rabbits and the resulting safety margins, the risk of teratogenicity should aprocitentan be used during pregnancy seems to be lower than that of other ERAs.
Safety pharmacology studies	
In safety pharmacology studies, aprocitentan showed no effect on physiological functions of the central nervous, or respiratory systems up to the highest tested dose. In normotensive Beagle dogs equipped with telemetry devices, aprocitentan induced decreases in systolic, diastolic, and mean arterial BP. The BP effect was associated with a compensatory heart rate increase. The finding is not considered to be adverse as BP decrease is an expected pharmacological effect of aprocitentan. Treatment with aprocitentan had no effect on ECG variables at any dose in these animals. In vitro hERG channel measurements revealed a high IC_{20} of ~ 7.2 µM on repolarising currents. Such concentrations are far above the expected free plasma concentration in humans at the maximum recommended human dose. Therefore, aprocitentan is not expected to elicit QT prolongation at therapeutic doses.	There is no relevant risk indicated based on the results of the safety pharmacology studies.

PART II: MODULE SIII – CLINICAL TRIAL EXPOSURE

Clinical trial exposure in subjects with hypertension

The aprocitentan clinical development programme for hypertension is based on data from a Phase 2 dose-finding study (AC-080A201; hereafter referred to as study 201) and a Phase 3 study (ID-080A301 / PRECISION; hereafter referred to as study 301).

During the development programme, 1051 subjects with hypertension were exposed to aprocitentan at doses of 5, 10, 12.5, 25, and 50 mg corresponding to a total of 554.0 subject-years of exposure to aprocitentan. 526 subjects received placebo in these studies, corresponding to 97.3 subject-years.

Out of 1051 subjects with hypertension exposed to aprocitentan, 724 subjects had RHT.

633 out of the 1051 subjects were treated with any dose of aprocitentan for at least 26 weeks; 192 subjects were treated with aprocitentan for at least 47 weeks and 99 subjects for at least 48 weeks. A total of 325 subjects and 795 subjects were exposed to aprocitentan 10/12.5 or 25 mg, respectively, corresponding to 31.7 and 498.6 subject-years of exposure, respectively.

Study 201 was a double-blind, randomised, placebo- and active-reference dose-finding study, which evaluated the efficacy of 8-week double-blind aprocitentan monotherapy at doses of 5, 10, 25, and 50 mg in subjects with hypertension, treatment-naïve or treatment-washed out, as compared to placebo, with lisinopril 20 mg as an active reference. A 2-week single-blind placebo withdrawal period was introduced at the end of the study to investigate the rebound effect on BP.

Study 301 was a large, blinded, randomised study investigating the effect of aprocitentan as add-on therapy to guideline-recommended antihypertensive medications, thereby exploring the utility of a dual ERA as a complementary therapeutic approach for the treatment of RHT. Randomised subjects had uncontrolled BP despite treatment with at least 3 antihypertensive drugs of different pharmacological classes, including a diuretic. The study comprised 3 sequential parts with a total duration of up to 48 weeks:

- Double-blind (DB) part 1: Subjects were randomised to aprocitentan 12.5 mg, aprocitentan 25 mg or placebo for a duration of 4 weeks.
- Single-blind (SB) part 2: Subjects received aprocitentan 25 mg for 32 weeks.
- Double-blind withdrawal (DB-WD) part 3: Subjects were re-randomised to aprocitentan 25 mg or placebo for a duration of 12 weeks.

The study assessed the short-term and long-term (durability) efficacy of aprocitentan on lowering BP.

The overall number of subjects exposed and the duration of exposure to aprocitentan in the 201 and 301 studies are presented in Table 4 to Table 6.

Table 4 Clinical trial exposure (studies 201 and 301)

	Aprocitentan					Placebo [b]	Lisinopril
	5 mg	**10 mg/12.5 mg**	**25 mg [a]**	**50 mg**	**Any dose[c]**		**20 mg**
Study 301							
N	NA	243	713	NA	724	444	NA
Subject-years	NA	19.5	486.4	NA	505.8	85.5	NA
At least 4 weeks	NA	191	687	NA	699	397	NA
At least 8 weeks	NA	1	671	NA	675	293	NA
At least 12 weeks	NA	NA	661	NA	667	171	NA
At least 24 weeks	NA	NA	633	NA	635	NA	NA
At least 26 weeks	NA	NA	630	NA	633	NA	NA
At least 32 weeks	NA	NA	536	NA	572	NA	NA
At least 34 weeks	NA	NA	419	NA	516	NA	NA
At least 35 weeks	NA	NA	409	NA	502	NA	NA
At least 36 weeks	NA	NA	391	NA	461	NA	NA
At least 39 weeks	NA	NA	304	NA	307	NA	NA
At least 40 weeks	NA	NA	297	NA	301	NA	NA
At least 44 weeks	NA	NA	183	NA	241	NA	NA
At least 46 weeks	NA	NA	104	NA	196	NA	NA
At least 47 weeks	NA	NA	100	NA	192	NA	NA
At least 48 weeks	NA	NA	50	NA	99	NA	NA
Study 201							
N	82	82	82	81	327	82	81
Subject-years	12.1	12.2	12.2	11.7	48.2	11.8	12.0
At least 4 weeks	77	79	77	75	308	77	78
At least 8 weeks	56	54	57	54	221	52	53
At least 12 weeks	NA	NA	1	NA	1	NA	NA
Overall							
N	82	325	795	81	1051	526	81
Subject-years	12.1	31.7	498.6	11.7	554.0	97.3	12.0
At least 4 weeks	77	270	764	75	1007	474	78
At least 8 weeks	56	55	728	54	896	345	53
At least 12 weeks	NA	NA	662	NA	668	171	NA
At least 24 weeks	NA	NA	633	NA	635	NA	NA
At least 26 weeks	NA	NA	630	NA	633	NA	NA
At least 32 weeks	NA	NA	536	NA	572	NA	NA
At least 34 weeks	NA	NA	419	NA	516	NA	NA
At least 35 weeks	NA	NA	409	NA	502	NA	NA
At least 36 weeks	NA	NA	391	NA	461	NA	NA
At least 39 weeks	NA	NA	304	NA	307	NA	NA
At least 40 weeks	NA	NA	297	NA	301	NA	NA
At least 44 weeks	NA	NA	183	NA	241	NA	NA
At least 46 weeks	NA	NA	104	NA	196	NA	NA
At least 47 weeks	NA	NA	100	NA	192	NA	NA

	Aprocitentan					Placebo [b]	Lisinopril
	5 mg	**10 mg/12.5 mg**	**25 mg [a]**	**50 mg**	**Any dose[c]**		**20 mg**
At least 48 weeks	NA	NA	50	NA	99	NA	NA

[a] For study 301, exposure on aprocitentan 25 mg is the total exposure during the study regardless of study part.
[b] For study 301, total exposure on placebo in the study regardless of study part (i.e., not continuous as treatment in placebo received in DB and DB-WD).
[c] Any dose combines all aprocitentan doses and there can be more subjects in "any dose" than in other doses, for example for study 301 the duration a subject was exposed to 12.5 mg is combined with the duration of exposure to 25 mg.
Source: table iss-1.3.1.
DB = double-blind; DB-WD = double-blind withdrawal; NA = not applicable.
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Table 5 Clinical trial exposure by age group and sex (studies 201 and 301)

	Number (%) of subjects by sex		
Age group	***Male (n = 686)***	***Female (n = 453)***	***Total (n =1139)***
Adults			
18–64 years	472 (68.8)	285 (62.9)	757 (66.5)
Elderly			
65–74 years	178 (25.9)	132 (29.1)	310 (27.2)
75–84 years	36 (5.2)	36 (7.9)	72 (6.3)
≥ 85 years	0	0	0

Percentages are based on respective n.
n = number of male / female subjects exposed to aprocitentan or placebo during study 201 and 301 regardless of any dose.
Source: table iss-1.2.1, table iss-1.2.2.

Table 6 Clinical trial exposure by racial origin (studies 201 and 301)

Racial origin	**Number (%) of subjects per racial group (N = 1139)**	
White	861	(75.6)
Black or African American	228	(20.0)
Asian	41	(3.6)
Other [a]	9	(0.8)
Total	1139	

n = number of subjects exposed to aprocitentan or placebo
[a] 'Other' includes: American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, Not permitted as per legislation/regulation, Unknown.
Source: D-17.023 table 10-2, D-22.269 table 10-3.

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

The safety profile of aprocitentan has been investigated in 2 multicentre, randomised, placebo-controlled trials.

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

Important exclusion criteria in the pivotal Phase 3 study in the development programme are summarised in Table 7.

Table 7 Important exclusion criteria in the pivotal study in the development programme (study 301)

(1) Comorbidities	
Congestive heart failure NYHA stage III or IV	
Reason for exclusion:	To minimise a potentially confounding underlying condition when assessing the safety profile of the compound. Patients with NYHA stage II heart failure were also excluded if they were unstable or had relevant underlying valvular disease or aortic stenosis.
Considered to be included as missing information?	No
Rationale for not including as missing information	Based on the data generated in the aprocitentan clinical development programme, there was no clear evidence that aprocitentan may cause any worsening in patients with heart failure. "Heart failure due to fluid retention in predisposed patients" has been included as an important potential risk and therefore, will be closely monitored. Furthermore, a special warning about the higher risk of fluid retention in patients with pre-existing heart failure, and the recommendation to monitor patients with risk factor for developing congestive heart failure or other CV events have been included in the SmPC. Aprocitentan has not been evaluated in patients with unstable or severe cardiac disease, such as heart failure NYHA stage III–IV or stage II with relevant valve disease; therefore, its use is not recommended in these patients and this information is provided in the SmPC.
End stage renal disease (CKD stage 5), i.e., eGFR < 15 mL/min/1.73 m^2	
Reason for exclusion:	To minimise a potentially confounding underlying condition when assessing the safety profile of the compound.
Considered to be included as missing information?	No

Rationale for not including as missing information	Based on single-dose (aprocitentan 50 mg) PK in subjects with renal impairment, no dose adjustment is needed in subjects with mild, moderate, or severe (i.e., eGFR ≥ 15 mL/min) renal function impairment. No difference in safety profile was seen between subjects with severe renal impairment and healthy subjects. Aprocitentan has not been evaluated in subjects with end stage CKD (i.e., CKD stage 5; eGFR < 15 mL/min/1.73 m^2) or in patients undergoing dialysis; therefore, its use is not recommended in these patients and this information is provided in the SmPC. Furthermore, the subgroup of patients with eGFR < 15 mL/min/1.73 m^2 or undergoing dialysis represents a small proportion of the CKD population. These patients are closely monitored in nephrology centres where specialised clinicians will determine whether aprocitentan treatment is appropriate or not as these patients may have severe anaemia and/or fluid retention due to their underlying medical condition.

Severe hypertension (Grade 3) i.e., mean SiSBP ≥ 180 mmHg and/or sitting diastolic blood pressure (SiDBP) ≥ 110 mmHg

Reason for exclusion:	To avoid CV complications in the frail, high-risk population of patients with severe hypertension receiving placebo during the study. The reason for exclusion in both clinical trials (201 and 301) was because receiving placebo was considered risky and unethical in these high-risk uncontrolled patients even for a short period of time.
Considered to be included as missing information?	No
Rationale for not including as missing information	It is expected that this population will be treated with aprocitentan in combination with other antihypertensives within the context of the approved indication and no different safety profile is expected in these patients with severe hypertension.

Type 1 Diabetes mellitus

Reason for exclusion:	Patients with Type 1 DM are considered not suitable for clinical trials due to the need to regularly adapt their insulin dose to minimise the risk of hypoglycaemic crisis.
Considered to be included as missing information?	No

Rationale for not including as missing information	Patients with Type 1 DM are only marginally represented in the RHT population.

Laboratory values: Hb < 100 g/L at screening and randomisation

Reason for exclusion:	Patients with Hb < 100 g/L were excluded from the pre-authorisation clinical trials as a precautionary measure because Hb decreases have been observed with other marketed ERAs. To minimise a potentially confounding underlying condition when assessing the safety profile of the compound.
Considered to be included as missing information?	No
Rationale for not including as missing information	Mild to moderate Hb decrease was observed with other ERAs and in the aprocitentan development programme and is considered to reflect a nonserious (generally mild) and reversible effect, unrelated to bone marrow disease or haemorrhage. Hb decrease is considered most likely secondary to haemodilution (plasma volume expansion). Hb decrease is included as an ADR; in addition, a special warning that JERAYGO is not recommended in patients with severe anaemia (< 8 g/dL), and the need to measure haemoglobin concentrations prior to initiation of treatment and during treatment if clinically indicated are included in the SmPC.

Laboratory values: NT-proBNP ≥ 500 pg/mL at screening

Reason for exclusion:	To minimise potentially confounding severe heart failure when assessing the safety profile of the compound.
Considered to be included as missing information?	No
Rationale for not including as missing information	19 of 730 randomised subjects (2.6%) had TEAEs denoting heart failure during the study (18 subjects on aprocitentan and 1 subject on placebo) irrespective of study period. 11 subjects had SAEs (requiring hospitalisation) and 8 subjects had nonserious AEs denoting heart failure. All 11 subjects with hospitalisation for heart failure had multiple risk factors, including: diabetes (all 11 subjects), CKD stage 3–4, i.e., eGFR < 60 mL/min/1.73m^2 (6 subjects, 54.5%), older age (3 subjects [27.3%] aged ≥ 75 years), obesity (2 subjects [18.2%] were severely obese, i.e., BMI ≥ 40 kg/m^2), and a medical history of heart failure (5 subjects, 45.5%).

	The overall incidence rate of reported TEAEs denoting heart failure leading to hospitalisation is consistent with that published in the scientific literature in a similar population. "Heart failure due to fluid retention in predisposed patients" has been included as an important potential risk and will therefore be closely monitored. Aprocitentan has not been evaluated in subjects with NT-proBNP plasma concentration ≥ 500 pg/mL; therefore, its use is not recommended in these patients and this information is provided in the SmPC.
ALT or AST > 3 × ULN, or Severe hepatic impairment	
Reason for exclusion	Patients with aminotransferases > 3 × ULN or severe hepatic impairment were excluded from the pre-authorisation clinical trials as a precautionary measure because hepatic enzyme elevations have been observed with other marketed ERAs. To minimise a potentially confounding underlying condition when assessing the safety profile of the compound.
Considered to be included as missing information?	No
Rationale for not including as missing information	Based on a single-dose (aprocitentan 25 mg) PK study in subjects with moderate hepatic impairment, no dose adjustment is needed in these subjects and the same conclusion is applicable to subjects with mild hepatic impairment. No difference in safety profile was seen between subjects with moderate hepatic impairment and healthy subjects. Aprocitentan has not been evaluated in patients with severe hepatic impairment and a higher exposure cannot be excluded with administration of aprocitentan; therefore, JERAYGO is contraindicated in these patients, as per section 4.3 of the SmPC. In the aprocitentan studies 201 and 301, there was no evidence of drug-induced hepatotoxicity. This conclusion derives from the fact that (a) elevations in aminotransferases were also observed during the screening and run-in periods; (b) there was no difference between aprocitentan groups vs placebo and no evidence of a dose relationship; and (c) there was no indication of a causal association with aprocitentan based on identified underlying risk factors in most cases and/or non-suggestive chronology of the events. Nevertheless, because hepatotoxicity is a known risk for ERAs, "Severe liver injury" has been included as an important potential risk and will therefore be closely monitored.

	In addition, a special warning is included in the SmPC stating that JERAYGO is not recommended in patients with elevated aminotransferases (> 3 × ULN).
(2) Concomitant treatments that either have an impact on BP or might impact efficacy or safety	
Reason for exclusion:	To avoid having an impact on BP (efficacy) and/or proper safety assessment.
Considered to be included as missing information?	No
Rationale for not including as missing information	Aprocitentan will be prescribed in addition to at least 3 antihypertensive medicinal products. Aprocitentan is not expected to interact with other concomitant medications based on its low propensity to elicit drug-drug interactions.
High dose of loop diuretics (i.e., furosemide > 80 mg/day, or equivalent dosage of other loop diuretics)	
Reason for exclusion:	To minimise possible biases in assessing the safety of the compound. Based on the study 301 protocol, patients were required to switch their antihypertensive medications (including diuretics) to a standard background antihypertensive therapy of 3 medications including a moderate dose (25 mg) of hydrochlorothiazide; subjects on high dose loop diuretics (usually given to treat fluid retention in subjects at risk of cardiac failure) were excluded to avoid a potential worsening of their underlying condition.
Considered to be included as missing information?	No
Rationale for not including as missing information	Loop diuretics are used to treat patients predisposed to oedema / fluid retention. Indeed, the use of diuretics (including high dose loop diuretics) was allowed during study 301 to treat oedema / fluid retention. 45.3% (87/192) of subjects with treatment-emergent oedema / fluid retention received diuretic treatment, mainly loop diuretics (any dose). In contrast to study 301, in the real-world setting, background antihypertensive medications including diuretics will usually not be modified when starting aprocitentan therapy (and they are not recommended to be modified). For this reason, the following text was added in section 4.4 of the SmPC:

	In patients treated with loop diuretics before starting therapy with JERAYGO, the loop diuretic should not be switched to a less effective diuretic treatment at initiation.
3) Other exclusion criteria	
Pregnancy: Pregnant women	
Reason for exclusion:	Pregnant women were excluded from aprocitentan clinical trials. Based on data from animal reproduction studies with other ERAs, aprocitentan may have potential embryo-foetal toxicity, including birth defects and foetal death, when administered to a pregnant woman.
Considered to be included as missing information?	No
Rationale for not including as missing information	JERAYGO is contraindicated in pregnancy. In addition, JERAYGO is contraindicated in WOCBP who are not using reliable contraception. Recommendations for WOCBP to use reliable methods of contraception during treatment with JERAYGO and for one month after treatment discontinuation, and to perform a pregnancy test before the start of treatment, monthly during treatment and one month after stopping treatment are included in the SmPC. "Teratogenicity" has been included as an important identified risk and will therefore be closely monitored.
Breastfeeding: Breastfeeding women	
Reason for exclusion:	Breastfeeding women should normally be excluded from clinical trials. Based on animal data with other ERAs, a risk to the breastfed child cannot be excluded.
Considered to be included as missing information?	No
Rationale for not including as missing information	JERAYGO is contraindicated during breastfeeding.

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

The clinical development programme is unlikely to detect rare adverse reactions (with a frequency ≥ 1/10,000 to < 1/1000). Since the clinical development programme did not include placebo-controlled data beyond 16 weeks (4-week DB in part 1, 12-week DB-WD in part 3), the safety concern "Long-term cardiovascular safety under controlled clinical

setting" has been included as missing information. A broader exposure in the post-marketing setting may address such limitations and identify rare ADRs and potential long-term CV safety risks.

Long-term safety has been assessed in study 301 in 192 subjects with RHT who were treated with aprocitentan for at least 47 weeks and 99 subjects for at least 48 weeks. A total of 633 subjects were treated with aprocitentan for at least 6 months (including 630 subjects on aprocitentan 25 mg).

The ADRs reported during long-term treatment up to 48 weeks were consistent with those reported during short-term treatment.

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

Table 8 Exposure of special populations included or not in clinical development programmes

Type of special population	Exposure
Pregnant women	Pregnant women were not included in the clinical development programme. Use in pregnant women is contraindicated, as reflected in section 4.3 of the SmPC.
Breastfeeding women	Breastfeeding women were not included in the clinical development programme. Use in breastfeeding women is contraindicated, as reflected in section 4.3 of the SmPC.
Paediatric population	Subjects ≤ 18 years old were not included in the clinical development programme. The safety and efficacy of aprocitentan in paediatric subjects have not been established.
Elderly patients	In study 301, the number of elderly subjects (≥ 65 years) included was considerable, as reflected by the provided age group numbers and percentages mentioned below. Study 301 included safety data from a total of 730 subjects with RHT. The Phase 3 subjects (mean age: 61.7 years) were aged from 24 to 84 years and comprised 409 (56%) adult subjects (18–64 years) and 321 (44%) elderly subjects (≥ 65 years); of these, 72 subjects (9.9%) were aged ≥ 75 years.

Type of special population	Exposure
	Overall, the efficacy and safety of aprocitentan were similar for subjects < 65 years of age compared to subjects ≥ 65 years.
Patients with hepatic impairment	A dedicated clinical pharmacology study including 8 subjects with moderate hepatic impairment has been conducted (ID-080-109). Based on the results of this study, aprocitentan can be administered to subjects with moderate hepatic impairment and, therefore, to subjects with mild hepatic impairment without the need for dose adjustment. Aprocitentan has not been studied in subjects with severe hepatic impairment (Child-Pugh class C) and its use in these subjects is contraindicated, as reflected in section 4.3 of the SmPC.
Patients with renal impairment	In study 301, the number of subjects with renal impairment at baseline was considerable, as reflected by the subgroups and percentages mentioned below. • CKD stage 3–4 (eGFR = 15 to < 60 mL/min/1.73 m^2): 162 subjects (22.2%): - CKD stage 3a (eGFR 45 - < 60 mL/min/1.73 m^2): 93 subjects (12.7%). - CKD stage 3b (eGFR 30 - < 45 mL/min/1.73 m^2): 48 subjects (6.6%). - CKD stage 4 (eGFR 15 - < 30 mL/min/1.73 m^2): 21 subjects (2.9%). Subjects with end stage CKD (CKD grade 5; eGFR < 15 mL/min/1.73 m^2) and subjects undergoing dialysis were not included in the clinical development programme; therefore, the use of JERAYGO is not recommended in these patients, as reflected in sections 4.2 and 4.4 of the SmPC. A dedicated clinical pharmacology study assessing the effect of severe renal function impairment on the PK of aprocitentan has been conducted (AC-080-105). Based on the results of this study, aprocitentan can be administered to patients with renal impairment (including severe impairment with eGFR 15–29 mL/min/1.73 m^2) without the need for dose adjustment.

Type of special population	Exposure
Patients with cardiovascular impairment	In study 301, the number of subjects with congestive heart failure was 143 (19.6%). Subjects with congestive heart failure NYHA stage III and IV were not included in the clinical development programme; therefore, the use of aprocitentan is not recommended in these patients, as reflected in section 4.4 of the SmPC.
Population with relevant different ethnic origin	Study 301 included a population with different race / ethnic origins [for exposure by race, see Table 6]. PK and safety variables were similar between different races including the Black / African American subpopulation. In an ethnic sensitivity study conducted in Japanese and Caucasian healthy subjects (ID-080-107), PK and safety variables after multiple-dose 25 mg aprocitentan were similar for Caucasian and Japanese subjects.

PART II: MODULE SV – POST-AUTHORISATION EXPERIENCE

Not applicable; aprocitentan had not been authorised in any country at the time of data lock point for this RMP (1 December 2022).

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

Potential for medication errors

The main risk related to medication errors is patients taking the wrong dose. Clear instructions on the recommended posology are given in the product labelling (section 4.2 of the SmPC and section 3 of the PL).

The recommended starting dose of JERAYGO is 12.5 mg orally once daily and then the dose may be increased to 25 mg once daily, if needed.

The film-coated tablet containing 12.5 mg is yellow to orange, round biconvex (6 mm diameter), debossed with “AN” on one side and plain on the other side; the film-coated tablet containing 25 mg is pink, round biconvex (6 mm diameter), debossed with “AN” on one side and “25” on the other side. This visual differentiation between the 2 dose strengths will minimise the risk of medication errors. The 2 dose strengths come in different packaging clearly identifying the contained dose strength.

Administration of the incorrect prescribed dose may lead to patient underdosing or overdosing with limited consequences.

Overall, the risk of potential medication errors and any resulting safety risks are deemed to be low.

Potential for overdose

There is limited clinical experience with aprocitentan overdose.

At a single dose of up to and including 600 mg and at multiple doses of up to and including 100 mg daily administered to healthy subjects (24 and 4 times the maximum recommended dose, respectively), adverse reactions of headache, nasal congestion, nausea, and upper respiratory tract infection were observed.

There were no reports of intentional overdose in clinical studies with aprocitentan. In study 201, aprocitentan 50 mg was used for up to 8 weeks in subjects with essential hypertension. In this population, the safety profile of the 50 mg dose group was similar to the 25 mg dose group.

In the event of an overdose, standard supportive measures should be taken, as required. Because of the possibility of QT interval prolongation at very high concentrations (i.e., more than 22 tablets of aprocitentan 12.5 mg), ECG monitoring should be considered. Dialysis is unlikely to be effective because aprocitentan is highly protein-bound.

Potential for paediatric off-label use

In paediatric patients, RHT has not been proven to exist and uncontrolled BP almost invariably indicates a secondary form of hypertension (i.e., having an identifiable cause) requiring specific treatment of the underlying cause (most frequently renal disease).

For paediatric patients with hypertension requiring pharmacological treatment, several safe and efficacious therapeutic classes of antihypertensive drugs can be used: renin-angiotensin-aldosterone system inhibitors, diuretics, beta-blockers, calcium channel blockers, alpha-blockers, central agents, and vasodilators such as dihydralazine. Several antihypertensive drugs belonging to these classes are available as paediatric formulations or as fixed combinations which can improve adherence.

The PDCO granted a product-specific waiver for aprocitentan, for all subsets of the paediatric population, for the treatment of hypertension, in accordance with Articles 11(1)(a) and (c) of Regulation (EC) No 1901/2006 as amended, on the grounds that aprocitentan is likely to be ineffective or unsafe in the paediatric population and does not represent a significant therapeutic benefit over existing treatments for paediatric patients.

The proposed aprocitentan SmPC states that the safety and efficacy of aprocitentan in children and adolescents aged less than 18 years have not been established, and that the EMA has waived the obligation to submit the results of studies with JERAYGO in all subsets of the paediatric population in treatment of hypertension.

Overall, the potential for paediatric off-label use is deemed to be low.

PART II: MODULE SVII – IDENTIFIED AND POTENTIAL RISKS

Safety concerns

Table 9 provides an overview of the proposed safety concerns for aprocitentan.

Table 9 Safety concerns

Important identified risks	• Teratogenicity
Important potential risks	• Heart failure due to fluid retention in predisposed patients • Severe liver injury • Male infertility
Missing information	• Long-term cardiovascular safety under controlled clinical setting

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

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

The following risks were not considered important for inclusion in the list of safety concerns.

They will continue to be closely monitored via routine pharmacovigilance activities.

Table 10 Risks not considered important for inclusion in the list of safety concerns

Risk	Reason for not including in the list of safety concerns
Peripheral oedema / fluid retention	**Background information** Oedema is an accumulation of fluid in the interstitial space due to a dysregulation between the hydrostatic pressure and the oncotic pressure within the capillaries and/or due to permeability changes of the vessel wall [Trayes 2013]. Peripheral oedema is a comorbidity of RHT, particularly in subjects predisposed to fluid retention or with a dysfunctional heart pump. In an RHT clinical development programme, the incidence of peripheral oedema / fluid retention in the placebo group ranged from 5% to 12–14%, over a monitoring period of 10 and 14 weeks, respectively [Bakris 2010, Black 2007, Weber 2009]. Virtually all ERAs have been associated with peripheral oedema which is thought to be due to a combination of factors

Risk	Reason for not including in the list of safety concerns
	including plasma volume expansion, fluid retention, and changes in capillary permeability. The severity and frequency of peripheral oedema observed with ERAs depends on the clinical context (significant fluid retention is frequently observed in conditions of pre-existing fluid retention such as chronic heart failure and chronic renal failure), the dose (oedema is usually dose-dependent), and the degree of selectivity between ET_A and ET_B receptors (in an animal setting, blockade of both receptors is less likely to cause fluid retention than single-receptor blockade) [de Mussy 2021, Smolander 2009, Vercauteren 2017]. Widely used antihypertensive medications such as calcium channel blockers and direct vasodilators have also been associated with peripheral oedema. Calcium channel blockers induce peripheral oedema because vasodilation is more selective to the arterioles than to other blood vessels and this form of oedema is typically diuretic-resistant [Opie 1986]. In contrast, direct vasodilators (such as minoxidil and diazoxide) enhance renal sodium reabsorption through their BP effect (reduced renal perfusion) and activation of the renin-angiotensin-aldosterone system [Cho 2002]. Among calcium channel blockers, dihydropyridines are most frequently associated with peripheral oedema, with up to 50% of patients developing peripheral oedema in a dose-dependent manner [Ely 2006]. **Evaluation of oedema** ***Nonclinical data*** No relevant findings from aprocitentan nonclinical studies. ***Clinical data*** *Study AC-080-101 (healthy subjects):* • One subject reported a nonserious AE of peripheral oedema in the 100 mg aprocitentan elderly group [1/6 subjects (16.7%)]. • The 100 mg dose appeared to increase body weight in both healthy adults and healthy elderly subjects compared to placebo and lower doses of aprocitentan. *Study AC-080-102 (healthy subjects on high sodium diet):* • No AEs of oedema / fluid retention were reported.

Risk	Reason for not including in the list of safety concerns
	• A mean body weight increase of 0.83 kg (90% CI: 0.33–1.32) was observed in the 50 mg dose group as compared to placebo after 9 days of treatment. A mean body weight increase of 0.77 kg (90% CI: 0.03–1.51) was observed for the 25 mg dose group as compared to placebo. No relevant change in body weight was observed in the 10 mg dose group or when subjects were on placebo. • Aprocitentan did not affect sodium excretion in a clear way in the healthy salt-loaded subjects in this study. Other exploratory renal function variables assessed in this study did not identify clear signs of sodium retention, even though the observed increases in body weight suggested that some extent of sodium retention should have at least been transiently present. *Study ID-080-108 (healthy subjects):* • All 9 subjects (20.9%) who reported peripheral oedema experienced the event after treatment with the supratherapeutic dose of 100 mg aprocitentan (i.e., 4 times the maximum therapeutic dose). *Study AC-080A201 (hypertension, Grade 1 and 2)* • 5 mild to moderate nonserious AEs of peripheral oedema were reported in 4 subjects, 2 in the aprocitentan 25 mg group and 2 in the aprocitentan 50 mg group. • No SAEs denoting oedema / fluid retention were reported. • 1 AE leading to discontinuation (face oedema with aprocitentan 50 mg) was reported. • No evidence of body weight increase in the aprocitentan groups vs placebo. *Study ID-080A301 (resistant hypertension)* • Out of the 192 subjects (26.3%) who had at least 1 treatment-emergent oedema / fluid retention AEs, 32 subjects (16.7%) had a medical history of oedema / fluid retention. • In the 4-week DB period, there was a higher incidence of oedema / fluid retention in the aprocitentan groups compared to placebo, with a dose-dependent effect (9.1%, 18.4%, 2.1%, in aprocitentan 12.5 mg, 25 mg, and placebo groups, respectively). In the subgroup with CKD stage 3–4, the incidence was 18.2%, 24.2%, and 2.2% in

Risk	Reason for not including in the list of safety concerns
	aprocitentan 12.5 mg, 25 mg, and placebo groups, respectively. • In the long-term 32-week SB period, the incidence of oedema / fluid retention in the aprocitentan 25 mg group was 18.2%. In the subgroup with CKD stage 3–4, the incidence was 27.0%. • In the 12-week DB-WD period, the incidence of oedema / fluid retention was 2.6% in the aprocitentan 25 mg group and 1.3% in the placebo group. • Oedema / fluid retention tended to occur early on treatment and was mild to moderate in severity in most cases; oedema / fluid retention was reported as severe for only 7 of the 192 subjects (3.6%) with treatment-emergent oedema/fluid retention AEs. • Oedema / fluid retention led to administration of additional diuretics (mostly loop diuretics) in 87 of the 192 subjects (45.3%) with treatment-emergent oedema / fluid retention AEs. The majority (75.3%) of patients who developed an AE denoting oedema / fluid retention during the course of the study and were treated with diuretics recovered from the event. • Only 7 of the 192 subjects (3.6%) with treatment-emergent oedema / fluid retention AEs discontinued due to oedema / fluid retention; of these, 6 subjects were not treated with diuretics before discontinuation. • 4 SAEs of oedema / fluid retention were reported in 3 subjects on aprocitentan 25 mg. 3 of these 4 SAEs of oedema / fluid retention (2 pulmonary oedema and 1 oedema peripheral) were reported in the context of hospitalisation for heart failure [see important potential risk "Heart failure due to fluid retention in predisposed patients" in Table 15] while the remaining SAE of brain oedema occurred in the context of cerebral haemorrhage. **Rationale for not being assessed as an important risk** Oedema / fluid retention was frequently reported for aprocitentan in patients with resistant hypertension. This risk was generally nonserious, mild to moderate in intensity, occurred early on treatment, and was manageable (only rarely warranted treatment discontinuation).

Risk	Reason for not including in the list of safety concerns
	In summary, in line with the amended RMP guideline, the inclusion of peripheral oedema in the RMP is not justified based on the following reasons: • Diuretic treatment is available, and a high-resolution rate was observed following diuretic administration. • Peripheral oedema is not a life-threatening condition and is considered acceptable in relation to the severity of the indication treated. Of note, pulmonary oedema is covered under the important potential risk of "Heart failure due to fluid retention in predisposed patients" [see Module SVII.1.2]. • Risk has minimal clinical impact in relation to the severity of the event (mostly mild to moderate and manageable with diuretic treatment). Although oedema / fluid retention is not included as a safety concern, the important safety concern of heart failure due to fluid retention in predisposed patients is included as an important potential risk. In addition, while peripheral oedema / fluid retention is not considered an important risk, the following is reflected in section 4.4 of the SmPC: <u>*Fluid retention*</u> *Peripheral oedema and fluid retention are known effects of ERAs and were observed in clinical studies with aprocitentan (see section 4.8). After treatment initiation, patients should be monitored for signs of fluid retention such as oedema or weight gain. If clinically significant fluid retention develops, the patient should be evaluated to determine the cause and the need for additional supportive treatment, including additional diuretics or increase of dose of currently prescribed diuretic (as appropriate), before considering dose reduction or discontinuation of JERAYGO.* *In patients treated with loop diuretics before starting therapy with JERAYGO, the loop diuretic should not be switched to a less effective diuretic at initiation.* *Patients with underlying renal impairment (eGFR < 60 mL/min/1.73 m^2) or pre-existing heart failure taking JERAYGO may be at a higher risk of developing fluid retention, as may elderly patients (> 65 years), patients with diabetes, or*

Risk	Reason for not including in the list of safety concerns
	severely obese patients (BMI ≥ 40 kg/m^2). When switching to 25 mg, the risk of increasing fluid retention, potentially aggravating heart failure or CV events, has to be taken into consideration in these patients.
Anaemia / Hb decrease	**Background information** Hb decrease has been associated with marketed ERAs since the first clinical studies were initiated. The decrease in Hb is considered secondary to plasma volume expansion since alternative potential aetiologies, including red blood cell changes, bone marrow depression, haemolysis, or bleeding, have been excluded [Vercauteren 2017]. In a meta-analysis of placebo-controlled clinical trials the relative risk of Hb decrease with ERAs vs placebo was 2.69 (95% CI: 1.78–4.07) and was dose-dependent [Wei 2016]. In the SERAPHIN trial investigating macitentan in PAH, the incidence of AEs denoting anaemia / Hb decrease in the 3 mg macitentan dose, 10 mg macitentan dose, and placebo groups was 8.8%, 13.2%, and 3.2%, respectively, which confirms a dose-dependent effect of macitentan treatment [Pulido 2013]. **Evaluation of anaemia / Hb decrease** ***Clinical data*** Hb decrease was carefully assessed throughout study 301. Hb decrease was observed in the aprocitentan groups but not in the placebo group. Hb remained stable over time and the decrease was quickly reversible after treatment discontinuation during the DB-WD part 3. In subjects with CKD stage 3–4, Hb decrease from baseline was slightly more pronounced than in subjects with CKD 1–2. **Rationale for not being assessed as an important risk** Hb decreased is included as an ADR in the JERAYGO SmPC. In addition, a special warning that JERAYGO is not recommended in patients with severe anaemia (< 8 g/dL), and the need to measure haemoglobin concentrations prior to initiation of treatment and during treatment if clinically indicated is also included in the SmPC. Although the risk of anaemia / Hb decrease was included previously as an important identified risk in the RMPs of other authorised ERA products, based on the new definition of "important" risk [EMA 2017], this risk is sufficiently

Risk	Reason for not including in the list of safety concerns
	minimised by the information included in the SmPC sections 4.4, 4.8 and does not have an impact on the B/R balance of the product which would require further characterisation. As such, anaemia/Hb decrease do not qualify as an important identified risk in the context of the RMP.

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

Table 11 Important identified risks

Important identified risk	Risk-benefit impact
Teratogenicity	ERAs have shown serious teratogenic effects, mainly craniofacial and cardiovascular malformations, in offspring of rats and/or rabbits during pregnancy [Ruest 2009]. Because of this risk, ERAs are contraindicated in pregnancy and WOCBP must use a reliable method of contraception and perform monthly pregnancy tests [Opsumit® SmPC, Tracleer® SmPC, Volibris® SmPC]. As a result of these routine and additional risk minimisation measures (e.g., strict labelling and educational programmes) there has been limited post-marketing exposure during pregnancy. Nevertheless, several cases of ERA use during pregnancy in women with pulmonary hypertension have been presented in the literature, and none of these reported teratogenic effects [Hitzerd 2019]. In addition, no indication of human teratogenicity arose from the review of the few cases of congenital malformation reported with marketed ERAs. In the aprocitentan development programme, pregnancy was an exclusion criterion and WOCBP had to use a highly effective method of contraception and perform monthly pregnancy tests. Overall, there was 1 subject who became pregnant during treatment with aprocitentan (study 301; the estimated exposure was approximately 1.5 months with 25 mg dose). Aprocitentan was immediately discontinued, and pregnancy was successfully completed (normal baby) without any evidence of teratogenicity. Further details are provided in Module SVII.3.1.

Important identified risk	Risk-benefit impact
	Aprocitentan did not induce teratogenicity in studies with pregnant rats and rabbits with safety margins of 2 (6)- and 14 (3)-fold the total (free) exposure at MRHD, respectively. Although the risk of teratogenicity is only based on nonclinical findings observed with other ERAs, teratogenicity was included as an important identified risk in order to be consistent with other ERAs RMPs where it is considered a class important identified risk. The impact on benefit-risk could be significant in the WOCBP population.

Important potential risks

Table 12 Important potential risks

Important potential risk	Risk-benefit impact
Heart failure due to fluid retention in predisposed patients	RHT is a condition with high CV morbidity and mortality, including congestive heart failure [Daugherty 2012]. Patients with congestive heart failure are predisposed to fluid accumulation as a consequence of reduced renal blood flow and activation of the renin-angiotensin-aldosterone system, which in turn leads to sodium and water retention with further worsening of heart failure and reduced renal blood flow perpetuating the vicious cycle [Pellicori 2015]. Fluid retention is a common and well-recognised side effect of ERAs [Wei 2016]. The intensity of fluid retention and its clinical impact vary among ERAs as some led to worsening of heart failure and a trend toward an increased mortality was observed [Mann 2010], whereas others did not [Vachiery 2018]. Study 301 by design included a 4-week parallel group placebo-controlled part in which subjects were randomised to receive aprocitentan 25 mg, 12.5 mg, or placebo (part 1), followed by a 32-week part on aprocitentan 25 mg (part 2), and a 12-week placebo-controlled withdrawal part in which subjects were re-randomised to aprocitentan 25 mg or placebo (part 3). In the placebo-controlled parts of the study, cases of heart failure were reported at low frequency but higher in the aprocitentan groups compared to placebo. In total, including all study parts, there were 11 subjects who reported hospitalisation

Important potential risk	Risk-benefit impact
	for heart failure irrespective of study periods; out of which 10 subjects experienced the event on aprocitentan. The incidence of heart failure leading to hospitalisation in study 301 was consistent with that from published articles in the RHT population [Bhatt 2014, Bhandari 2016, Muntner 2014] and from a real-world study. Congestive heart failure, which may deteriorate due to fluid retention, is considered an important potential risk, particularly in predisposed patients (e.g., those with a medical history of heart disease, CKD, and other risk factors such as diabetes, older age and obesity). Further details are provided in Module SVII.3.1. The impact on benefit-risk could be significant in the RHT patient population, in predisposed patients.
Severe liver injury	ERAs have been associated with occasional serum enzyme elevations during therapy; however only bosentan and sitaxentan have been clearly linked to hepatotoxicity with different mechanisms [LiverTox 2017]. A meta-analysis of 24 randomised double-blind placebo-controlled clinical trials with ERAs showed that bosentan (RR 3.78, 95% CI: 2.42–5.91) but not macitentan (RR 1.17, 95% CI: 0.42–3.31) or ambrisentan (RR 0.06, 95% CI: 0.01–0.45) significantly increased the risk of abnormal liver function [Wei 2016]. The mechanism of hepatotoxicity is known for bosentan and is based on the inhibition of the canalicular bile salt export pump [Fattinger 2001]. In the RHT population, several comorbidities coexist (including obesity, type 2 diabetes, dyslipidaemia, and hypertension) which represent the main features of metabolic syndrome and contribute to the development of hepatic steatosis [Godoy-Matos 2020]. The presence of hepatic steatosis is considered the most common explanation for abnormal liver function tests in the absence of other apparent causes of acute or chronic liver injury [Hall 2017]. In study 301, elevation in liver enzymes > 3 × ULN has been reported with a similar incidence in aprocitentan groups and placebo in both DB part and DB-WD part. There were no SAEs, and no cases met the Hy's rule. Overall, there was no indication of a causal association with aprocitentan based on

Important potential risk	Risk-benefit impact
	underlying risk factors in most cases and/or non-suggestive chronology of the events. Further details are provided in Module SVII.3.1. Severe liver injury is included as an important potential risk due to hepatotoxicity reported with some drugs belonging to the same class. The impact of severe liver injury on benefit-risk could be significant in this population.
Male infertility	ERAs were described as inducing dilation of seminiferous tubules in the testes of laboratory animals that can secondarily result in tubular degeneration after long-term treatment, due to backlog of seminal fluid and increasing pressure on the tubular epithelium. Such histological changes did not result in an effect on fertility of male rats in studies with bosentan, macitentan [Tracleer® EPAR, Opsumit® EPAR] and aprocitentan. These observations are of questionable toxicological relevance and their relevance for humans is unknown. Nevertheless, male infertility is included as an important potential risk to be consistent with other ERAs RMPs where it is considered a class important potential risk. Further details are provided in Module SVII.3.1.

Missing information

Table 13 Missing information

Missing information	Risk-benefit impact
Long-term cardiovascular safety under controlled clinical setting	Long-term post-marketing exposure under controlled clinical setting will allow further characterization of potential long-term cardiovascular safety risks.

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

Not applicable, as this is the first version of the RMP.

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

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

Details of important identified and potential risks, based on nonclinical and clinical data, are presented in this section.

Important identified risks

Table 14 Details of important identified risks

Important identified risk: Teratogenicity	
Potential mechanisms:	A functional involvement of ET-1 or ET_A receptors in embryonic development was shown by the occurrence of malformations in studies with homozygous ET-1 or ET_A receptor knock-out mice [Kurihara 1994] or with other ERAs. Based on the phenotype of affected foetuses and their similarity to foetuses with gene knockouts of ET-1 or the ET_A receptor [Clouthier 1998], the observed alterations are considered to be a pharmacologically mediated effect of an ERA on cranial neural crest cells [Spence 1999].
Evidence source(s) and strength of evidence:	Evidence of teratogenicity with ERAs is limited to animal data. ERAs have shown teratogenic effects in rats and/or rabbits, mainly craniofacial and cardiovascular malformations, in offspring of animals during pregnancy [Ruest 2009]. There is limited post-marketing experience in humans [Hitzerd 2019, Kamp 2021]. Based on the limited post-marketing experience in humans, there is no indication of human teratogenicity: Cumulatively, 261 pregnancies have been reported for bosentan from 20 November 2001 through 19 November 2021 [Bosentan PBRER 2022], and 115 pregnancies have been reported for macitentan from 18 October 2013 through 19 August 2021 (Safety update - NDA 204410), resulting in a total of 102 live births. While the ERA exposure during pregnancy is usually limited to the first trimester, 6 separate exposures throughout pregnancy were reported for bosentan (none for macitentan): 1 had no reported outcome apart from the fact that a caesarean section was performed due to foetal distress; five resulted in healthy babies with one suffering neonatal respiratory problems related to prematurity, but none had congenital anomalies.

Important identified risk: Teratogenicity	
	In total, 3 cases of congenital anomaly were reported in babies of mothers treated with bosentan and 2 congenital anomalies were reported in babies of mothers treated with macitentan. Of the 3 cases reported with bosentan: • 1 case referred to cleft lip and palate in a baby with a family medical history of cleft lip and palate that were likely to have an inherited genetic cause. • 1 case referred to a premature baby with a small patent foramen ovale. • 1 case referred to a premature baby with patent ductus arteriosus and ventricular septal defect (no longer seen in a follow-up echocardiogram) which were likely confounded by a transmitted genetic factor (Eisenmenger physiology) and could be explained by the prematurity of the baby. Of the 2 cases reported with macitentan: • 1 case, referring to a premature baby with bilaterally shortened second digits on hands and feet, diagnosed as chondrodysplasia, was confounded by the mother's underlying systemic lupus erythematosus disease and concomitant medications. • 1 case referred to a premature baby with secundum-type atrial septal defect. In summary, there was no evidence of a contributory role of the dual ERAs (bosentan or macitentan) in any of the 5 cases of congenital abnormalities out of 102 live births. The cases were confounded by the underlying disease, maternal or paternal history, inherited genetic disorders, or prematurity. Furthermore, the anomalies did not correspond to the pattern of malformations that may be expected from ERAs based on nonclinical findings i.e., defects in neural crest derivatives. Overall, no indication of human teratogenicity arose from the review of these cases. In the US general population, the estimated background risk of major birth defects and miscarriage in clinically recognised pregnancies is 2–4% and 15–20%, respectively [FDA 2014]. Based on available information from macitentan and bosentan experience [data on file and Bosentan PBRER 2022, respectively], the prevalence of congenital anomalies and spontaneous abortion is consistent with the background risk:

Important identified risk: Teratogenicity	
	• Bosentan: 1.1% for congenital anomalies and 14.6% for spontaneous abortion. • Macitentan: 1.7% for congenital anomalies and 14.8% for spontaneous abortion.
Characterisation of the risk:	**Nonclinical studies** Embryo-foetal development studies were conducted in rats and rabbits [T-22.027, T-22.028, T-22.029, T-22.030]. Aprocitentan did not induce teratogenicity at systemic exposures that result in safety margins of 2 (6)- and 14 (3)-fold the total (free) exposure at MRHD, respectively. **Clinical studies** In clinical studies, pregnancy was an exclusion criterion; in addition, all WOCBP enrolled in the study were asked to use a highly effective method of contraception as per protocol and perform monthly pregnancy tests. Despite these strict requirements, there was one isolated case of post-randomisation exposure during pregnancy during the SB period of study 301. The case refers to a female subject with previous pregnancies and exposed to 25 mg aprocitentan during the first trimester (total estimated exposure was approximately 1.5 months). No foetal abnormalities were detected on obstetrical ultrasound at 12 weeks and 21 weeks gestational age and a normal baby was delivered at term. There was no neonatal illness, no need for resuscitation, no need for admission to an Intensive Care Unit, and no congenital anomalies.
Risk factors and risk groups:	WOCBP who are not using a reliable method of contraception.

Important identified risk: Teratogenicity	
Preventability:	Pregnancy and WOCBP who are not using reliable contraception are contraindications (section 4.3 of the SmPC). Additionally, sections 4.4 and 4.6 of the SmPC specify that: • Treatment with JERAYGO is to be initiated only if WOCBP are using reliable contraception and pregnancy test is negative. • Monthly pregnancy tests are recommended during treatment and for one month after treatment discontinuation. For this specific safety concern, an additional risk minimisation measure (patient card) is proposed, to remind WOCBP patients of teratogenicity risk and appropriate use of aprocitentan [see Module V.2, Annex 6, and Annex III – A. of the Product Information].
Impact on the risk-benefit balance of the product:	Provided the product labelling as well as other risk minimisation measures are adhered to, the potential of aprocitentan to lead to teratogenicity is considered low, and its impact on the benefit-risk balance is considered minimal.
Public health impact:	The public health impact is considered low.

Important potential risks

Table 15 Details of important potential risks

Important potential risk: Heart failure due to fluid retention in predisposed patients	
Potential mechanisms:	RHT is a condition with high CV morbidity and mortality including congestive heart failure [Daugherty 2012]. Patients with congestive heart failure are predisposed to fluid accumulation as a consequence of reduced renal blood flow and activation of the renin-angiotensin-aldosterone system, which in turn leads to sodium and water retention with further worsening of heart failure and reduced renal blood flow, perpetuating the vicious cycle [Pellicori 2015]. Endothelin is known to have an important role in the regulation of salt and water excretion by the kidney [Kohan 2011]. It has been suggested that, of the two endothelin receptor subtypes, ET_B receptors should not be blocked because of their involvement in natriuresis and diuresis. Nevertheless, predominant ET_A receptor blockers produced dose-dependent

Important potential risk: Heart failure due to fluid retention in predisposed patients	
	antidiuresis through non-specific blockade of ET_B receptors in anaesthetised rats [Baltatu 2012]. A study evaluating the contribution of each endothelin receptor to fluid retention and vascular permeability in rats concluded that by activating ET_B receptors, ERAs (particularly ET_A-selective antagonists) favour oedema formation by causing: 1) fluid retention resulting from arginine vasopressin and aldosterone activation secondary to vasodilation, and 2) increased vascular permeability [Vercauteren 2017].
Evidence source(s) and strength of evidence:	Aprocitentan is developed for the treatment of RHT in a population with high CV morbidity and mortality. In study 301, there was a small and slightly higher incidence of treatment-emergent heart failure leading to hospitalisation in the aprocitentan groups vs placebo in the 2 short-term double-blind placebo-controlled parts of the study. Of note, when the incidence of heart failure leading to hospitalisation was calculated taking into account the entire duration of exposure to aprocitentan (48 weeks), which included the 2 short-term double-blind parts and the long-term uncontrolled part, the incidence was consistent with that reported in published articles in the RHT population [Bhatt 2014, Bhandari 2016, Muntner 2014] and in a real-world study (see Characterisation of the risk for further details). Furthermore, all subjects randomised in the study had multiple risk factors (heart failure, CKD, diabetes, CHD, older age, and obesity) at baseline. Of note, 19.6% of study 301 patients had a medical history of heart failure.
Characterisation of the risk:	**Phase 2 study (AC-080A201)** There were no treatment-emergent AEs of heart failure. 2 subjects, who were not randomised, had congestive heart failure (1 serious and 1 nonserious) after or during the RI period. **Phase 3 (ID-080A301)** Out of the 730 subjects with RHT treated for up to 48 weeks, cumulatively, there were 19 subjects (2.6%) with treatment-emergent events of heart failure irrespective of study treatment period: 8 subjects with only nonserious AEs and 11 subjects with at least one SAE (i.e., requiring hospitalisation) as per Central Adjudication Committee adjudication.

Important potential risk: Heart failure due to fluid retention in predisposed patients	
	Of note, 2 additional subjects had heart failure during placebo RI prior to randomization (1 SAE in a non-randomised subject and 1 nonserious AE in a randomised subject). Furthermore, 19.6% of all 730 randomised subjects reported a medical history of heart failure at baseline. Of the 11 subjects with hospitalisation for heart failure in all study treatment periods (including the aprocitentan 25 mg SB 32-week period), 10 subjects experienced the event on 25 mg aprocitentan; however, there was a low rate of discontinuation (n = 2), low attribution of heart failure aggravation to the study drug by treating physicians (n = 1), a low rate of pulmonary oedema (n = 3), and no case of fatal outcome was reported. Of note, by study design 85% of exposure occurred on aprocitentan and only 15% on placebo. In the 4-week DB period, heart failure AEs were reported in 3 subjects, 2 (0.8%) in the aprocitentan 25 mg group (both SAEs), 1 (0.4%) in the aprocitentan 12.5 mg group (nonserious AE), and none in the placebo group. The 3 AEs occurred in elderly subjects with multiple risk factors for heart failure, such as history of heart failure, CKD, or obesity, and were assessed as unrelated by the investigator. One of the SAE was likely triggered by hypertensive crisis leading to hospitalisation. In the SB period (aprocitentan 25 mg), heart failure AEs were reported in 12 subjects (1.7%, 6 SAEs and 6 nonserious AEs). 11 out of 12 subjects had treatment-emergent heart failure assessed as unrelated to aprocitentan by the investigator. Alternative explanations included infections (3 subjects), atrial fibrillation (1 subject), worsening of coronary artery disease (1 subject), and hypertensive crisis (1 subject). There was a single SAE (verbatim reported as cardiac failure chronic aggravated) of heart failure assessed as related to aprocitentan by the investigator due to fluid retention. This obese and diabetic subject had a medical history of chronic heart failure and other comorbidities including cardiac diseases. The 12 subjects had the following risk factors (each subject had multiple risk factors): • 9 out of 12 subjects had a medical history of cardiac disease including 4 subjects with chronic heart failure, 3 subjects with CHD, 1 subject with congestive cardiomyopathy, 1

Important potential risk: Heart failure due to fluid retention in predisposed patients	
	with left ventricular hypertrophy, and 1 with atrial fibrillation. • 5 out of 12 subjects had a medical history of CKD. • 11 out of 12 subjects had diabetes. • 8 out of 12 subjects were ≥ 65 years of age (including 4 subjects ≥ 75 years). • 7 out of 12 subjects were obese with BMI ≥ 35 kg/m^2 (including 4 subjects with BMI ≥ 40 kg/m^2). • 7 out 12 subjects were on loop diuretics (including 1 subject on 160 mg furosemide) and/or aldosterone receptor blocking diuretics at screening and were switched to standard background antihypertensive therapy as per protocol. In the DB-WD period, heart failure was reported in 4 subjects, 3 (1%) in the aprocitentan 25 mg group (2 SAEs and 1 nonserious AE) and 1 (0.3%) in the placebo group (SAE). The 4 AEs/SAEs reported during the DB-WD period occurred in subjects with multiple risk factors for heart failure, such as history of heart failure, CKD, diabetes or obesity, and were assessed as unrelated by the investigator: *Comparison of hospitalisation for heart failure in study 301 to external data:* To account for the absence of a placebo control during the long-term (32 weeks) uncontrolled part of study 301, a systematic literature review and a real-world study were performed to compare the incidence of hospitalisation for heart failure to external data. Further details about the methodology used in the systematic literature review and real-world study can be found in the Summary of Clinical Safety. In study 301, a total of 10 subjects on aprocitentan (any dose) were hospitalised for heart failure up to EOT +10 days (i.e., within 5 half-lives of aprocitentan); this corresponds to an incidence rate of 1.92 per 100 subjects-years (95% CI, 0.92, 3.53). The incidence rate reported in the literature for an RHT population was 2.32 (95% CI, 1.96–2.76) per 100 person-years [Muntner 2014], 2.62 (95% CI, 2.41–2.84) per 100 person-years [Bhandari 2016], and 4.5 (95% CI, 2.5–7.8) per 100 person-years [Bhatt 2014].

Important potential risk: Heart failure due to fluid retention in predisposed patients	
	The incidence rate in the IQVIA real-world study conducted in an uncontrolled hypertensive population was 2.34 (95% CI, 2.17–-2.52) per 100 person-years. Overall, taking into account the high prevalence of risk factors in the RHT population, the incidence of hospitalisation for heart failure in study 301 is consistent with what has been reported in the systematic literature review of the RHT population and from the real-world study of an uncontrolled hypertensive population. Despite the slight numerical imbalance in the double-blind parts of the 301 study, the reported cases of heart failure seem to reflect the expected occurrence and natural progression in an RHT population with multiple pre-existing risk factors and cardiac comorbidities including heart failure. Of note, the design of study 301 may have contributed to the occurrence of heart failure, particularly in subjects with pre-existing heart failure, due to the requirement for subjects to switch their individual background antihypertensive medications to a fixed dose combination (SBAT: valsartan 160 mg, amlodipine 10/5 mg and hydrochlorothiazide 25 mg).
Risk factors and risk groups:	Patients with underlying heart disease are considered at higher risk of aggravation of heart failure. Other important risk factors commonly observed in the RHT population which may predispose to fluid retention include CKD and diabetes. Risk groups mainly include the elderly and obese patients.
Preventability:	Preventability of heart failure due to fluid retention is based on a combination of actions including lifestyle modifications (e.g., low-sodium diet, body weight reduction), monitoring of patient after initiation of aprocitentan, no change in loop diuretic treatment of patients before initiating aprocitentan, and use of effective diuretics dose reduction / treatment discontinuation when signs/symptoms of fluid retention occur. The following recommendations are included in section 4.4 of the SmPC: <u>*Cardiovascular events*</u> *Aprocitentan has not been studied in patients with unstable or severe cardiac disease, such as uncontrolled symptomatic arrhythmia (including atrial fibrillation), heart failure New York Heart Association stage III–IV or stage II with relevant valve disease, with NT-proBNP plasma concentration*

Important potential risk: Heart failure due to fluid retention in predisposed patients	
	≥ 500 pg/mL, or with recent (within 6 months) unstable angina, myocardial infarction, transient ischemic attack or stroke. JERAYGO is not recommended in these patients. *Due to the general risk of CV events in patients with resistant hypertension and since aprocitentan can cause fluid retention, patients at high risk of developing congestive heart failure or other CV events should be monitored for signs and symptoms of fluid retention.* *Fluid retention* *Peripheral oedema and fluid retention are known effects of ERAs and were observed in clinical studies with aprocitentan (see section 4.8). After treatment initiation, patients should be monitored for signs of fluid retention such as oedema or weight gain. If clinically significant fluid retention develops, the patient should be evaluated to determine the cause and the need for additional supportive treatment, including additional diuretics or increase of dose of currently prescribed diuretic (as appropriate), before considering dose reduction or discontinuation of JERAYGO.* *In patients treated with loop diuretics before starting therapy with JERAYGO, the loop diuretic should not be switched to a less effective diuretic at initiation.* *Patients with underlying renal impairment (eGFR < 60 mL/min/1.73 m^2) or pre-existing heart failure taking JERAYGO may be at a higher risk of developing fluid retention, as may elderly patients (> 65 years), patients with diabetes, or severely obese patients (BMI ≥ 40 kg/m^2). When switching to 25 mg, the risk of increasing fluid retention, potentially aggravating heart failure or CV events, has to be taken into consideration in these patients.*
Impact on the risk-benefit balance of the product:	Based on the data generated so far, the potential for aprocitentan to lead to heart failure is considered low, and its impact on the benefit-risk balance of aprocitentan is considered minimal.
Public health impact:	Public health impact is considered low.

Important potential risk: Severe liver injury	
Potential mechanisms:	The mechanism of hepatotoxicity is known for bosentan and is based on the inhibition of the canalicular bile salt export pump [Fattinger 2001]. This mode of action is not shared by other ERAs [Treiber 2014].
Evidence source(s) and strength of evidence:	Class labelling related to increased liver enzymes/hepatotoxicity is in place for all marketed ERAs, i.e., bosentan, ambrisentan, and macitentan, all approved for PAH. This was due to the safety profile of the first approved ERA, bosentan, which caused dose-dependent liver toxicity [Denton 2008, Rubin 2002]. Other approved ERAs, such as ambrisentan and macitentan, do not appear to confer the same risk of hepatotoxicity as bosentan, based on meta-analyses of clinical trials [Pan 2017, Wei 2016] and the accumulating post-marketing experience. Of note, darusentan, the first ERA developed (but not commercialised) for the treatment of RHT, was also not associated with an increased risk of abnormal aminotransferase levels [Bakris 2010, Black 2007, Weber 2009]. In the aprocitentan programme, there was no evidence of drug-induced hepatotoxicity based on the absence of an imbalance between treatment groups, the presence of underlying risk factors / alternative causes in most cases and/or the non-suggestive chronology of the events. There were no cases meeting the Hy's rule. Marked elevation of transaminases was neither dose-dependent nor different from placebo in the DB periods of Phase 2 and Phase 3 studies.
Characterisation of the risk:	**Phase 2 study AC-080A201** In the Phase 2 study, 2 nonserious cases of ALT/AST > 3 × ULN were observed: one in the placebo arm and one in the aprocitentan 5 mg arm. There were no SAEs or cases meeting the Hy's rule. **Phase 3 study (ID-080A301)** In total, there were 25 randomised subjects with ALT/AST > 3 × ULN at any time during the study; in 17 subjects the increase in liver enzymes was treatment-emergent, in 7 subjects the increase in liver enzymes occurred during screening/RI, in

Important potential risk: Severe liver injury	
	1 subject the increase in liver enzymes occurred during the follow-up period. The treatment-emergent liver enzymes marked abnormalities were well balanced between aprocitentan and placebo groups during the 2 placebo-controlled parts of the study (4-week DB part 1 and 12-week DB-WD part 3), as described below: In the DB part 1, ALT/AST > 3 × ULN was reported in 3 subjects, 2 (0.8%) in the placebo group (1 with ALT/AST > 10 × ULN) and 1 (0.4%) in the aprocitentan 25 mg group (ALT/AST > 3 × ULN and ≤ 5 × ULN). In the SB part 2 (aprocitentan 25 mg), ALT/AST > 3 × ULN was reported in 9 (1.3%) subjects, 3 with ALT/AST > 5 × ULN and ≤ 10 × ULN and 1 with ALT/AST > 10 × ULN. In the DB-WD part 3, ALT/AST > 3 × ULN was reported in 7 subjects, 4 (1.3%) in the aprocitentan 25 mg group (1 with ALT/AST > 5 × ULN and ≤ 10 × ULN; 1 out of these 4 had the ALT/AST increase 33 days after EOT) and 3 (1.0%) in the placebo group (1 with ALT/AST > 10 × ULN). There were no SAEs or cases meeting the Hy's rule. 1 subject on 25 mg aprocitentan had treatment-emergent total bilirubin > 2 × ULN with normal aminotransferase during the study. The total bilirubin values during the study ranged between 2 and 3 × ULN, which was similar to baseline values. This subject completed the study with no action taken with the study medication. 13 subjects experienced ALT/AST > 3 × ULN during exposure to aprocitentan, all were asymptomatic and with normal bilirubin. Overall, there is no evidence of drug-induced hepatotoxicity based on the absence of an imbalance between treatment groups, the presence of underlying risk factors / alternative causes in most cases and/or the non-suggestive chronology of the events.
Risk factors and risk groups:	Subjects with pre-existing severe liver disease.

Important potential risk: Severe liver injury	
Preventability:	The use of JERAYGO in patients with severe hepatic impairment (Child-Pugh class C; with or without cirrhosis) is contraindicated (section 4.3 of the SmPC). Additionally, section 4.4 of the SmPC states: *Elevations of aminotransferases and hepatotoxicity are known effects of other ERAs.* *JERAYGO must not be initiated in patients with severe hepatic impairment (see section 4.3) and is not recommended in patients with elevated aminotransferases (> 3 × ULN). Liver enzyme tests should be obtained prior to initiation of JERAYGO.* *During treatment, monitoring of liver enzymes is recommended. If sustained, unexplained, clinically relevant aminotransferase elevations occur, or if elevations are accompanied by an increase in bilirubin > 2 × ULN, or by clinical symptoms of hepatotoxicity, JERAYGO should be discontinued.* In addition, a patient card explains the hepatic risk associated with the administration of aprocitentan and the need to report symptoms and signs of any potential hepatic ADR.
Impact on the risk-benefit balance of the product:	Based on the data generated so far, the potential for aprocitentan to lead to severe liver injury is considered low, and its impact on the benefit-risk balance of aprocitentan is considered minimal.
Public health impact:	Public health impact is considered low.

Important potential risk: Male infertility	
Potential mechanisms:	Dilation of seminiferous tubules is considered to be related with the pharmacodynamic effect of aprocitentan as an ERA on smooth muscle cells. Tubular degeneration might occur as a secondary effect based on long-term dilation with backlog of seminal fluid and increasing pressure on the tubular epithelium.
Evidence source(s) and strength of evidence:	Male infertility is an important potential risk for all marketed ERAs. In nonclinical studies, aprocitentan had no effects on male fertility.

Important potential risk: Male infertility	
	Decreased sperm count has been observed in patients taking other ERAs.
Characterisation of the risk:	***Nonclinical data*** There were no effects on fertility in male rats after treatment for 10 weeks prior to pairing with untreated female rats at dose levels up to 26 (67) -fold the human exposure at MRHD, based on total (free) concentrations. In one out of two 26-week repeated dose toxicity study in rats, there were histological changes such as dilation of seminiferous tubules accompanied by minimal to slight tubular degeneration at dose levels corresponding to 21 (54) -fold the human exposure at MRHD based on total (free) concentrations. In dogs, similar effects were observed at exposure corresponding to 26 (88)-fold the human exposure at MRHD based on total (free) concentrations. ***Clinical data*** There is no evidence of male infertility based on post-marketing experience with other ERAs.
Risk factors and risk groups:	Fertile male subjects
Preventability:	Section 4.6 of the SmPC states: *Decreased sperm count has been observed in patients taking other ERAs. It is not known if aprocitentan may adversely affect spermatogenesis in men.*
Impact on the risk-benefit balance of the product:	Based on the data generated so far, the potential for aprocitentan to lead to male infertility is considered very low, and its impact on the benefit-risk balance of aprocitentan is considered minimal.
Public health impact:	Public health impact is considered very low.

SVII.3.2 Presentation of the missing information

Missing Information: Long-term cardiovascular safety under controlled clinical setting	
Evidence source:	Study 301 included a 32-week non-controlled SB part 2 and 16-week placebo-controlled data (4-week DB in part 1, 12-week

	DB-WD in part 3) in RHT population with underlying high CV risk.
Population in need of further characterisation:	RHT population treated with aprocitentan for a long-term duration under controlled clinical setting.

PART II: MODULE SVIII – SUMMARY OF THE SAFETY CONCERNS

Table 16 Summary of safety concerns

Summary of safety concerns	
Important identified risks	• Teratogenicity
Important potential risks	• Heart failure due to fluid retention in predisposed patients • Severe liver injury • Male infertility
Missing information	• Long-term cardiovascular safety under controlled clinical setting

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

III.1 Routine pharmacovigilance activities

Planned routine pharmacovigilance activities relevant to centrally authorised medicinal products for human use apply to aprocitentan.

Routine pharmacovigilance activities beyond adverse reaction reporting, signal detection and evaluation in aggregated PSUR:

- Specific AE follow-up questionnaire for the risk of severe liver injury. The hepatic AE questionnaire will be used to collect information on all hepatic AEs in order to closely monitor and further characterise the risk, and to assess causal relationship.

III.2 Additional pharmacovigilance activities

Additional pharmacovigilance activities to assess long-term controlled cardiovascular safety include:

- PASS ID-080A401 (study 401): A multicenter, randomized, open-label, active-controlled pragmatic trial in patients with resistant hypertension.

Summary of study 401

Rationale and study objectives

While the benefit of aprocitentan was established in a large Phase 3 clinical trial (ID-080A301/PRECISION), controlled long-term safety data were limited in this trial due to a 32-week single-arm aprocitentan 25 mg period, especially for major adverse cardiac events and hospitalization for heart failure.

The PASS ("study 401") will be conducted to assess the missing information in the RMP "long-term CV safety under controlled clinical setting". Study 401 is a Phase 4 study in adult patients with RHT, which aims to further characterize the long-term CV safety profile of aprocitentan when used in clinical practice.

Study design

Study 401 is a multicenter, international, randomised, open-label, active-controlled, parallel-group, pragmatic trial in patients with RHT newly treated with aprocitentan or any other antihypertensive drug recommended by local guidelines, in clinical practice. Patients will be randomized in a 1:1 ratio to the following groups:

- Aprocitentan added to the existing antihypertensives (henceforth, Apro group).

  or

- Any other antihypertensive therapy added to the existing antihypertensives, according to local guidelines (henceforth, SoC group).

The primary objective of the study is to compare MACE-plus rates between the aprocitentan group and the SoC group.

The secondary objective of the study is to further characterize the long-term safety profile of aprocitentan in adult subjects with RHT in a randomized and active-controlled (aprocitentan vs standard of care) setting. Specifically, the incidence rates will be estimated for the following potential risks:

- Heart failure due to fluid retention in predisposed patients
- Severe liver injury.

Study population

The study will include all eligible adult patients with RHT, i.e., uncontrolled BP despite use of at least 3 antihypertensives including a diuretic and in need of an additional BP lowering therapy.

Milestones

Study 401 is planned to start once the protocol is approved by EMA/PRAC (protocol submission planned for 30 September 2024). The final analysis will be conducted when all subjects have completed the study, and the final study report is planned to be submitted on

31 March 2031. Interim safety data will be reviewed on an ongoing basis and updates provided in the yearly progress report.

III.3 Summary table of additional pharmacovigilance activities

Table 17 provides an overview of all ongoing and planned additional pharmacovigilance activities.

Table 17 Ongoing and planned additional pharmacovigilance activities

Study; Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 – Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorisation				
Study 401 PASS – Multicenter, randomized, open-label, active-controlled, pragmatic trial in patients with RHT. (Planned)	Primary objective: • Compare MACE-plus rates between the aprocitentan group and the SoC group Secondary objective: • Characterize the long-term safety profile of aprocitentan in adult subjects with RHT including on: ▪ Heart failure due to fluid retention in predisposed patients ▪ Severe liver injury	Long-term CV safety profile of aprocitentan under controlled clinical setting Heart failure due to fluid retention in predisposed patients Severe liver injury.	Protocol submission	30 September 2024
			Progress reports	Annual update
			Final study report	31 March 2031
Category 2 – Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorisation or a marketing authorisation under exceptional circumstances				
Not applicable.				
Category 3 – Required additional pharmacovigilance activities				
Not applicable				

CV = cardiovascular; MACE = major adverse cardiac event(s); PASS = post-authorisation safety study; PRAC = Pharmacovigilance Risk Assessment Committee; RHT = resistant hypertension.

PART IV: PLANS FOR POST-AUTHORISATION EFFICACY STUDIES

None.

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

V.1 Routine risk minimisation measures

Table 18 Description of routine risk minimisation measures by safety concern

Safety concern	Routine risk minimisation activities
Important identified risk: Teratogenicity	**Routine risk communication:** SmPC sections 4.3, 4.4, 4.5, 4.6, and 5.3 PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Instructions for the use of JERAYGO in WOCBP and recommendation for pregnancy tests before the start of treatment, monthly during treatment and one month after stopping treatment are provided in SmPC sections 4.4 and 4.6, and PL section 2. **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to medical prescription.
Important potential risk: Heart failure due to fluid retention in predisposed patients	**Routine risk communication:** SmPC section 4.4 PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendation not to use JERAYGO in patients with unstable or severe cardiac disease, such as uncontrolled symptomatic arrhythmia (including atrial fibrillation), heart failure NYHA stage III–IV or stage II with relevant valve disease, with NT-proBNP plasma concentration ≥ 500 pg/mL, or with recent (within 6 months) unstable angina, myocardial infarction, transient ischemic attack or stroke. Recommendations to monitor patients (especially patients with underlying renal impairment or pre-existing heart failure, elderly patients, patients with diabetes, or severely obese patients) for signs of fluid retention and heart failure are included in SmPC section 4.4. Information on how to detect signs and symptoms of oedema (swelling) / fluid retention and heart disease and what to do

Safety concern	Routine risk minimisation activities
	(i.e., contact the doctor) in the event such signs occur is provided in PL section 2. **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to medical prescription.
Important potential risk: Severe liver injury	**Routine risk communication:** SmPC sections 4.3, 4.4, and 4.8 PL section 2 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** Recommendation not to use JERAYGO in patients with elevated aminotransferases (> 3 × ULN) and for liver enzyme monitoring are included in the SmPC section 4.4. Information on how to detect signs and symptoms of liver injury is provided in PL section 2. **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to medical prescription.
Important potential risk: Male infertility	**Routine risk communication:** SmPC sections 4.6 and 5.3 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to medical prescription.
Missing information: Long-term cardiovascular safety under controlled clinical setting	**Routine risk communication:** SmPC section 5.1 **Routine risk minimisation activities recommending specific clinical measures to address the risk:** None. **Other routine risk minimisation measures beyond the Product Information:** Medicinal product subject to medical prescription.

V.2 Additional risk minimisation measures

Patient Card

For the specific safety concern "teratogenicity" (important identified risk) and "severe liver injury" (important potential risk), an additional risk minimisation measure (patient card; see Annex 6) is proposed to remind patients of the teratogenicity and hepatotoxicity risks, and appropriate use of JERAYGO.

Objectives

To educate patients treated with JERAYGO about:

- The risks for the foetus if a patient becomes pregnant during treatment with JERAYGO.
- Actions to be taken in the event of pregnancy, e.g., to report immediately to their prescribing physician any pregnancy that may occur.
- Actions to be taken to avoid pregnancy, i.e., use a reliable form of birth control (contraception).
- Actions to be taken for early detection of pregnancy, i.e., perform pregnancy tests.
- The risk of hepatotoxicity that medicines like JERAYGO may cause.
- The recommendation for regular monitoring of liver function by their doctor, the potential signs of hepatotoxicity, and the actions to be taken if any sign of liver dysfunction occurs (i.e., inform their doctor).

Rationale for the additional risk minimisation activity

Teratogenicity is considered an important identified risk due to class effect. Severe liver injury is considered an important potential risk due to class effect.

To strengthen labelling recommendations for JERAYGO in the treatment of RHT, a patient card is proposed. The patient card will reinforce patient knowledge regarding the safe use of JERAYGO, thereby mitigating the potential risk of teratogenicity and severe liver injury associated with JERAYGO treatment.

Target audience

Patients.

Planned distribution path

- The patient card will be a small credit-card sized folding card addressed to patients prescribed JERAYGO. It will highlight information on the potential risks of teratogenicity and liver problems, the need to use a reliable method of contraception, perform monthly pregnancy tests, and the need to report immediately any pregnancy that may occur and to inform the doctor in case of any signs of hepatotoxicity. In addition, it will contain a space to add the name and contact details of the prescribing doctor.

- The patient card will be included within the JERAYGO packaging, together with the patient leaflet.
- Patients would be able to show the card to inform health care professionals of their treatment.

Evaluation of the effectiveness

Reporting trend analyses from post-marketing safety data are to be monitored in the PSUR. Assessments will start one year after launch and will be done at the end of each PSUR reporting interval.

Stable reporting trend analysis of post-marketing safety data is the criterion for success.

V.3 Summary of risk minimisation measures

Safety concern	Risk minimisation measures	Pharmacovigilance activities
Important identified risk: Teratogenicity	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4, 4.5, 4.6, and 5.3 PL section 2. Medicinal product subject to medical prescription. **Additional risk minimisation measures:** Patient card.	No routine pharmacovigilance activities beyond adverse reaction reporting, signal detection and evaluation in aggregated PSUR are planned.
Important potential risk: Heart failure due to fluid retention in predisposed patients	**Routine risk minimisation measures:** SmPC section 4.4 PL section 2 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** None	No routine pharmacovigilance activities beyond adverse reaction reporting, signal detection and evaluation in aggregated PSUR are planned. Additional pharmacovigilance activities: PASS (study 401); final study report due date: 31 March 2031.
Important potential risk: Severe liver injury	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4, and 4.8	Routine pharmacovigilance activities beyond

Safety concern	Risk minimisation measures	Pharmacovigilance activities
	PL section 2 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** Patient card	adverse reaction reporting, signal detection and evaluation in aggregated PSUR: targeted hepatic AE questionnaire. Additional pharmacovigilance activities: PASS (study 401); final study report due date: 31 March 2031.
Important potential risk: Male infertility	**Routine risk minimisation measures:** SmPC sections 4.6 and 5.3 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** None	No routine pharmacovigilance activities beyond adverse reaction reporting, signal detection and evaluation in aggregated PSUR are planned.
Missing information: Long-term cardiovascular safety under controlled clinical setting	**Routine risk minimisation measures:** SmPC section 5.1 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** None	Additional pharmacovigilance activities: PASS (study 401); final study report due date: 31 March 2031.

PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for JERAYGO (aprocitentan)

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

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

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

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

I. The medicine and what it is used for

JERAYGO is authorised for the treatment of resistant hypertension (see SmPC for the full indication). It contains aprocitentan as the active substance and it is given as film-coated tablets for oral use.

Further information about the evaluation of JERAYGO's benefits can be found in JERAYGO's EPAR, including in its plain-language summary, available on the EMA website, under the medicine's webpage <link to the EPAR summary landing page>.

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

Important risks of JERAYGO, together with measures to minimise such risks, are outlined below.

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

- Specific information, such as warnings, precautions, and advice on correct use, in the package leaflet and SmPC addressed to patients and healthcare professionals.

- Important advice on the medicine's packaging.
- The authorised pack size — the amount of medicine in a pack is chosen so to ensure that the medicine is used correctly.
- The medicine's legal status — the way a medicine is supplied to the patient (e.g., with or without prescription) can help to minimise its risks.

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

In the case of JERAYGO, these measures are supplemented with one ***additional risk minimisation measure*** *(Patient Card)* mentioned under the relevant important risks of teratogenicity and severe liver injury (see below).

In addition to these measures, information about adverse reactions is collected continuously and regularly analysed, including Periodic Safety Update Report (PSUR) assessment, so that immediate action can be taken as necessary. These measures constitute ***routine pharmacovigilance activities***.

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

II.A List of important risks and missing information

Important risks of JERAYGO are risks that need special risk management activities to further investigate or minimise the risk, so that the medicinal product can be safely taken.

Important risks can be regarded as identified or potential. Identified risks are concerns for which there is sufficient proof of a link with the use of JERAYGO. Potential risks are concerns for which an association with the use of this medicine is possible based on available data, but this association has not been established yet and needs further evaluation.

Missing information refers to information on the safety of the medicinal product that is currently missing and needs to be collected.

List of important risks and missing information	
Important identified risks	Teratogenicity
Important potential risks	Heart failure due to fluid retention in predisposed patients Severe liver injury Male infertility
Missing information	Long-term cardiovascular safety under controlled clinical setting

II.B Summary of important risks

Important identified risk: teratogenicity	
Evidence for linking the risk to the medicine	Evidence of teratogenicity with ERAs is limited to animal data. ERAs have shown teratogenic effects in rats and/or rabbits, mainly craniofacial and cardiovascular malformations, in offspring of animals during pregnancy [Ruest 2009]. There is limited post-marketing experience in humans [Hitzerd 2019, Kamp 2021]. Based on the limited post-marketing experience in humans, there is no indication of human teratogenicity.
Risk factors and risk groups	Women of childbearing potential who are not using a reliable method of contraception.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4, 4.5, 4.6, and 5.3 PL section 2 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** Patient card

Important potential risk: Heart failure due to fluid retention in predisposed patients	
Evidence for linking the risk to the medicine	Aprocitentan is developed for the treatment of RHT in a population with high CV morbidity and mortality. In study 301, there was a small and slightly higher incidence of treatment-emergent heart failure leading to hospitalisation in the aprocitentan groups vs placebo during the double-blind periods; however, when the incidence of heart failure leading to hospitalisation was calculated taking into account the entire duration of exposure to aprocitentan (48 weeks), the incidence was consistent with that reported in published articles in the RHT population [Bhatt 2014, Bhandari 2016, Muntner 2014] and in a real-world study. Furthermore, all subjects randomised in the study had multiple risk factors (heart failure, CKD, diabetes, CHD, older age and obesity) at baseline. Of note, 19.6% of study 301 patients had a medical history of heart failure.
Risk factors and risk groups	Patients with underlying heart disease are considered at higher risk of aggravation of heart failure. Other important risk factors commonly observed in the RHT population which may predispose to fluid retention include CKD and diabetes. Risk groups mainly include the elderly and obese patients.

Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.4 PL section 2 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS (study 401) See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Severe liver injury	
Evidence for linking the risk to the medicine	Class labelling related to increased liver enzymes/hepatotoxicity is in place for all marketed ERAs, i.e., bosentan, ambrisentan, and macitentan, all approved for PAH. This was due to the safety profile of the first approved ERA, bosentan, which caused dose-dependent liver toxicity [Denton 2008, Rubin 2002]. Other approved ERAs, such as ambrisentan and macitentan, do not appear to confer the same risk of hepatotoxicity as bosentan, based on meta-analyses of clinical trials [Pan 2017, Wei 2016] and the accumulating post-marketing experience. Of note, darusentan, the first ERA developed (but not commercialised) for the treatment of RHT, was also not associated with an increased risk of abnormal aminotransferase levels [Bakris 2010, Black 2007, Weber 2009]. In the aprocitentan programme, there was no evidence of drug-induced hepatotoxicity based on the absence of an imbalance between treatment groups, the presence of underlying risk factors / alternative causes in most cases and/or non-suggestive chronology of the events. There were no cases meeting the Hy's rule. Marked elevation of transaminases was neither dose-dependent nor different from placebo in the double-blind periods of Phase 2 and Phase 3 studies.
Risk factors and risk groups	Subjects with pre-existing severe liver disease.
Risk minimisation measures	**Routine risk minimisation measures:** SmPC sections 4.3, 4.4, and 4.8 PL section 2 Medicinal product subject to medical prescription.

	Additional risk minimisation measures: Patient card
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS (study 401) See Section II.C of this summary for an overview of the post-authorisation development plan.

Important potential risk: Male infertility	
Evidence for linking the risk to the medicine	*Nonclinical data* There were no effects on fertility in male rats after treatment for 10 weeks prior to pairing with untreated female rats at dose levels up to 26 (67)-fold the human exposure at MRHD, based on total (free) concentrations. In one out of two 26-week repeated dose toxicity study in rats, there were histological changes such as dilation of seminiferous tubules accompanied by minimal to slight tubular degeneration at dose levels corresponding to 21 (54)-fold the human exposure at MRHD based on total (free) concentrations. In dogs, similar effects were observed at exposure corresponding to 26 (88)-fold the human exposure at MRHD based on total (free) concentrations. *Clinical data* There is no evidence of male infertility based on post-marketing experience with other ERAs.
Risk factors and risk groups	Fertile male subjects
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 4.6 and 5.3 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** None

Missing information: Long-term cardiovascular safety under controlled clinical setting	
Risk minimisation measures	**Routine risk minimisation measures:** SmPC section 5.1 Medicinal product subject to medical prescription. **Additional risk minimisation measures:** None
Additional pharmacovigilance activities	**Additional pharmacovigilance activities:** PASS (study 401) See Section II.C of this summary for an overview of the post-authorisation development plan.

II.C Post-authorisation development plan

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

The following studies are conditions of the marketing authorisation:

PASS ID-080A401 (study 401)

Purpose of the study: Phase 4 study in adult patients with RHT, which aims to further characterise the long-term safety profile of aprocitentan when used in clinical practice.

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

There are no studies required for JERAYGO.

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[D-17.023] AC-080A201: A Multi-center, double-blind, double-dummy, randomized, placebo- and active-reference, parallel group, Phase 2 dose-finding study with ACT-132577 in subjects with essential hypertension (grade 1 and 2). Idorsia Pharmaceuticals Ltd; Clinical Study Report AC-080A201, 20 December 2017.

[D-22.269] Multi-center, blinded, randomized, PaRallEl-group, Phase 3 study with aproCItentan in Subjects with ResIstant HypertensiON (RHT). Idorsia Pharmaceuticals Ltd; Clinical Study Report ID-080A301, 27 October 2022.

[T-14.022] ACT-132577 - 4-week oral (capsules) toxicity study in the Harlan beagle dog followed by a 4-week treatment-free period (WIL Research study no. AB20497). Actelion Pharmaceuticals Ltd; 27 January 2015.

[T-14.036] ACT-132577E: 26 week oral (gavage) administration toxicity study in the rat followed by a 9 week treatment-free period (Covance study no. 8310210). Actelion Pharmaceuticals Ltd; 9 May 2017.

[T-14.072] ACT-132577: 13 week oral (capsule) administration toxicity study in the dog followed by a 9 week treatment-free period (Covance study no. 8310211). Actelion Pharmaceuticals Ltd; 12 April 2017.

[T-15.053] ACT-132577: 39 week oral (capsule) administration toxicity study in the dog followed by a 13 week treatment-free period (Covance study no. 8322373). Idorsia Pharmaceuticals Ltd; 26 April 2018.

[T-16.001] ACT-132577E - Fertility toxicity study by the oral route (gavage) in the male rat (Segment I) (Charles River Laboratories study no. AB21284). Idorsia Pharmaceuticals Ltd; 27 April 2018.

[T-16.021] ACT-132577E: 26-week toxicity study by the oral route (gavage) in the male rat followed by a 9-week treatment-free period (Charles River Laboratories study no. AB21338). Idorsia Pharmaceuticals Ltd; 26 April 2018.

[T-22.027] ACT-132577E: A Preliminary Dose Range-Finding Embryo-fetal Development Study by Oral (Stomach Tube) in Rabbits (Charles River Laboratories study no. 20391790). Idorsia Pharmaceuticals Ltd; 30 March 2023.

[T-22.028] ACT-132577E: An Embryo-fetal Development Study by Oral (Stomach Tube) Administration in Rabbits (Charles River Laboratories study no. 20391791). Idorsia Pharmaceuticals Ltd; 5 June 2023.

[T-22.029] ACT-132577E: A Preliminary Dose Range-Finding Embryo-fetal Development Study by Oral (Gavage) Administration in Rats (Charles River Laboratories study no. 20391792). Idorsia Pharmaceuticals Ltd; 30 March 2023.

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PART VII: ANNEXES

Annex 4

Specific adverse drug reaction follow-up forms

HEPATIC EVENT – ADVERSE EVENT QUESTIONNAIRE

idorsia

To: _____ **From:** _____

Date: DD-Mmm-YYYY **MCN:**

Origin of report: ☐ Spontaneous **Study protocol #:** _____

Idorsia study: ☐ Yes ☐ No **Study name:**

I. PATIENT INFORMATION

Initials: ..... ☐ Male ☐ Female	**Age** (yr):	**Height:** ..... ☐ cm ☐ in	**Weight:** ..... ☐ kg ☐ lbs

RELEVANT MEDICAL HISTORY (prior to product initiation/ongoing at time of product initiation) – **please tick all that apply:**

- ☐ Hepatic enzyme increases, i.e. .....
- ☐ Bilirubin increase, i.e. .....
- ☐ Non-alcoholic steatohepatitis
- ☐ Viral hepatitis, i.e. .....
- ☐ Autoimmune hepatitis
- ☐ Alcoholic hepatitis
- ☐ Cirrhosis
- ☐ Alcohol use (# drinks per week): ☐ <5 ☐ 5-10 ☐ >10
- ☐ Connective tissue disease, i.e. .....
- ☐ Autoimmune disease, i.e. .....
- ☐ Cholelithiasis
- ☐ Cholecystitis
- ☐ Other infections, i.e. .....
- ☐ Blood transfusion
- ☐ Drug abuse, i.e. .....

Other medical history (specify): .....

.....

II. ADVERSE EVENT

Main adverse event: ..... Onset date: .....

ASSOCIATED SIGNS/SYMPTOMS/OTHER CONDITIONS:

☐ Abdominal pain	☐ Encephalopathy	☐ Fever	☐ Ascites
☐ Asthenia	☐ Coma	☐ Infections	☐ Hypotension
☐ Nausea	☐ Pruritus	☐ Sepsis	☐ Signs of right heart failure
☐ Vomiting	☐ Rash	☐ Hepatomegaly	
☐ Jaundice	☐ Adenopathy	☐ Splenomegaly	

Other(specify): .....

SERIOUSNESS: If this event is <u>serious</u> please check all criteria which apply: ☐ Death ☐ Life-threatening ☐ Congenital abnormality ☐ New Hospitalization ☐ Prolonged Hospitalization ☐ Medically significant

EVENT OUTCOME: ☐ Liver transplant Resolved: ☐ with sequelae ☐ without sequelae ☐ Not resolved ☐ Unknown/lost to follow-up ☐ Death

Date of death: (DD-Mmm-YYYY) .....

Cause of death: ..... Autopsy performed? ☐ Yes ☐ No

If Yes, please provide autopsy results

III. INFORMATION REGARDING IDORSIA PRODUCT

Name of product: .....

Indication for use	Start date (DD-Mmm-YYYY)	Stop date (DD-Mmm-YYYY)	Batch #

Dechallenge: Did the reaction (event) abate after product discontinuation? ☐ Yes ☐ No ☐ N/A

Rechallenge: Did the reaction (event) reoccur after product reintroduction? ☐ Yes ☐ No ☐ N/A

IV. OVERALL CAUSALITY ASSESSMENT REGARDING IDORSIA PRODUCT

Is there a reasonable possibility that the events were related to the use of product? ☐ Yes ☐ No

V. CONCOMITANT MEDICATIONS

Name	Route	Dose	Duration	Start date DD-Mmm-YYYY	Stop date DD-Mmm-YYYY	Indication	Suspect (y/n)

VI. INVESTIGATIONS FOR LIVER INJURY

1. LIVER BIOPSY: ☐ Yes ☐ No

If yes, please provide a brief description: .....

.....

.....

2. ABDOMINAL ULTRASOUND: ☐ Yes ☐ No If yes: ☐ Normal ☐ Abnormal

3. ABDOMINAL CT/MRI: ☐ Yes ☐ No If yes: ☐ Normal ☐ Abnormal

If abnormal, please specify: .....

.....

.....

4. BIOCHEMICAL MARKERS AND LABORATORY DATA:

Marker values	Normal range; units	Dates (DD-Mmm-YYYY) Baseline Date:	First abnormal Date:	Most abnormal Date:	Resolution Date: .....
ALT					
AST					
ALP					
Bilirubin total					
Bilirubin direct					
GGT					
Albumin					
PT					
INR					

Marker	Not tested	Absent	Present
HBs Ag	☐	☐	☐
Anti-HBs Ab	☐	☐	☐
Anti-HBc Ab	☐	☐	☐
Anti-HBc/IgM Ab	☐	☐	☐
Anti-HAV/IgM Ab	☐	☐	☐
Anti-HCV Ab	☐	☐	☐
Anti-CMV IgM Ab	☐	☐	☐
Anti-EBV Ab	☐	☐	☐
Anti-HEV	☐	☐	☐
Other (specify)	.....	.....	.....
.....			
.....			

Marker	Not tested	Absent	Present
Anti-nuclear Ab	☐	☐	☐
Anti-native DNA Ab	☐	☐	☐
Anti-smooth muscle Ab	☐	☐	☐
Anti-mitochondrial Ab	☐	☐	☐
Anti-actin Ab	☐	☐	☐
Immuno-globulin G (IgG)	☐	☐	☐

	Ref. range	Date (DD-Mmm-YYYY)	Result
WBC			
Eosinophils			
Sedimentation rate			
CRP			
Amylase			
Lipase			

Titre (if any of above is ticked): .....

.....

.....

VI. DESCRIBE EVENT OR PROBLEM

Briefly describe the sequence of symptom onset, time course, treatment therapies and response, diagnosis and outcome. Additional events or problems may also be listed below.

WAS A HEPATOLOGIST OR GASTROENTEROLOGIST CONSULTED WITH REFERENCE TO THE LIVER EVENTS?

☐ Yes ☐ No If yes, please provide his conclusion:

.....

VII. REPORTER INFORMATION

Reporter name: _____ **Healthcare professional:** ☐ Yes ☐ No

Institution: _____ **Occupation:** _____

Address: _____ **Telephone #:** _____

_____ **Fax #:** _____

E-mail address:

Please sign this form and return by fax or email to .....

Signature: _____ Printed name: _____ Date: _____

All information received is kept confidential. **Thank you for your cooperation.**

Annex 6

Details of proposed additional risk minimisation activities

Patient Card

The Marketing Authorisation Holder shall ensure that in each Member State where JERAYGO is marketed, all patients who are expected to use JERAYGO have access to/are provided with a patient card, which will inform and explain to patients the risks of teratogenicity and hepatotoxicity.

The patient card for patients prescribed JERAYGO should include the following key elements/instructions:

Teratogenicity:

- JERAYGO may harm the development of the unborn child.
- Pregnant women must not take JERAYGO.
- Women of childbearing potential must use a reliable form of birth control (contraception).
- The recommendation for a pregnancy test before initiation of JERAYGO, monthly during treatment, and one month after treatment discontinuation.
- The need to report immediately to the treating physician any pregnancy that may occur.

Liver injury:

- Regular monitoring of liver function is recommended because, like other medicines of the same class, JERAYGO might cause liver injury.
- Description of the signs that can occur in case of liver problems.
- The need to report to the treating physician any of the signs that could be due to liver problems.

The content of the patient card is available in Annex III – A. Labelling of the Product Information.