ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

▼This medicinal product is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse reactions. See section 4.8 for how to report adverse reactions.

1. NAME OF THE MEDICINAL PRODUCT

JERAYGO 12.5 mg film-coated tablets
JERAYGO 25 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

JERAYGO 12.5 mg film-coated tablets

Each film-coated tablet contains 12.5 mg aprocitentan.

Excipients with known effect
Each 12.5 mg film-coated tablet contains 54 mg lactose monohydrate.

JERAYGO 25 mg film-coated tablets

Each film-coated tablet contains 25 mg aprocitentan.

Excipients with known effect
Each 25 mg film-coated tablet contains 45.7 mg lactose monohydrate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

JERAYGO 12.5 mg film-coated tablets

Yellow to orange, round biconvex (6 mm diameter), debossed with “AN” on one side, and plain on the other side.

JERAYGO 25 mg film-coated tablets

Pink, round biconvex (6 mm diameter), debossed with “AN” on one side, and “25” on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

JERAYGO is indicated for the treatment of resistant hypertension in adult patients in combination with at least three antihypertensive medicinal products (see section 5.1).

4.2 Posology and method of administration

Posology

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 blood pressure (BP) control (see section 4.4).

Missed dose
If the patient misses a dose, the patient should be told to resume treatment the next day and not take two doses in the same day.

Special populations

Elderly
No dose adjustment is required in patients over the age of 65 years (see section 5.2). There is limited clinical experience in patients over the age of 75 years (see section 4.4).

Renal impairment
No dose adjustment is required in patients with renal impairment (including severe impairment with estimated glomerular filtration rate [eGFR] 15–29 mL/min) (see sections 4.4 and 5.2).

Aprocitentan has not been studied in patients with eGFR < 15 mL/min or in patients undergoing dialysis; JERAYGO is not recommended in these patients (see section 4.4).

Hepatic impairment
No dose adjustment is required in patients with mild or moderate hepatic impairment (Child-Pugh class A or B, respectively) (see section 5.2).

Aprocitentan has not been studied in patients with severe hepatic impairment (Child-Pugh class C); JERAYGO must not be initiated in these patients (see sections 4.3 and 4.4).

Paediatric population
The safety and efficacy of aprocitentan in children and adolescents aged less than 18 years have not been established. No data are available.

Method of administration

Oral use.

JERAYGO may be taken with or without meals (see section 5.2).

The film-coated tablets are not scored and are designed to be swallowed whole.

4.3 Contraindications

- Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.
- Pregnancy (see section 4.6).
- Women of childbearing potential who are not using reliable contraception (see sections 4.4 and 4.6).
- Breast-feeding (see section 4.6).
- Patients with severe hepatic impairment (Child-Pugh class C; with or without cirrhosis) (see section 4.4).

4.4 Special warnings and precautions for use

Women of childbearing potential, pregnant and breast-feeding women

JERAYGO is contraindicated for use in women who are pregnant, breast-feeding and in women of childbearing potential who are not using reliable contraception (see sections 4.3 and 4.6).

Pregnancy tests are recommended before the start of treatment, monthly during treatment, and one month after stopping treatment to allow detection of pregnancy (see section 4.6).

Hepatotoxicity

Elevations of aminotransferases and hepatotoxicity are known effects of other endothelin receptor antagonists (ERAs). Elevations of transaminases have been reported infrequently in clinical trials of aprocitentan (see section 4.8).

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 × upper limit of normal [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.

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 (body mass index [BMI] ≥ 40 kg/m^2). When switching to 25 mg, the risk of increasing fluid retention, potentially aggravating heart failure or cardiovascular (CV) events, has to be taken into consideration in these patients.

Cardiovascular events

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 ≥ 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.

The benefit and risk of continuation or discontinuation of JERAYGO if patients experience CV events while on treatment should be assessed on an individual basis.

Haemoglobin decrease

Decreases in haemoglobin concentration and haematocrit have occurred following administration of ERAs and were observed in clinical studies with aprocitentan (see section 4.8). These decreases have been attributed to plasma volume expansion (haemodilution). In the clinical studies of aprocitentan, they stabilised after 4 weeks of treatment, remained stable during chronic treatment, and were reversible within 4 weeks after discontinuation.

Initiation of JERAYGO is not recommended in patients with severe anaemia (< 8 g/dL). If clinically indicated, haemoglobin concentrations should be measured prior to initiation of treatment and during treatment. If clinically relevant signs and symptoms related to haemoglobin decrease are observed, consider discontinuation of JERAYGO.

Renal impairment

Patients with eGFR below 60 mL/min/1.73 m^2 may have a higher risk of experiencing anaemia and oedema/fluid retention during treatment with JERAYGO. Therefore, it is recommended to monitor haemoglobin, and for signs of fluid retention or heart failure.

There is no clinical experience with the use of aprocitentan in patients with resistant hypertension and eGFR < 15 mL/min/1.73 m^2 or in patients undergoing dialysis; therefore, JERAYGO is not recommended in these patients.

Patients ≥ 75 years of age

Patients ≥ 75 years of age may have a higher risk of experiencing anaemia, oedema/fluid retention, heart failure, and cerebrovascular events. It is recommended to monitor haemoglobin, and for signs of fluid retention or heart failure.

Excipients with known effect

Lactose monohydrate
JERAYGO contains lactose monohydrate. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency, or glucose-galactose malabsorption should not take this medicinal product.

Sodium
JERAYGO contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Interaction with other medicinal products and other forms of interaction

Effect of other medicinal products on the pharmacokinetics of aprocitentan

Based on its pharmacokinetic (PK) profile, aprocitentan exposure is not expected to be impacted by other medicinal products that are inhibitors or inducers of transporters and/or CYP enzymes.

Effect of aprocitentan on the pharmacokinetics of other medicinal products

CYP enzymes and BCRP substrates
In a clinical study conducted in healthy subjects, co-administration of once daily 50 mg aprocitentan with the sensitive CYP3A4 substrate midazolam did not affect the PK of midazolam, leading to the conclusion of the absence of interaction with CYP enzymes, with the exception of the potential induction of CYP2B6 and CYP1A2 enzymes described below.

In vitro studies are inconclusive regarding the potential of aprocitentan to induce CYP2B6 and CYP1A2. In vivo induction cannot be excluded. Caution is recommended when aprocitentan is co-administered with CYP1A2 substrates with a narrow therapeutic index (e.g., tizanidine).

In a clinical study conducted in healthy subjects receiving 25 mg aprocitentan and rosuvastatin, a BCRP substrate, once daily dosing of aprocitentan increased C_{max} of rosuvastatin by 40%; however, the total exposure to rosuvastatin expressed as $AUC_{0-\infty}$ was unchanged. Therefore, BCRP substrates can be administered with aprocitentan.

Aprocitentan does not impact the PK of medicinal products for which PK is dependent on active transport, with the exception of OAT3 substrates described below.

OAT3 substrates
In vitro, aprocitentan is an OAT3 inhibitor. Therefore, aprocitentan may increase plasma concentrations of medicinal products for which excretion is dependent upon OAT3. Whether this would result in a clinically relevant effect on the PK of concomitantly administered substrates of OAT3 cannot be excluded as a dedicated interaction study has not been performed. Therefore, caution should be exercised when OAT3 substrates with a narrow therapeutic index (e.g., methotrexate) are given concomitantly.

Hormonal contraceptives
The potential interaction between aprocitentan and hormonal contraceptives has not been studied. Therefore, women using hormonal contraceptives should add a barrier method.

4.6 Fertility, pregnancy and lactation

Use in women of childbearing potential/Contraception in females

JERAYGO is contraindicated for use in women of childbearing potential not using contraception.

Women of childbearing potential must be advised to use reliable methods of contraception during treatment and for one month after treatment discontinuation, as women should not become pregnant during this time. Since the potential interaction between aprocitentan and hormonal contraceptives has not been studied, women using hormonal contraceptives should add a barrier method.

Women of childbearing potential are recommended to perform a pregnancy test before the start of treatment, monthly during treatment, and one month after stopping treatment to allow for the early detection of pregnancy. If pregnancy is detected, JERAYGO must be discontinued (see sections 4.3 and 4.4).

A card addressed to the patient is included in the packaging. It contains information regarding the risk of harm to the unborn child, the need to use contraceptive measures and the recommendation for pregnancy testing.

Pregnancy

There are no or limited amount of data on the use of aprocitentan in pregnant women. Since studies in animals with other ERAs have shown reproductive toxicity, JERAYGO is contraindicated during pregnancy (see section 4.3).

Breast-feeding

It is unknown whether aprocitentan/metabolites are excreted in human milk. In rats, aprocitentan was excreted into milk during lactation.

A risk to the breastfed infant cannot be excluded. JERAYGO is contraindicated during breast-feeding (see section 4.3).

Fertility

An increased incidence of testicular tubular dilation, and, as a long-term consequence, of tubular degeneration/atrophy in male rats was observed after treatment with aprocitentan, similarly to other ERAs. However, such effects were only observed at aprocitentan doses that are much higher than the maximum recommended human dose, and no effects on fertility occurred (see section 5.3).

Decreased sperm count has been observed in patients taking other ERAs. It is not known if aprocitentan may adversely affect spermatogenesis in men.

In female rats, aprocitentan slightly increased pre-implantation loss (see section 5.3).

4.7 Effects on ability to drive and use machines

Aprocitentan has negligible influence on the ability to drive and use machines. However, adverse reactions (e.g., headache or hypotension) may occasionally occur that may influence the ability to drive and use machines.

4.8 Undesirable effects

Summary of safety profile

The most frequently reported adverse reactions with aprocitentan were oedema/fluid retention (9.1% [12.5 mg] and 18.4% [25 mg]) and haemoglobin decreased (3.7% [12.5 mg] and 1.2% [25 mg]) (see section 4.4).

Tabulated list of adverse reactions

The safety of aprocitentan was evaluated in one placebo-controlled Phase 3 clinical study (see section 5.1). In this study, 724 patients received aprocitentan, with 633 patients treated for at least 26 weeks, 192 patients for at least 47 weeks, and 99 patients for at least 48 weeks.

The frequency of adverse reactions is defined using the following convention: very common (≥ 1/10); common (≥ 1/100 to < 1/10); uncommon (≥ 1/1 000 to < 1/100); rare (≥ 1/10 000 to < 1/1 000); very rare (< 1/10 000); not known (cannot be estimated from the available data).

Table 1: Adverse reactions

System organ class	Adverse reaction	Frequency
Infections and infestations	Upper respiratory tract infection[a]	Common
Blood and lymphatic system disorders	Haemoglobin decreased[b]	Common
Immune system disorders	Hypersensitivity[c]	Common
Nervous system disorders	Headache	Common
Vascular disorders	Hypotension	Uncommon
	Flushing	Uncommon
Respiratory, thoracic and mediastinal disorders	Dyspnoea[d]	Common
Hepatobiliary disorders	Transaminase increased	Uncommon
General disorders and administration site conditions	Oedema/fluid retention[e]	Very common
Investigations	Glomerular filtration rate decreased during initial treatment	Uncommon
	Weight increased during initial treatment	Uncommon

[a] Upper respiratory tract infection includes pharyngitis, nasopharyngitis.

[b] Haemoglobin decreased includes anaemia.
[c] Hypersensitivity includes rash, erythema, allergic oedema, dermatitis allergic.
[d] Dyspnoea includes dyspnoea exertional.
[e] Oedema/fluid retention includes mainly oedema peripheral, fluid retention, face oedema.

Description of selected adverse reactions

Oedema/fluid retention
Oedema/fluid retention events appear to be dose-related (9.1% [12.5 mg] and 18.4% [25 mg] during the 4-week double-blind [DB] treatment.

Over the entire study, 0.8% of patients discontinued treatment of aprocitentan 25 mg due to oedema/fluid retention.

Actions to be taken if oedema/fluid retention occurs are described in section 4.4.

A mean increase in body weight of +0.4 kg and +0.6 kg was observed in patients on aprocitentan 12.5 and 25 mg, respectively, compared to –0.2 kg in patients on placebo during the 4-week DB treatment (part 1). This increase disappeared during the 32-week single-blind (SB) treatment (part 2).

Transaminases increased
Alanine/aspartate aminotransferase (ALT/AST) elevations > 3 × ULN were reported in 0% and 0.4% of patients receiving JERAYGO 12.5 mg and 25 mg, respectively, compared to 0.9% in placebo patients during the initial 4-week DB treatment (part 1). 1.5% of patients reported these events during the 32-week SB treatment (part 2) when all subjects received 25 mg. 1.3% of patients reported these events during the 12-week double-blind withdrawal (DB-WD) treatment (part 3) on 25 mg, compared to 1.0% on placebo. There were no reports of patients with ALT and/or AST > 3 × ULN and total bilirubin > 2 × ULN in the study.

Hypersensitivity reactions
Cases of hypersensitivity reactions (i.e., rash, erythema, allergic oedema, dermatitis allergic) occurred within the first 2 weeks of treatment and were mild to moderate. There were 2 patients who discontinued treatment, 1 of whom was hospitalised.

Haemoglobin decreased
Mean haemoglobin at baseline was 13.9, 13.9, and 14.1 g/dL for aprocitentan 12.5 mg, 25 mg, and placebo, respectively. During the 4-week DB treatment (part 1), a mean decrease in haemoglobin of 0.80 and 0.85 g/dL was reported in patients receiving aprocitentan 12.5 and 25 mg, respectively, compared to a decrease of 0.4 g/dL in patients receiving placebo. At the end of the 32-week SB treatment (part 2), during which all patients received aprocitentan 25 mg, the mean decrease in haemoglobin remained unchanged at 0.87 g/dL compared to baseline. Reversibility of the effect was observed within 4 weeks after discontinuation.

A decrease from baseline in haemoglobin concentration to below 10 g/dL was reported in 6.4% of patients during the 48-week exposure to aprocitentan 25 mg. Of these patients, the range for haemoglobin at baseline was 10.3 to 15.4 g/dL.

Actions to be taken if haemoglobin decrease occurs are described in section 4.4.

Glomerular filtration rate decreased
Mean eGFR at baseline was 76.2, 76.7, and 76.2 mL/min/1.73 m^2 for aprocitentan 12.5 mg, 25 mg, and placebo, respectively. During the 4-week DB treatment (part 1), a mean decrease in eGFR of 1.2 and 2.4 mL/min/1.73 m^2 was reported in patients receiving aprocitentan 12.5 and 25 mg, respectively, compared to a decrease of 0.6 mL/min/1.73 m^2 in patients receiving placebo. At the end of the 32-week SB treatment (part 2), the mean decrease in eGFR was 2.3 mL/min/1.73 m^2; it remained stable until the end of the study.

Reporting of suspected adverse reactions

Reporting suspected adverse reactions after authorisation of the medicinal product is important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions via the national reporting system listed in Appendix V.

4.9 Overdose

Aprocitentan has been administered as a single dose of up to 600 mg, and as multiple doses of up to 100 mg daily to healthy subjects (24 and 4 times the maximum approved dose, respectively).

Adverse reactions of headache, nasal congestion, nausea and upper respiratory tract infection were observed.

In the event of an overdose, standard supportive measures should be taken, as required. Because of possible 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 (see section 5.2).

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antihypertensives, other antihypertensives, ATC code: C02KN01

Mechanism of action

Endothelin (ET)-1, via its receptors (ET_A and ET_B), mediates a variety of effects such as vasoconstriction, fibrosis, cell proliferation, and inflammation and is upregulated in hypertension. Aprocitentan is a dual ERA that inhibits the binding of ET-1 to ET_A and ET_B receptors and hence the effects mediated by these receptors.

Pharmacodynamic effects

Cardiac electrophysiology
In a thorough QT study in healthy subjects, once-daily administration of 25 mg (maximum therapeutic dose) aprocitentan at steady state did not prolong the QTc interval as the upper limit of the 90% confidence interval of the mean change from baseline in placebo-corrected QTc was less than 10 ms.

At four times the maximum therapeutic dose (100 mg), the upper limit of the 90% confidence interval of the mean change from baseline in placebo-corrected QTc was 10.4 ms.

Clinical efficacy and safety

The efficacy of aprocitentan was evaluated in one randomized, double-blind, placebo-controlled Phase 3 multicentre study.

Patients with uncontrolled BP (systolic blood pressure [SBP] ≥ 140 mmHg) despite the use of at least three antihypertensive medicinal products and following exclusion of pseudo-resistant hypertension (e.g., white coat effect, inappropriate BP measurement, secondary causes of hypertension) were considered to have resistant hypertension.

The patients were switched to standardised background antihypertensive therapy consisting of an angiotensin receptor blocker (valsartan 160 mg), a calcium channel blocker (amlodipine 5 or 10 mg), and a diuretic (hydrochlorothiazide 25 mg) throughout the study. Patients with concomitant use of

beta-blockers continued this treatment throughout the study, in addition to the standardised background antihypertensive therapy and study treatment.

A total of 730 patients received either aprocitentan 12.5 mg, aprocitentan 25 mg, or placebo once daily during the initial 4-week DB treatment (part 1). Thereafter, patients received aprocitentan 25 mg once daily during the 32-week SB treatment (part 2). At the end of the 32 weeks, patients were re-randomised to receive either aprocitentan 25 mg or placebo, once daily, during the 12-week DB-WD treatment (part 3) (Table 2).

Table 2: Design of the Phase 3 study

	Treatment	**Part 1 (4 weeks)**	**Part 2 (32 weeks)**	**Part 3 (12 weeks)**
Design		DB, placebo-controlled, randomized (1:1:1)	SB	DB-WD, placebo-controlled, randomized (1:1)
Duration		Week 0 – Week 4	Week 4 – Week 36	Week 36 – Week 48
Treatment as add-on to background therapy*	Aprocitentan 25 mg Aprocitentan 12.5 mg Placebo	N = 243 N = 243 N = 244	N = 704	N = 307 N = 307

* ARB, CCB, and a diuretic.
ARB = angiotensin receptor blocker; CCB = calcium channel blocker; DB = double-blind; DB-WD = double-blind withdrawal; N = number of patients; SB = single-blind.

The primary efficacy endpoint was the change in sitting SBP (SiSBP) from baseline to Week 4 during DB treatment (part 1), measured at trough by unattended automated office blood pressure (uAOBP).

The key secondary endpoint was the change in SiSBP measured at trough by uAOBP from DB-WD baseline (Week 36) to Week 40 (part 3).

Patients had a mean age of 61.7 years (range 24 to 84 years; 34.1% were ≥ 65 and < 75 years; 9.9% were ≥ 75 years) and 59.5% were male. Patients were White (82.9%), African American (11.2%) or Asian (5.2%). The mean body weight was 97.6 kg (range 46 to 196 kg) and mean BMI was 33.7 kg/m^2 (range 18 to 64 kg/m^2).

Patients had a medical history of type 2 diabetes mellitus (54.1%), ischaemic heart disease (30.8%), central nervous system vascular disorders (23.0%), chronic kidney disease stages 3 and 4 (22.2%; 19.3% of patients had eGFR 30–59 mL/min/1.73 m^2 and 2.9% had eGFR 15–29 mL/min/1.73 m^2), congestive heart failure (19.6%), and sleep apnoea syndrome (14.1%). 63.0% of patients had four or more antihypertensive medicinal products.

Populations not studied in the Phase 3 study are described in sections 4.2, 4.3 and 4.4.

Doses of aprocitentan 12.5 and 25 mg showed a statistically significant reduction vs placebo on SiSBP at Week 4. The treatment effect was consistent for sitting diastolic BP (SiDBP) (Table 3).

Table 3: Reduction in sitting trough BP (mmHg) measured by uAOBP at Week 4 of DB treatment

Treatment group	N	Baseline # Mean	LS Mean	Difference to placebo	
				LS Mean	p-value
SiSBP (primary endpoint)			LS Mean (97.5% CL)	LS Mean (97.5% CL)	
12.5 mg	243	153.2	−15.3 (−17.4, −13.2)	−3.8 (−6.8, −0.8)	0.0042*
25 mg	243	153.3	−15.2 (−17.3, −13.1)	−3.7 (−6.7, −0.8)	0.0046*
Placebo	244	153.3	−11.5 (−13.6, −9.4)	-	-
SiDBP			LS Mean (95% CL)	LS Mean (95% CL)	
12.5 mg	243	87.9	−10.4 (−11.6, −9.3)	−3.9 (−5.6, −2.3)	<0.0001
25 mg	243	87.7	−11.0 (−12.1, −9.8)	−4.5 (−6.1, −2.9)	<0.0001
Placebo	244	87.1	−6.5 (−7.6, −5.3)	-	-

Observed baseline value.
* Statistically significant at the 2.5% level as prespecified in the testing strategy.
CL = confidence limit; DB = double-blind; DB-WD = double-blind withdrawal; LS Mean = least squares mean; SiDBP = sitting diastolic blood pressure; SiSBP = sitting systolic blood pressure.

The persistence of the BP-lowering effect of aprocitentan was shown in DB-WD treatment (part 3). In patients re-randomised to placebo, the mean SiSBP increased, whereas in patients re-randomised to aprocitentan 25 mg the mean effect on SiSBP was stable, resulting in a statistically significant difference. The treatment effect was consistent for SiDBP (Table 4).

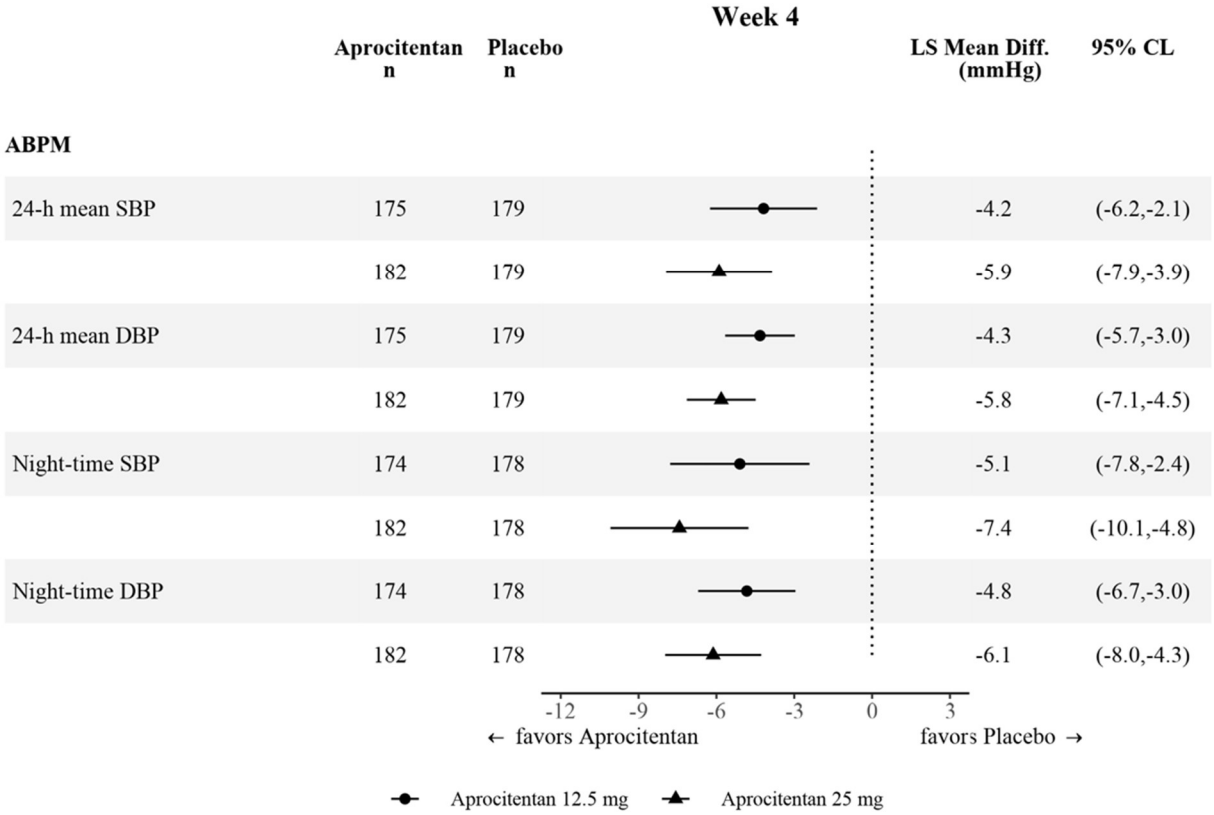
Table 4: Sustained reduction in sitting trough BP (mmHg) measured by uAOBP at Week 40 of DB-WD treatment

Treatment group	N	DB-WD Baseline# Mean	LS Mean (95% CL)	Difference to placebo	
				LS Mean (95% CL)	p-value
SiSBP (key secondary endpoint)					
25 mg	307	135.3	−1.5 (−3.0, 0.0)	−5.8 (−7.9, −3.7)	<0.0001*
Placebo	307	136.4	4.4 (2.9, 5.8)	-	-
SiDBP					
25 mg	307	76.1	−0.5 (−1.5, 0.5)	−5.2 (−6.6, −3.8)	<0.0001
Placebo	307	76.3	4.7 (3.7, 5.7)	-	-

Observed baseline value. DB-WD baseline: Week 36.
* Statistically significant at the 5% level as prespecified in the testing strategy.
CL = confidence limit; DB-WD = double-blind-withdrawal; LS Mean = least squares mean; SiDBP = sitting diastolic blood pressure; SiSBP = sitting systolic blood pressure.

The effect was also consistent across SBP and DBP measured by ambulatory BP monitoring (ABPM) and assessed as daytime, night-time, and 24 h periods at Week 4 (Figure 1) and Week 40.

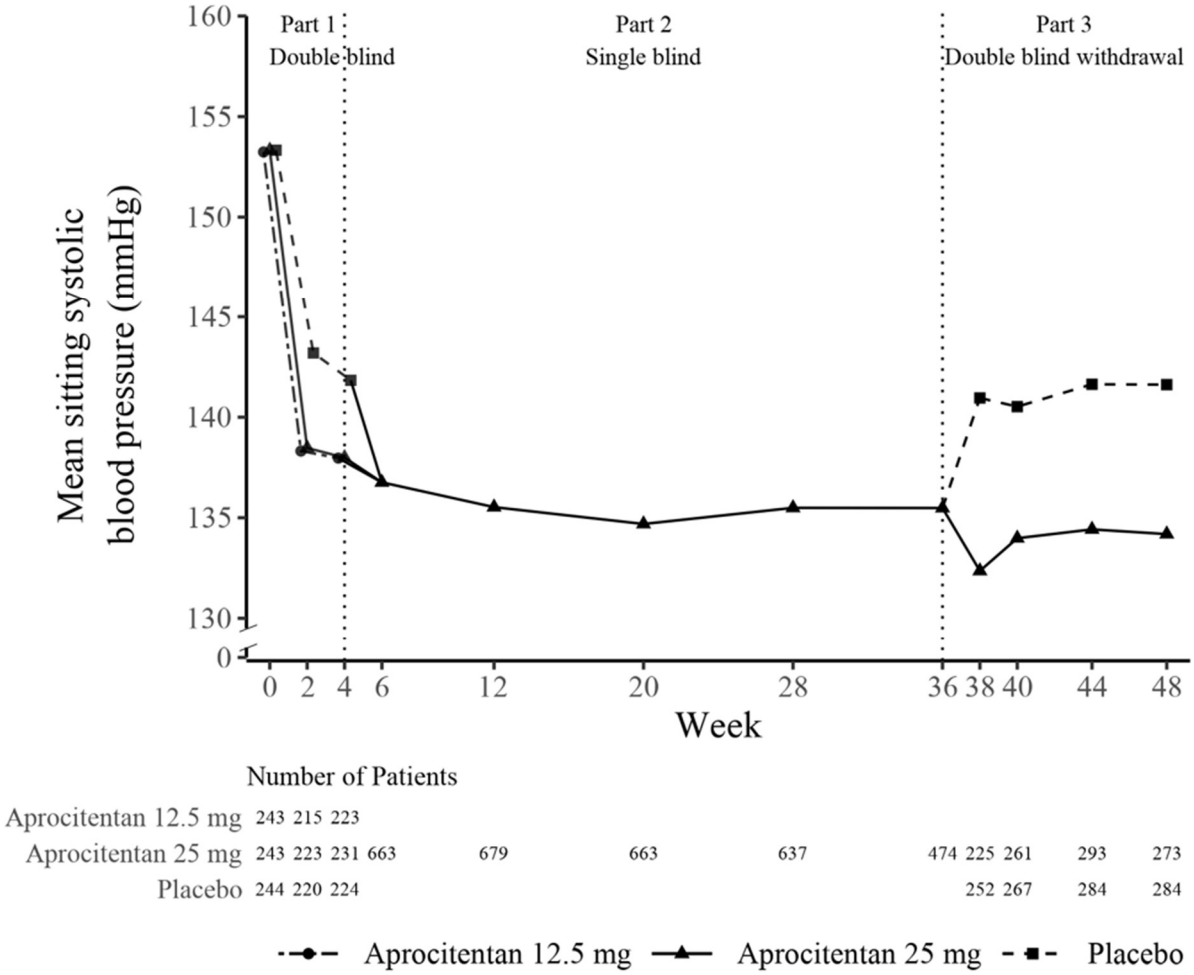
Figure 1: Placebo-corrected changes from baseline in systolic and diastolic BP measured by ABPM at Week 4



ABPM = ambulatory blood pressure monitoring; BP = blood pressure; CL = confidence limits; DBP = diastolic blood pressure; LS Mean Diff. = least squares mean difference versus placebo; SBP = systolic blood pressure.

A substantial proportion (i.e., at least 90%) of the BP-lowering effect was observed within the first two weeks of treatment with aprocitentan.

Figure 2: Mean sitting systolic BP measured by uAOBP over 48 weeks



The effect of aprocitentan was consistent across subgroups of age (including patients ≥ 75 years), sex, race (including patients with Black or African American origin), BMI, baseline urine albumin-to-creatinine ratio (UACR), baseline eGFR and medical history of diabetes, and was consistent with the effect in the overall population.

Effects on UACR/eGFR
At 4 weeks, a reduction in UACR of 30% (95% confidence limits 20–39%) and 34% (95% confidence limits 25–42%) was observed with aprocitentan 12.5 and 25 mg, respectively, compared to subjects randomised to placebo. This effect disappeared upon treatment discontinuation. As for eGFR, a mean decrease of −1.2 mL/min /1.73 m^2 for aprocitentan 12.5 mg and −2.4 mL/min /1.73 m^2 for aprocitentan 25 mg occurred during the first 4 weeks of treatment (vs −0.6 mL/min /1.73 m^2 for placebo), followed by a stabilisation of eGFR, including in patients with low (< 60 mL/min) baseline values, until the end of the study. The effect of aprocitentan on end organ protection has not been studied.

Effects on mortality and cardiovascular morbidity
The effects of aprocitentan on mortality and cardiovascular morbidity have not been studied.

Paediatric population

The European Medicines Agency has waived the obligation to submit the results of studies with aprocitentan in all subsets of the paediatric population in the treatment of hypertension (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Absorption

Maximum plasma concentration (C_{max}) of aprocitentan was achieved between 4 and 5 h after administration of 25 mg. Concentrations in plasma increased in a dose-proportional manner following once daily administration of 5 mg, 25 mg, and 100 mg. The absolute bioavailability after oral administration is not known.

With once daily administration, steady-state conditions were reached by Day 8 and accumulation compared to Day 1 was approximately 3-fold.

Effect of food
When a capsule formulation (used in early clinical studies) was taken with a high-fat, high-calorie meal by healthy subjects, aprocitentan median time to C_{max} (t_{max}) was reached approximately one hour earlier, with a C_{max} approximately 1.7-fold that in the fasted condition. Total exposure expressed as $AUC_{0-\infty}$ was approximately 1.2-fold that observed in the fasted condition. Food effect has not been specifically studied for the film-coated tablet. In the pivotal Phase 3 study, aprocitentan film-coated tablets were administered irrespective of food intake. The absorption of aprocitentan is not expected to be affected by meals.

Distribution

Aprocitentan had an apparent volume of distribution of approximately 20 L and was highly bound to plasma proteins (> 99%). The blood-to-plasma ratio was 0.63.

Biotransformation

Aprocitentan was almost exclusively detected unchanged in plasma.

The main metabolic pathways of aprocitentan were N-glucosidation of the sulfamide moiety catalysed by the glucuronyl transferases UGT1A1 and UGT2B7, and hydrolysis of the sulfamide moiety to the corresponding aminopyrimidine. Hydrolysis was mostly non-enzymatic.

Elimination

After administration of a radiolabelled dose of aprocitentan, approximately 52% of radioactive drug-related material was eliminated via urine and 25% via faeces. A total of 0.2% and 6.8% of the administered dose was recovered in urine and faeces as unchanged aprocitentan, respectively.

The apparent oral body clearance is 0.30 L/h. The terminal plasma half-life of aprocitentan is approximately 46 h.

Pharmacokinetics in special populations

There were no clinically relevant effects of age (18–84 years), sex, body weight, or race on the PK of aprocitentan.

Renal impairment
Total exposure to aprocitentan (AUC) in patients with severe renal impairment (eGFR 15–29 mL/min) compared to healthy subjects was increased by an average of 40%. This increase is not considered clinically relevant (see section 4.2). Aprocitentan binding to plasma proteins was not influenced by renal function.

Hepatic impairment
Total exposure to aprocitentan (AUC) in patients with moderate hepatic impairment (Child-Pugh class B) compared to healthy subjects was increased by an average of 23%. This increase is not considered

clinically relevant (see section 4.2). Aprocitentan binding to plasma proteins was not influenced by hepatic function.

5.3 Preclinical safety data

Non-clinical data reveal no special hazard for humans based on conventional studies of safety pharmacology, repeated-dose toxicity, genotoxicity, carcinogenic potential, and phototoxicity.

Histological findings in repeated-dose toxicity studies (degenerative liver changes, nasal cavity findings, and testicular changes) were observed only at exposures sufficiently in excess of the maximum human exposure, indicating low relevance in clinical use.

Toxicity to reproduction and development

Testicular tubular degeneration was observed after repeated dosing in rats and dogs with safety margins of 8 (20.6)- and 4.9 (16.6)-fold the total (free) exposure at the maximum recommended human dose, respectively. However, no effects were noted on fertility or spermatogenesis in male rats.

In female rats, minimally increased pre-implantation loss (lower number of corpora lutea, implantation sites, and live embryos) was observed at 11 (29)-fold the total (free) exposure at the maximum recommended human dose. No effects on mating behaviour and reproductive performance were noted.

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 the maximum recommended human dose, respectively. However, ERAs as a class have shown teratogenicity in rats and rabbits, where the observed malformations indicate serious effects on developmental processes early in pregnancy (neural crest cell migration). Since teratogenic potential of aprocitentan was investigated only at exposures slightly above the exposure at the maximum recommended human dose, it is not known which exposures may elicit adverse effects on embryo-foetal development.

In pre- and post-natal development studies, female rats treated from late pregnancy through lactation showed reduced pup survival and impairment of the reproductive capability of the offspring.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Croscarmellose sodium
Hydroxypropylcellulose
Lactose monohydrate
Magnesium stearate
Cellulose, microcrystalline

Film coat
Poly(vinyl alcohol)
Hydroxypropylcellulose
Triethyl citrate
Talc
Silica, colloidal hydrated
Titanium dioxide
Iron oxide red (E172)
Iron oxide yellow (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

30 months.

6.4 Special precautions for storage

Store in the original package (HDPE bottle or blisters) in order to protect from moisture (no special temperature storage conditions are required).

Keep the HDPE bottles tightly closed in order to protect from moisture.

6.5 Nature and contents of container

JERAYGO 12.5 mg film-coated tablets

White, opaque, HDPE bottle with child-resistant closure and induction seal liner, containing silica gel desiccant and 30 film-coated tablets.

Perforated unit dose blisters in aluminium cold-form film with desiccant and aluminium push-through lidding foil containing 10 × 1 film-coated tablets.

JERAYGO 25 mg film-coated tablets

White, opaque, HDPE bottle with child-resistant closure and induction seal liner, containing silica gel desiccant and 30 film-coated tablets.

Perforated unit dose blisters in aluminium cold-form film with desiccant and aluminium push-through lidding foil containing 10 × 1 film-coated tablets.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

7. MARKETING AUTHORISATION HOLDER

Idorsia Pharmaceuticals Deutschland GmbH
Marie-Curie-Strasse 8
79539 Lörrach
Germany

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1818/001
EU/1/24/1818/002
EU/1/24/1818/003
EU/1/24/1818/004

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 27 June 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Idorsia Pharmaceuticals Deutschland GmbH
Marie-Curie-Strasse 8
79539 Lörrach
Germany

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to medical prescription.

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of PSURs for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

The marketing authorisation holder (MAH) shall submit the first PSUR for this product within 6 months following authorisation.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk management plan (RMP)**

The marketing authorisation holder (MAH) shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:
- At the request of the European Medicines Agency;
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

- **Additional risk minimisation measures**

The MAH 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 the following educational material:

- Patient card

The Patient Card, which is addressed to 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 any of the signs that could be due to liver problems to the treating physician.

- **Obligation to conduct post-authorisation measures**

The MAH shall complete, within the stated timeframe, the below measures:

Description	**Due date**
Interventional post-authorisation safety study (PASS): In order to further characterise the long-term cardiovascular safety of aprocitentan in patients with resistant hypertension, the MAH should conduct and submit the results of a randomized, active-controlled study in adult patients with resistant hypertension, according to an agreed protocol.	Final report: 31 March 2031

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BOTTLE)

1. NAME OF THE MEDICINAL PRODUCT

JERAYGO 12.5 mg film-coated tablets

aprocitentan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 12.5 mg aprocitentan

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in original bottle. Keep the bottle tightly closed to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Idorsia Pharmaceuticals Deutschland GmbH
Marie-Curie-Strasse 8
79539 Lörrach
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1818/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

JERAYGO 12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

JERAYGO 12.5 mg film-coated tablets

aprocitentan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 12.5 mg aprocitentan

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in original bottle. Keep the bottle tightly closed to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Idorsia Pharmaceuticals Deutschland GmbH
Marie-Curie-Strasse 8
79539 Lörrach
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1818/001

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BOTTLE)

1. NAME OF THE MEDICINAL PRODUCT

JERAYGO 25 mg film-coated tablets

aprocitentan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 25 mg aprocitentan

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in original bottle. Keep the bottle tightly closed to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Idorsia Pharmaceuticals Deutschland GmbH
Marie-Curie-Strasse 8
79539 Lörrach
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1818/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

JERAYGO 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

PARTICULARS TO APPEAR ON THE IMMEDIATE PACKAGING

BOTTLE LABEL

1. NAME OF THE MEDICINAL PRODUCT

JERAYGO 25 mg film-coated tablets

aprocitentan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 25 mg aprocitentan

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

30 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in original bottle. Keep the bottle tightly closed to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Idorsia Pharmaceuticals Deutschland GmbH
Marie-Curie-Strasse 8
79539 Lörrach
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1818/003

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BLISTER)

1. NAME OF THE MEDICINAL PRODUCT

JERAYGO 12.5 mg film-coated tablets

aprocitentan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 12.5 mg aprocitentan

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

10 × 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in original blisters in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Idorsia Pharmaceuticals Deutschland GmbH
Marie-Curie-Strasse 8
79539 Lörrach
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1818/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

JERAYGO 12.5 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

UNIT DOSE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

JERAYGO 12.5 mg tablets

aprocitentan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Idorsia

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON (BLISTER)

1. NAME OF THE MEDICINAL PRODUCT

JERAYGO 25 mg film-coated tablets

aprocitentan

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each film-coated tablet contains 25 mg aprocitentan

3. LIST OF EXCIPIENTS

Contains lactose. See package leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablets

10 × 1 film-coated tablets

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.

Oral use

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

Store in original blisters in order to protect from moisture.

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Idorsia Pharmaceuticals Deutschland GmbH
Marie-Curie-Strasse 8
79539 Lörrach
Germany

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/24/1818/004

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

JERAYGO 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER – HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

UNIT DOSE BLISTER

1. NAME OF THE MEDICINAL PRODUCT

JERAYGO 25 mg tablets

aprocitentan

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Idorsia

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Patient card

PATIENT CARD

JERAYGO (aprocitentan)

For the treatment of resistant high blood pressure (hypertension)

This card contains important safety information you need to be aware of when receiving treatment with JERAYGO.

Show this card to any doctor involved in your medical care.

EN

It is important that if you notice signs of liver problems or become pregnant during your treatment with JERAYGO you report it immediately to your prescribing doctor.

Name of prescribing doctor:

Phone number of prescribing doctor:

Pregnancy
JERAYGO may harm the development of the unborn child. Therefore, you must not take JERAYGO if you are pregnant, and you must also not become pregnant while taking JERAYGO.

You are recommended to take a pregnancy test before starting treatment with JERAYGO, once a month during treatment, and one month after stopping treatment even if you think that you are not pregnant.

Contraception
You need to use a reliable form of birth control (contraception) while you are taking JERAYGO and for one month after stopping treatment.

Be sure to discuss the method of contraception and any questions you may have with your doctor.

Liver problems
JERAYGO might cause liver problems. Your doctor will do a blood test before you start taking JERAYGO and during treatment to check your liver. Signs that your liver may not be working properly include:
- feeling sick (nausea) or vomiting
- fever
- pain in your upper right stomach (abdomen)

- yellowing of your skin or the whites of your eyes (jaundice)
- dark-coloured urine
- itching of your skin
- unusual tiredness or exhaustion (lethargy or fatigue)
- loss of appetite

If you notice any of these signs, **tell your doctor immediately**.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

JERAYGO 12.5 mg film-coated tablets
JERAYGO 25 mg film-coated tablets
aprocitentan

▼This medicine is subject to additional monitoring. This will allow quick identification of new safety information. You can help by reporting any side effects you may get. See the end of section 4 for how to report side effects.

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.

In addition to this leaflet, a patient card is included in the carton of this medicine. This card contains important safety information that you need to know before, during and after treatment with this medicine.

- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor or pharmacist.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What JERAYGO is and what it is used for

JERAYGO contains the active substance called aprocitentan, which belongs to the class of medicines called “endothelin receptor antagonists”.

This medicine is used to treat hypertension (high blood pressure) in adults whose blood pressure cannot be adequately controlled by at least three other medicines (so-called resistant hypertension).

This medicine works by helping to stop the blood vessels from tightening; as a result, the blood vessels relax and blood pressure is lowered.

2. What you need to know before you take JERAYGO

Do not take JERAYGO
- if you are allergic to aprocitentan, or any of the other ingredients of this medicine (listed in section 6).
- if you are pregnant, if you are planning to become pregnant, or if you could become pregnant because you are not using a reliable form of birth control (contraception). See section 2, ‘Pregnancy and breast-feeding’.
- if you are breast-feeding. See section 2, ‘Pregnancy and breast-feeding’.
- if you have severe liver disease. See section 2, ‘Warnings and precautions’.

Warnings and precautions
Tell your doctor if you have any of the following conditions before starting treatment or if you develop the following signs while taking this medicine.

Liver problems
Like other medicines of the same class, JERAYGO might cause liver injury. Your doctor should do blood tests to check that your liver is working properly before starting treatment and may also check during treatment. Tell your doctor immediately if you develop symptoms of liver problems including:
- nausea (feeling sick) or vomiting;
- fever;
- pain in the upper right area of your abdomen (belly);
- jaundice (yellowing of your skin or the whites of your eyes);
- dark-coloured urine;
- itching of your skin;
- unusual tiredness or exhaustion;
- loss of appetite.

Oedema (swelling/fluid retention)
If you have signs of oedema when using this medicine, such as unusual weight gain or swelling of the ankles, feet or legs, especially in the early weeks of the treatment, tell your doctor immediately. They will help you manage this side effect.

Heart disease
JERAYGO is not recommended in patients with unstable or severe cardiac disease. Tell your doctor immediately if you develop any of the following symptoms:
- shortness of breath;
- waking up with shortness of breath at night;
- getting tired easily after light physical activity such as walking;
- rapid increase in your weight;
- swollen ankles or feet;
- chest pain and discomfort.

Anaemia (low number of red blood cells)
Decreases in haemoglobin (the protein in red blood cells that carries oxygen around the body) and haematocrit (the amount of blood that is made up of red blood cells), which can result in anaemia, have occurred with this medicine and other endothelin receptor antagonists. Tell your doctor if you develop symptoms of anaemia during treatment including:
- dizziness;
- fatigue/malaise/weakness;
- fast heart rate, palpitations;
- pallor.

Kidney problems
Patients with moderate kidney function decrease may have an increased risk of developing oedema and anaemia during treatment. Treatment with JERAYGO is not recommended in patients with severe kidney function decrease.

Patients aged 75 or older
If you are 75 years or older, you may have a higher risk of developing oedema, anaemia, and cardiovascular conditions during treatment. As a result, your doctor should monitor your levels of haemoglobin and any symptoms of oedema or heart disease.

Children and adolescents
This medicine is not for children and adolescents below 18 years of age, because JERAYGO has not been tested in this age group.

Other medicines and JERAYGO
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicine. It is especially important that you tell your doctor if you are also taking methotrexate (medicine used to treat cancer, rheumatoid arthritis or psoriasis) or tizanidine (medicine used to treat muscle spasms). JERAYGO may interfere with the effects of these medicines.

Pregnancy and breast-feeding
If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, do not take this medicine.

Babies exposed to JERAYGO in the womb may be harmed.
- **Do not take** this medicine if you are pregnant or if you are planning to become pregnant.
- If you become pregnant or think that you may be pregnant while you are taking this medicine, or shortly after stopping it (up to one month), **see your doctor immediately**.
- If you are a woman who could become pregnant, use a reliable form of birth control (contraception) while you are taking this medicine and for one month after you stop treatment. This medicine could reduce the effectiveness of hormonal contraceptives, therefore it is recommended to add a barrier method. Talk to your doctor about this.
- If you are a woman who could become pregnant, your doctor will recommend that you take a pregnancy test before you start taking this medicine, every month while you are taking this medicine, and once in the month after you stopped taking the medicine.

This information is summarised in your patient card, which is attached to the packaging of this medicine.

If you become pregnant, stop taking this medicine (see section 2, 'Do not take JERAYGO').

It is not known if JERAYGO is transferred to breast milk. Do not breast-feed while you are taking this medicine (see section 2, 'Do not take JERAYGO'). Talk to your doctor about this.

Driving and using machines
JERAYGO can cause side effects such as headache or low blood pressure (hypotension) (listed in section 4), which may affect your ability to drive and use machines.

JERAYGO contains lactose and sodium
This medicine contains a sugar called lactose. If you have an intolerance to some sugars, contact your doctor before taking this medicine.

This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say, it is essentially 'sodium-free'.

3. How to take JERAYGO

Always take this medicine exactly as your doctor or pharmacist has told you. Check with your doctor or pharmacist if you are not sure.

Your doctor will determine the dose of JERAYGO that you should take. The recommended dose is one 12.5 mg tablet once a day. Then, the dose may be increased to one 25 mg tablet once a day, if you do not have relevant side effects and if your doctor judges that your blood pressure should be further decreased.

Tablets are designed to be swallowed whole. You can take this medicine with or without meals.

If you take more JERAYGO than you should
If you take more of this medicine than you should, contact your doctor immediately.

If you forget to take JERAYGO
If you forget to take this medicine, take your usual dose the next day and do not take a double dose to make up for a missed dose. Two doses should not be taken on the same day.

If you stop taking JERAYGO
You need to keep taking this medicine to control your high blood pressure (hypertension). Do not stop taking JERAYGO unless you have agreed this with your doctor.

If you have any further questions on the use of this medicine, ask your doctor or pharmacist.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them. The following side effects may happen with this medicine:

Very common (may affect more than 1 in 10 people):
- Oedema (swelling, for example, of the ankles and feet) / Fluid retention (see section 2, 'Warnings and precautions')

Common (may affect up to 1 in 10 people):
- Anaemia (low number of red blood cells or reduced haemoglobin) (see section 2, 'Warnings and precautions')
- Hypersensitivity (allergic reactions)
- Dyspnoea (shortness of breath)
- Headache
- Upper respiratory tract (nose and throat) infections

Uncommon (may affect up to 1 in 100 people):
- Hypotension (low blood pressure)
- Elevated liver tests
- Flushing (redness of the skin)
- Decrease in kidney filtration rate when starting treatment
- Weight increase when starting treatment

Reporting of side effects
If you get any side effects, talk to your doctor or pharmacist. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side effects, you can help provide more information on the safety of this medicine.

5. How to store JERAYGO

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date, which is stated on the carton and package (bottle or blister) after "EXP". The expiry date refers to the last day of that month.

Store in original package (bottle or blisters) in order to protect from moisture. Keep the bottle closed tightly in order to protect from moisture.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What JERAYGO contains
The active substance is aprocitentan.

JERAYGO 12.5 mg film-coated tablets
Each tablet contains 12.5 mg of aprocitentan.

JERAYGO 25 mg film-coated tablets
Each tablet contains 25 mg of aprocitentan.

The other ingredients are:
Tablet cores: croscarmellose sodium (see section 2 "JERAYGO contains lactose and sodium"), hydroxypropylcellulose, lactose monohydrate (see section 2 "JERAYGO contains lactose and sodium"), magnesium stearate, and microcrystalline cellulose.

Film coating: poly(vinyl alcohol) (E1203), hydroxypropylcellulose (E463), triethyl citrate, talc (E553b), colloidal hydrated silica (E551), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172), iron oxide black (E172).

What JERAYGO looks like and contents of the pack

JERAYGO 12.5 mg is supplied as yellow to orange, round biconvex (6 mm diameter) film-coated tablet (tablet), debossed with "AN" on one side and plain on the other side.

JERAYGO 25 mg is supplied as pink, round biconvex (6 mm diameter) film-coated tablet (tablet), debossed with "AN" on one side and "25" on the other side.

JERAYGO (12.5 mg and 25 mg) is available in bottles of 30 film-coated tablets and in blister packs of 10 × 1 film-coated tablets in perforated unit dose blisters.

Not all pack sizes may be marketed.

Marketing Authorisation Holder
Idorsia Pharmaceuticals Deutschland GmbH
Marie-Curie-Strasse 8
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Manufacturer
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Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.