ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Rydapt 25 mg soft capsules

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each soft capsule contains 25 mg midostaurin.

Excipients with known effect

Each soft capsule contains approximately 83 mg ethanol anhydrous and 415 mg macrogolglycerol hydroxystearate.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Soft capsule (capsule).

Pale orange, oblong capsule with red imprint “PKC NVR”. The dimensions of the capsule are approximately 25.4 x 9.2 mm.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Rydapt is indicated:

- in combination with standard daunorubicin and cytarabine induction and high-dose cytarabine consolidation chemotherapy, and for patients in complete response followed by Rydapt single agent maintenance therapy, for adult patients with newly diagnosed acute myeloid leukaemia (AML) who are FLT3 mutation-positive (see section 4.2);
- as monotherapy for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL).

4.2 Posology and method of administration

Treatment with Rydapt should be initiated by a physician experienced in the use of anti-cancer therapies.

Before taking midostaurin, AML patients must have confirmation of FLT3 mutation (internal tandem duplication [ITD] or tyrosine kinase domain [TKD]) using a validated test.

Posology

Rydapt should be taken orally twice daily at approximately 12-hour intervals. The capsules should be taken with food (see sections 4.5 and 5.2).

Prophylactic antiemetics should be administered in accordance with local medical practice as per patient tolerance.

AML
The recommended dose of Rydapt is 50 mg orally twice daily.

Rydapt is dosed on days 8-21 of induction and consolidation chemotherapy cycles, and then for patients in complete response every day as single agent maintenance therapy until relapse for up to 12 cycles of 28 days each (see section 4.1). In patients receiving a haematopoietic stem cell transplant (SCT), Rydapt should be discontinued 48 hours prior to the conditioning regimen for SCT.

Dose modifications in AML
Recommendations for dose modifications of Rydapt in patients with AML are provided in Table 1.

Table 1 Rydapt dose interruption, reduction and discontinuation recommendations in patients with AML

Phase	**Criteria**	**Rydapt dosing**
Induction, consolidation and maintenance	Grade 3/4 pulmonary infiltrates	Interrupt Rydapt for the remainder of the cycle. Resume Rydapt at the same dose when infiltrate resolves to Grade ≤1.
	Other Grade 3/4 non-haematological toxicities	Interrupt Rydapt until toxicities considered at least possibly related to Rydapt have resolved to Grade ≤2, then resume Rydapt.
	QTc interval >470 msecs and ≤500 msecs	Decrease Rydapt to 50 mg once daily for the remainder of the cycle. Resume Rydapt at the initial dose in the next cycle provided that QTc interval improves to ≤470 msecs at the start of that cycle. Otherwise continue Rydapt 50 mg once daily.
	QTc interval >500 msecs	Withhold or interrupt Rydapt for the remainder of the cycle. If QTc improves to ≤470 msecs just prior to the next cycle, resume Rydapt at the initial dose. If QTc interval is not improved in time to start the next cycle do not administer Rydapt during that cycle. Rydapt may be held for as many cycles as necessary until QTc improves.
Maintenance only	Grade 4 neutropenia (ANC $<0.5 \times 10^9$/l)	Interrupt Rydapt until ANC $\geq 1.0 \times 10^9$/l, then resume at 50 mg twice daily. If neutropenia (ANC $<1.0 \times 10^9$/l) persists >2 weeks and is suspected to be related to Rydapt, discontinue Rydapt.
	Persistent Grade 1/2 toxicity	Persistent Grade 1 or 2 toxicity that patients deem unacceptable may prompt an interruption for as many as 28 days.
ANC: Absolute Neutrophil Count		

ASM, SM-AHN and MCL
The recommended starting dose of Rydapt is 100 mg orally twice daily.

Treatment should be continued as long as clinical benefit is observed or until unacceptable toxicity occurs.

Dose modifications in ASM, SM-AHN and MCL
Recommendations for dose modifications of Rydapt in patients with ASM, SM-AHN and MCL are provided in Table 2.

Table 2 Rydapt dose interruption, reduction and discontinuation recommendations in patients with ASM, SM-AHN or MCL

Criteria	**Rydapt dosing**
ANC <1.0 x 10^9/l attributed to Rydapt in patients without MCL, or ANC less than 0.5 x 10^9/l attributed to Rydapt in patients with baseline ANC value of 0.5-1.5 x 10^9/l	Interrupt Rydapt until ANC ≥1.0 x 10^9/l, then resume at 50 mg twice daily and, if tolerated, increase to 100 mg twice daily. Discontinue Rydapt if low ANC persists for >21 days and is suspected to be related to Rydapt.
Platelet count less than 50 x 10^9/l attributed to Rydapt in patients without MCL, or platelet count less than 25 x 10^9/l attributed to Rydapt in patients with baseline platelet count of 25-75 x 10^9/l	Interrupt Rydapt until platelet count greater than or equal to 50 x 10^9/l, then resume Rydapt at 50 mg twice daily and, if tolerated, increase to 100 mg twice daily. Discontinue Rydapt if low platelet count persists for >21 days and is suspected to be related to Rydapt.
Haemoglobin less than 8 g/dl attributed to Rydapt in patients without MCL, or life-threatening anaemia attributed to Rydapt in patients with baseline haemoglobin value of 8-10 g/dl	Interrupt Rydapt until haemoglobin greater than or equal to 8 g/dl, then resume Rydapt at 50 mg twice daily and, if tolerated, increase to 100 mg twice daily. Discontinue Rydapt if low haemoglobin persists for >21 days and is suspected to be related to Rydapt.
Grade 3/4 nausea and/or vomiting despite optimal anti-emetic therapy	Interrupt Rydapt for 3 days (6 doses), then resume at 50 mg twice daily and, if tolerated, gradually increase to 100 mg twice daily.
Other Grade 3/4 non-haematological toxicities	Interrupt Rydapt until event has resolved to Grade ≤2, then resume Rydapt at 50 mg twice daily and, if tolerated, increase to 100 mg twice daily. Discontinue Rydapt if toxicity is not resolved to Grade ≤2 within 21 days or severe toxicity recurs at a reduced dose of Rydapt.
ANC: Absolute Neutrophil Count CTCAE severity: Grade 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms.	

Missed doses
If a dose is missed, the patient should take the next dose at the scheduled time.

If vomiting occurs, the patient should not take an additional dose of Rydapt but should take the next scheduled dose.

Special populations
Elderly (≥65 years)
No dose adjustment is required in patients aged over 65 years (see section 5.2). In patients aged ≥60 years, Rydapt should be used only in patients eligible to receive intensive induction chemotherapy with adequate performance status and without significant comorbidities.

Renal impairment
No dose adjustment is required for patients with mild or moderate renal impairment. Clinical experience in patients with severe renal impairment is limited and no data are available in patients with end-stage renal disease (see sections 4.4 and 5.2).

Hepatic impairment
No dose adjustment is required in patients with mild or moderate (Child-Pugh A or B) hepatic impairment (see section 5.2). Exposure to midostaurin and its active metabolite CGP62221 is substantially lower in patients with severe hepatic impairment than that in patients with normal hepatic function (see section 5.2). However, there are insufficient efficacy data in patients with severe hepatic impairment to suggest a dose adjustment is required.

Acute promyelocytic leukaemia
Rydapt has not been studied in patients with acute promyelocytic leukaemia and therefore its use is not recommended in this patient population.

Paediatric population
Rydapt should not be used in combination with intensive paediatric AML combination chemotherapy regimens including anthracyclines, fludarabine and cytarabine because of the risk of prolonged haematological recovery (such as prolonged severe neutropenia and thrombocytopenia) (see sections 4.4 and 5.1).

Method of administration

Rydapt is for oral use.

The capsules should be swallowed whole with a glass of water. They should not be opened, crushed or chewed to ensure proper dosing and avoid the unpleasant taste of the capsule content.

4.3 Contraindications

Hypersensitivity to the active substance or to any of the excipients listed in section 6.1.

Concomitant administration of potent CYP3A4 inducers, e.g. rifampicin, St. John's Wort (*Hypericum perforatum)*, carbamazepine, enzalutamide, phenytoin (see section 4.5).

4.4 Special warnings and precautions for use

Neutropenia and infections

Neutropenia has occurred in patients receiving Rydapt as monotherapy and in combination with chemotherapy (see section 4.8). Severe neutropenia (ANC $<0.5 \times 10^9$/l) was generally reversible by withholding Rydapt until recovery and discontinuation in the ASM, SM-AHN and MCL studies. White blood cell counts (WBCs) should be monitored regularly, especially at treatment initiation.

In patients who develop unexplained severe neutropenia, treatment with Rydapt should be interrupted until ANC is ≥1.0 x 10^9/l, as recommended in Tables 1 and 2. Rydapt should be discontinued in patients who develop recurrent or prolonged severe neutropenia that is suspected to be related to Rydapt (see section 4.2).

Any active serious infection should be under control prior to starting treatment with Rydapt monotherapy. Patients should be monitored for signs and symptoms of infection, including any device-related infections, and if a diagnosis of infection is made appropriate treatment must be instituted promptly, including, as needed, the discontinuation of Rydapt.

Cardiac dysfunction

Patients with symptomatic congestive heart failure were excluded from clinical studies. In the ASM, SM-AHN and MCL studies cardiac dysfunction such as congestive heart failure (CHF) (including some fatalities) and transient decreases in left ventricular ejection fraction (LVEF) occurred. In the randomised AML study no difference in CHF was observed between the Rydapt + chemotherapy and placebo + chemotherapy arms. In patients at risk, Rydapt should be used with caution and the patient closely monitored by assessing LVEF when clinically indicated (at baseline and during treatment).

An increased frequency of QTc prolongation was noted in midostaurin–treated patients (see section 4.8), however, a mechanistic explanation for this observation was not found. Caution is warranted in patients at risk of QTc prolongation (e.g. due to concomitant medicinal products and/or electrolyte disturbances). Interval assessments of QT by ECG should be considered if Rydapt is taken concurrently with medicinal products that can prolong QT interval.

Pulmonary toxicity

Interstitial lung disease (ILD) and pneumonitis, in some cases fatal, have occurred in patients treated with Rydapt monotherapy or in combination with chemotherapy. Patients should be monitored for pulmonary symptoms indicative of ILD or pneumonitis and Rydapt discontinued in patients who experience pulmonary symptoms indicative of ILD or pneumonitis without an infectious aetiology that are ≥Grade 3 (NCI CTCAE).

Embryofoetal toxicity and breast-feeding

Pregnant women should be informed of the potential risk to a foetus; females of reproductive potential should be advised to have a pregnancy test within 7 days prior to starting treatment with Rydapt and to use effective contraception during treatment with Rydapt and for at least 4 months after stopping treatment.

Because of the potential for serious adverse reactions in breast-feeding infants from Rydapt, women should discontinue breast-feeding during treatment with Rydapt and for at least 4 months after stopping treatment (see section 4.6).

Paediatric patients

Rydapt should not be used in combination with intensive paediatric AML combination chemotherapy regimens including anthracyclines, fludarabine and cytarabine because of the risk of prolonged haematological recovery (such as prolonged severe neutropenia and thrombocytopenia) (see sections 4.2 and 5.1).

Severe renal impairment

Caution is warranted when considering the administration of midostaurin in patients with severe renal impairment or end-stage renal disease and patients should be carefully monitored for toxicity (see section 5.2).

Interactions

Caution is required when concomitantly prescribing with midostaurin medicinal products that are strong inhibitors of CYP3A4, such as, but not limited to, antifungals (e.g. ketoconazole), certain antivirals (e.g. ritonavir), macrolide antibiotics (e.g. clarithromycin) and nefazodone because they can increase the plasma concentrations of midostaurin especially when (re-)starting with midostaurin treatment (see section 4.5). Alternative medicinal products that do not strongly inhibit CYP3A4 activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for midostaurin-related toxicity.

Excipients

This medicinal product contains macrogolglycerol hydroxystearate, which may cause stomach discomfort and diarrhoea.

This medicinal product contains 666 mg of alcohol (ethanol) in each 200 mg dose (maximum daily dose), which is equivalent to 14 vol. % ethanol anhydrous. The amount in a 200 mg dose of this medicine is equivalent to 17 ml beer or 7 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects. Alcohol may be harmful in patients with alcohol-related problems, epilepsy or liver problems or during pregnancy or breast-feeding.

4.5 Interaction with other medicinal products and other forms of interaction

Midostaurin undergoes extensive hepatic metabolism mainly through CYP3A4 enzymes which are either induced or inhibited by a number of concomitant medicinal products.

Effect of other medicinal products on Rydapt

Medicinal products or substances known to affect the activity of CYP3A4 may affect the plasma concentrations of midostaurin and therefore the safety and/or efficacy of Rydapt.

Strong CYP3A4 inducers
Concomitant use of Rydapt with strong inducers of CYP3A4 (e.g. carbamazepine, rifampicin, enzalutamide, phenytoin, St. John's Wort [*Hypericum perforatum*]) is contraindicated (see section 4.3). Strong CYP3A4 inducers decrease exposure of midostaurin and its active metabolites (CGP52421 and CGP62221). In a study in healthy subjects, co-administration of the strong CYP3A4 inducer rifampicin (600 mg daily) to steady state with a 50 mg single dose of midostaurin decreased midostaurin C_{max} by 73% and AUC_{inf} by 96% on average, respectively. CGP62221 exhibited a similar pattern. The mean AUC_{last} of CGP52421 decreased by 60%.

Strong CYP3A4 inhibitors
Strong CYP3A4 inhibitors may increase midostaurin blood concentrations. In a study with 36 healthy subjects, co-administration of the strong CYP3A4 inhibitor ketoconazole to steady state with a single dose of 50 mg midostaurin led to a significant increase in midostaurin exposure (1.8-fold C_{max} increase and 10-fold AUC_{inf} increase) and 3.5-fold increase in AUC_{inf} of CGP62221, while the C_{max} of the active metabolites (CGP62221 and CGP52421) decreased by half (see section 5.2). At steady state of midostaurin (50 mg twice daily for 21 days), with the strong CYP3A4 inhibitor itraconazole at steady state in a subset of patients (N=7), midostaurin steady-state exposure (C_{min}) was increased by 2.09-fold. C_{min} of CGP52421 was increased by 1.3-fold, whereas no significant effect in exposure of CGP62221 was observed (see section 4.4).

Effect of Rydapt on other medicinal products

Substrates of CYP enzymes
In healthy subjects, co-administration of a single dose of bupropion (CYP2B6 substrate) with multiple doses of midostaurin (50 mg twice daily) at steady state decreased bupropion AUC_{inf} and AUC_{last} by 48% and 49% respectively and C_{max} by 55% compared to administration of bupropion alone. This

indicates that midostaurin is a mild inducer of CYP2B6. Medicinal products with a narrow therapeutic range that are substrates of CYP2B6 (e.g. bupropion or efavirenz) should be used with caution when administered concomitantly with midostaurin, and may need dose adjustment to maintain optimal exposure.

Based on *in-vitro* data, midostaurin and its active metabolites, CGP52421 and CGP62221, are inhibitors of CYP1A2 and CYP2E1 and inducers of CYP1A2. Therefore, medicinal products with a narrow therapeutic range that are substrates of CYP1A2 (e.g. tizanidine) and CYP2E1 (e.g. chlorzoxazone) should be used with caution when administered concomitantly with midostaurin, and may need dose adjustment to maintain optimal exposure.

Substrates of transporters
In healthy subjects, co-administration of a single dose of rosuvastatin (BCRP substrate) with a single dose of midostaurin (100 mg) increased rosuvastatin AUC_{inf} and AUC_{last} by 37% and 48% respectively; C_{max} was approximately doubled (2.01 times) compared to administration of rosuvastatin alone. This indicates that midostaurin has a mild inhibitory effect on BCRP substrates. Medicinal products with a narrow therapeutic range that are substrates of the transporter BCRP (e.g. rosuvastatin or atorvastatin) should be used with caution when administered concomitantly with midostaurin, and may need dose adjustment to maintain optimal exposure.

Hormonal contraceptives
There was no clinically significant pharmacokinetic drug-drug interaction between multiple doses of midostaurin (50 mg twice daily) at steady state and oral contraceptives containing ethinyl estradiol and levonorgestrel in healthy women. Therefore, it is not anticipated that the contraceptive reliability of this combination will be compromised by co-administration of midostaurin.

Food interactions

In healthy subjects, midostaurin absorption (AUC) was increased by an average of 22% when Rydapt was co-administered with a standard meal and by an average of 59% when co-administered with a high-fat meal. Peak midostaurin concentration (C_{max}) was reduced by 20% with a standard meal and by 27% with a high-fat meal versus on an empty stomach (see section 5.2).

Rydapt is recommended to be administered with food.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential

Women of childbearing potential should be informed that animal studies show midostaurin to be harmful to the developing foetus. Sexually active women of childbearing potential are advised to have a pregnancy test within 7 days prior to starting treatment with Rydapt and that they should use effective contraception (methods that result in less than 1% pregnancy rates) when using Rydapt and for at least 4 months after stopping treatment with Rydapt.

Pregnancy

Midostaurin can cause foetal harm when administered to a pregnant woman. There are no adequate and well-controlled studies in pregnant women. Reproductive studies in rats and rabbits demonstrated that midostaurin induced foetotoxicity (see section 5.3). Rydapt is not recommended during pregnancy or in women of childbearing potential not using contraception. Pregnant women should be advised of the potential risk to the foetus.

Breast-feeding

It is unknown whether midostaurin or its active metabolites are excreted in human milk. Available animal data have shown that midostaurin and its active metabolites pass into the milk of lactating rats.

Breast-feeding should be discontinued during treatment with Rydapt and for at least 4 months after stopping treatment.

Fertility

There are no data on the effect of Rydapt on human fertility. Animal studies with midostaurin have shown impaired fertility (see section 5.3).

4.7 Effects on ability to drive and use machines

Rydapt has minor influence on the ability to drive and use machines. Dizziness and vertigo have been reported in patients taking Rydapt and should be considered when assessing a patient's ability to drive or use machines.

4.8 Undesirable effects

Summary of the safety profile

AML
The safety evaluation of Rydapt (50 mg twice daily) in patients with newly diagnosed FLT3-mutated AML is based on a phase III, randomised, double-blind, placebo-controlled study with 717 patients. The overall median duration of exposure was 42 days (range 2 to 576 days) for patients in the Rydapt plus standard chemotherapy arm versus 34 days (range 1 to 465 days) for patients in the placebo plus standard chemotherapy arm. For the 205 patients (120 in Rydapt arm and 85 in placebo arm) who entered the maintenance phase, the median duration of exposure in maintenance was 11 months for both arms (16 to 520 days for patients in the Rydapt arm and 22 to 381 days in the placebo arm).

The most frequent adverse reactions (ARs) in the Rydapt arm were febrile neutropenia (83.4%), nausea (83.4%), exfoliative dermatitis (61.6%), vomiting (60.7%), headache (45.9%), petechiae (35.8%) and pyrexia (34.5%). The most frequent Grade 3/4 ARs were febrile neutropenia (83.5%), lymphopenia (20.0%), device-related infection (15.7%), exfoliative dermatitis (13.6%), hyperglycaemia (7.0%) and nausea (5.8%). The most frequent laboratory abnormalities were haemoglobin decreased (97.3%), ANC decreased (86.7%), ALT increased (84.2%), AST increased (73.9%) and hypokalaemia (61.7%). The most frequent Grade 3/4 laboratory abnormalities were ANC decreased (85.8%), haemoglobin decreased (78.5%), ALT increased (19.4%) and hypokalaemia (13.9%).

Serious ARs occurred at similar rates in patients in the Rydapt versus the placebo arm. The most frequent serious AR in both arms was febrile neutropenia (16%).

Discontinuation due to any adverse reaction occurred in 3.1% of patients in the Rydapt arm versus 1.3% in the placebo arm. The most frequent Grade 3/4 adverse reaction leading to discontinuation in the Rydapt arm was exfoliative dermatitis (1.2%).

Safety profile during maintenance phase
While Table 3 provides the incidence for ARs over the total duration of the study, when the maintenance phase (single agent Rydapt or placebo) was assessed separately, a difference in the type and severity of ARs was observed. The overall incidence of ARs during the maintenance phase was generally lower than during the induction and consolidation phase. Incidences of ARs were, however, higher in the Rydapt arm than in the placebo arm during the maintenance phase. ARs occurring more often in the midostaurin arm versus placebo during maintenance included: nausea (46.4% versus 17.9%), hyperglycaemia (20.2% versus 12.5%), vomiting (19% versus 5.4%) and QT prolongation (11.9% versus 5.4%).

Most of the haematological abnormalities reported occurred during the induction and consolidation phase when the patients received Rydapt or placebo in combination with chemotherapy. The most frequent Grade 3/4 haematological abnormalities reported in patients during the maintenance phase

with Rydapt were ANC decrease (20.8% versus 18.8%) and leukopenia (7.5% versus 5.9%).

ARs reported during the maintenance phase led to discontinuation of 1.2% of patients in the Rydapt arm and none in the placebo arm.

ASM, SM-AHN and MCL
The safety of Rydapt (100 mg twice daily) as a single agent in patients with ASM, SM-AHN and MCL was evaluated in 142 patients in two single-arm, open-label, multicentre studies. The median duration of exposure to Rydapt was 11.4 months (range: 0 to 81 months).

The most frequent ARs were nausea (82%), vomiting (68%), diarrhoea (51%), peripheral oedema (35%) and fatigue (31%). The most frequent Grade 3/4 ARs were fatigue (8.5%), sepsis (7.7%), pneumonia (7%), febrile neutropenia (7%), and diarrhoea (6.3%). The most frequent non-haematological laboratory abnormalities were hyperglycaemia (93.7%), total bilirubin increased (40.1%), lipase increased (39.4%), aspartate aminotransferase (AST) increased (33.8%), and alanine aminotransferase (ALT) increased (33.1%), while the most frequent haematological laboratory abnormalities were absolute lymphocyte count decreased (73.2%) and ANC decreased (58.5%). The most frequent Grade 3/4 laboratory abnormalities were absolute lymphocyte count decreased (45.8%), ANC decreased (26.8%), hyperglycaemia (19%), and lipase increased (17.6%).

Dose modifications (interruption or adjustment) due to ARs occurred in 31% of patients. The most frequent ARs that led to dose modification (incidence ≥5%) were nausea and vomiting.

ARs that led to treatment discontinuation occurred in 9.2% of patients. The most frequent (incidence ≥1%) were febrile neutropenia, nausea, vomiting and pleural effusion.

Tabulated lists of adverse reactions

ARs are listed according to MedDRA system organ class. Within each system organ class, the ARs are ranked by frequency, with the most frequent reactions first, using the following convention (CIOMS III): 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). Within each frequency grouping, adverse reactions are presented in the order of decreasing seriousness.

AML

Table 3 presents the frequency category of ARs reported in the phase III study in patients with newly diagnosed FLT3-mutated AML and during post-marketing experience.

Table 3 Adverse reactions observed in AML

Adverse reaction	All grades	Grades 3/4	Frequency category
	Rydapt + chemo n=229[1] %	Rydapt + chemo n=345[1] %	
Infections and infestations			
Device-related infection	24	15.7	Very common
Upper respiratory tract infection	5.2	0.6	Common
Neutropenic sepsis	0.9	3.5	Uncommon
Blood and lymphatic system disorders			
Febrile neutropenia	83.4	83.5	Very common
Petechiae	35.8	1.2	Very common
Lymphopenia	16.6	20	Very common
Immune system disorders			
Hypersensitivity	15.7	0.6	Very common
Metabolism and nutrition disorders			
Hyperuricaemia	8.3	0.6	Common
Psychiatric disorders			
Insomnia	12.2	0	Very common
Nervous system disorders			
Headache	45.9	2.6	Very common
Syncope	5.2	4.6	Common
Tremor	3.9	0	Common
Eye disorders			
Eyelid oedema	3.1	0	Common
Cardiac disorders			
Hypotension	14.4	5.5	Very common
Sinus tachycardia	9.6	1.2	Common
Hypertension	7.9	2.3	Common
Pericardial effusion	3.5	0.6	Common
Respiratory, thoracic and mediastinal disorders			
Epistaxis	27.5	2.6	Very common
Laryngeal pain	11.8	0.6	Very common
Interstitial lung disease/Pneumonitis[2]	11.4	4.9	Very common
Dyspnoea	10.9	5.5	Very common
Pleural effusion	5.7	0.9	Common
Nasopharyngitis	8.7	0	Common
Acute respiratory distress syndrome	2.2	2.3	Common
Gastrointestinal disorders			
Nausea	83.4	5.8	Very common
Vomiting	60.7	2.9	Very common
Stomatitis	21.8	3.5	Very common
Abdominal pain upper	16.6	0	Very common
Haemorrhoids	15.3	1.4	Very common
Anorectal discomfort	7	0.9	Common
Abdominal discomfort	3.5	0	Common

Skin and subcutaneous tissue disorders			
Dermatitis exfoliative	61.6	13.6	Very common
Hyperhidrosis	14.4	0	Very common
Dry skin	7	0	Common
Keratitis	6.6	0.3	Common
Acute febrile neutrophilic dermatosis[3]	-	-	Not known
Musculoskeletal and connective tissue disorders			
Back pain	21.8	1.4	Very common
Arthralgia	14	0.3	Very common
Bone pain	9.6	1.4	Common
Pain in extremity	9.6	1.4	Common
Neck pain	7.9	0.6	Common
General disorders and administration site conditions			
Pyrexia	34.5	3.2	Very common
Catheter-related thrombosis	3.5	2	Common
Investigations			
Haemoglobin decreased*	97.3	78.5	Very common
ANC decreased*	86.7	85.8	Very common
ALT increased*	84.2	19.4	Very common
AST increased*	73.9	6.4	Very common
Hypokalaemia*	61.7	13.9	Very common
Hyperglycaemia	20.1	7	Very common
Hypernatraemia*	20	1.2	Very common
Electrocardiogram QT prolonged[3]	19.7	5.8	Very common
Activated partial thromboplastin time prolonged	12.7	2.6	Very common
Hypercalcaemia*	6.7	0.6	Common
Weight increased	6.6	0.6	Common

[1]For trial sites in North America, all grades were collected for 13 pre-specified adverse events. For all other adverse events, only grades 3 and 4 were collected. Therefore, all grade AEs are summarised only for patients in non-North American trial sites, whereas Grades 3 and 4 are summarised for patients in all trial sites.
[2]This AR was included after identification in the post-marketing setting. Interstitial lung disease has been derived from post-marketing experience with Rydapt via spontaneous case reports and literature cases. No cases of interstitial lung disease were reported in the phase III study.
[3]These ARs were included after identification in the post-marketing setting.
* Frequency is based on laboratory values.

ASM, SM-AHN and MCL

Table 4 presents the frequency category of ARs based on pooled data from two studies in patients with ASM, SM-AHN and MCL.

Table 4 Adverse reactions observed in ASM, SM-AHN and MCL

Adverse reaction	Rydapt (100 mg twice daily) N=142		Frequency category
	All grades %	Grades 3/4 %	
Infections and infestations			
Urinary tract infection	13	2.8	Very common
Upper respiratory tract infection	11	1.4	Very common
Pneumonia	8.5	7.0	Common
Sepsis	7.7	7.7	Common
Bronchitis	5.6	0	Common
Oral herpes	4.9	0	Common
Cystitis	4.2	0	Common
Sinusitis	4.2	0.7	Common
Erysipelas	3.5	1.4	Common
Herpes zoster	3.5	0.7	Common
Blood and lymphatic system disorders			
Febrile neutropenia	7.7	7.0	Common
Immune system disorders			
Hypersensitivity	2.1	0	Common
Anaphylactic shock	0.7	0.7	Uncommon
Nervous system disorders			
Headache	26	1.4	Very common
Dizziness	13	0	Very common
Disturbance in attention	7	0	Common
Tremor	6.3	0	Common
Ear and labyrinth disorders			
Vertigo	4.9	0	Common
Vascular disorders			
Hypotension	9.2	2.1	Common
Haematoma	6.3	0.7	Common
Respiratory, thoracic and mediastinal disorders			
Dyspnoea	18	5.6	Very common
Cough	16	0.7	Very common
Pleural effusion	13	4.2	Very common
Epistaxis	12	2.8	Very common
Oropharyngeal pain	4.2	0	Common
Interstitial lung disease/Pneumonitis[1]	2.1	0	Common
Gastrointestinal disorders			
Nausea	82	5.6	Very common
Vomiting	68	5.6	Very common
Diarrhoea	51	6.3	Very common
Constipation	29	0.7	Very common
Dyspepsia	5.6	0	Common
Gastrointestinal haemorrhage	4.2	3.5	Common
General disorders and administration site conditions			
Oedema peripheral	35	3.5	Very common
Fatigue	31	8.5	Very common
Pyrexia	27	4.2	Very common
Asthenia	4.9	0.7	Common
Chills	4.9	0	Common
Oedema	4.2	0.7	Common

Investigations			
Hyperglycaemia (non-fasting)*	93.7	19.0	Very common
Absolute lymphocyte decreased*	73.2	45.8	Very common
ANC decreased*	58.5	26.8	Very common
Total bilirubin increased*	40.1	4.9	Very common
Lipase increased*	39.4	17.6	Very common
AST increased*	33.8	2.8	Very common
ALT increased*	33.1	3.5	Very common
Amylase increased*	20.4	7.0	Very common
Electrocardiogram QT prolonged[1]	10.6	0.7	Very common
Weight increased	5.6	2.8	Common
Injury, poisoning and procedural complications			
Contusion	6.3	0	Common
Fall	4.2	0.7	Common
* Frequency is based on laboratory values. [1]These ARs were included after identification in the post-marketing setting.			

Description of selected adverse reactions

Gastrointestinal disorders
Nausea, vomiting and diarrhoea were observed in AML, ASM, SM-AHN and MCL patients. In ASM, SM-AHN and MCL patients these events led to dose adjustment or interruption in 26% and to discontinuation in 4.2% of the patients. Most of the events occurred within the first 6 months of treatment and were managed with supportive prophylactic medicinal products.

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

Reported experience with overdose in humans is very limited. Single doses of up to 600 mg have been given with acceptable acute tolerability. Adverse reactions observed were diarrhoea, abdominal pain and vomiting.

There is no known specific antidote for midostaurin. In the event of an overdose, patients must be closely monitored for signs or symptoms of adverse reactions, and appropriate symptomatic and supportive treatment initiated.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01EX10

Mechanism of action

Midostaurin inhibits multiple receptor tyrosine kinases, including FLT3 and KIT kinase. Midostaurin inhibits FLT3 receptor signalling and induces cell cycle arrest and apoptosis in leukaemic cells expressing FLT3 ITD or TKD mutant receptors or over-expressing FLT3 wild type receptors. *In vitro* data indicate that midostaurin inhibits D816V mutant KIT receptors at exposure levels achieved in patients (average achieved exposure higher than IC_{50}). *In vitro* data indicate that KIT wild type receptors are inhibited to a much lesser extent at these concentrations (average achieved exposure

lower than IC_{50}). Midostaurin interferes with aberrant KIT D816V-mediated signalling and inhibits mast cell proliferation, survival and histamine release.

In addition, midostaurin inhibits several other receptor tyrosine kinases such as PDGFR (platelet-derived growth factor receptor) or VEGFR2 (vascular endothelial growth factor receptor 2), as well as members of the serine/threonine kinase family PKC (protein kinase C). Midostaurin binds to the catalytic domain of these kinases and inhibits the mitogenic signalling of the respective growth factors in cells, resulting in growth arrest.

Midostaurin in combination with chemotherapeutic agents (cytarabine, doxorubicin, idarubicin and daunorubicin) resulted in synergistic growth inhibition in FLT3-ITD expressing AML cell lines.

Pharmacodynamic effects

Two major metabolites have been identified in murine models and humans, i.e. CGP62221 and CGP52421. In proliferation assays with FLT3-ITD expressing cells, CGP62221 showed similar potency compared to the parent compound, however CGP52421 was approximately 10-fold less potent.

Cardiac electrophysiology
A dedicated QT study in 192 healthy subjects with a dose of 75 mg twice daily did not reveal clinically significant prolongation of QT by midostaurin and CGP62221 but the study duration was not long enough to estimate the QTc prolongation effects of the long-acting metabolite CGP52421. Therefore, the change from baseline in QTcF with the concentration of midostaurin and both metabolites was further explored in a phase II study in 116 patients with ASM, SM-AHN or MCL. At the median peak C_{min} concentrations attained at a dose of 100 mg twice daily, neither midostaurin, CGP62221 nor CGP52421 showed a potential to cause clinically significant QTcF prolongation, since the upper bounds of predicted change at these concentration levels were less than 10 msecs (5.8, 2.4, and 4.0 msecs, respectively). In the ASM, SM-AHN and MCL population, 25.4% of patients had at least one ECG measurement with a QTcF greater than 450 ms and 4.7% greater than 480 ms.

Clinical efficacy and safety

AML
The efficacy and safety of midostaurin in combination with standard chemotherapy versus placebo plus standard chemotherapy and as single agent maintenance therapy was investigated in 717 patients (18 to 60 years of age) in a randomised, double-blind, phase III study. Patients with newly diagnosed FLT3-mutated AML as determined by a clinical study assay were randomised (1:1) to receive midostaurin 50 mg twice daily (n=360) or placebo (n=357) sequentially in combination with standard daunorubicin (60 mg/m^2 daily on days 1-3) / cytarabine (200 mg/m^2 daily on days 1-7) induction and high-dose cytarabine (3 g/m^2 every 12 hours on days 1, 3, 5) consolidation, followed by continuous midostaurin or placebo treatment according to initial assignment for up to 12 additional cycles (28 days/cycle). While the study included patients with various AML-related cytogenetic abnormalities, patients with acute promyelocytic leukaemia (M3) or therapy-related AML were excluded. Patients were stratified by FLT3 mutation status: TKD, ITD with allelic ratio <0.7, and ITD with allelic ratio ≥0.7.

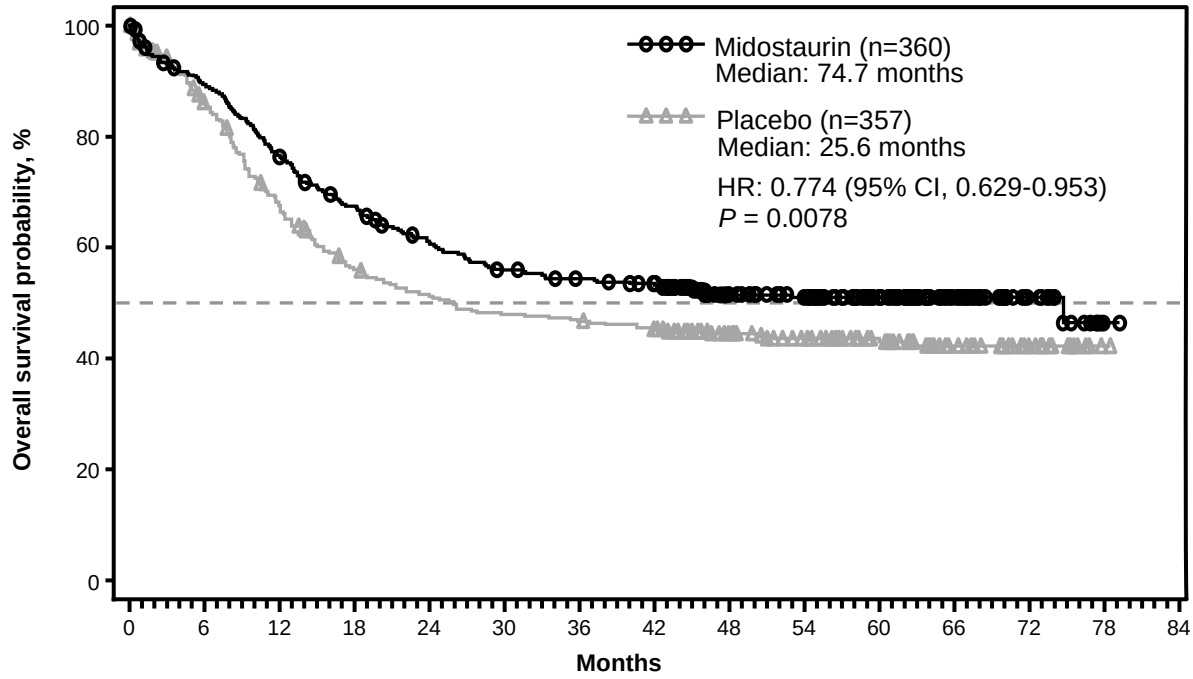
The two treatment groups were generally balanced with respect to the baseline demographics of disease characteristics. The median age of the patients was 47 years (range: 18 to 60 years), a majority of the patients had ECOG performance status of 0 or 1 (88.3%), and most patients had *de novo* AML (95%). Of the patients with race information reported, 88.1% were Caucasian. The majority of patients (77.4%) had FLT3-ITD mutations, most of them (47.6%) with a low allelic ratio (<0.7), and 22.6% of patients had FLT3-TKD mutations. Forty-eight per cent were male in the midostaurin arm and 41% in the placebo arm.

Patients who proceeded to haematopoietic stem cell transplant (SCT) stopped receiving study treatment prior to the start of the SCT conditioning regimen. The overall rate of SCT was 59.4%

(214/360) of patients in the midostaurin plus standard chemotherapy arm versus 55.2% (197/357) in the placebo plus standard chemotherapy arm. All patients were followed for survival.

The primary endpoint of the study was overall survival (OS), measured from the date of randomisation until death by any cause. The primary analysis was conducted after a minimum follow-up of approximately 3.5 years after the randomisation of the last patient. The study demonstrated a statistically significant improvement in OS with a 23% risk reduction of death for midostaurin plus standard chemotherapy over placebo plus standard chemotherapy (see Table 6 and Figure 1).

Figure 1 Kaplan-Meier curve for overall survival, non-censored for SCT



Patients at risk

Months	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72**	**78**	**84**
Midostaurin	360	314	269	234	208	189	181	174	133	120	77	50	22	1	0
Placebo	357	284	221	179	163	152	148	141	110	95	71	45	20	1	0

The key secondary endpoint was event-free survival (EFS; an EFS event is defined as a failure to obtain a complete remission (CR) within 60 days of initiation of protocol therapy, or relapse, or death from any cause). The EFS showed a statistically significant improvement for midostaurin plus standard chemotherapy over placebo plus standard chemotherapy (HR: 0.78 [95% CI, 0.66 to 0.93] p = 0.0024), and a median EFS of 8.2 months and 3.0 months, respectively; see Table 5.

Table 5 Efficacy of midostaurin in AML

Efficacy parameter	Midostaurin n=360	Placebo n=357	HR* (95% CI)	P-value¥
Overall survival (OS)[1]				
Median OS in months (95% CI)	74.7 (31.5, NE)	25.6 (18.6, 42.9)	0.77 (0.63, 0.95)	0.0078
Kaplan-Meier estimates at 5 years (95% CI)	0.51 (0.45, 0.56)	0.43 (0.38, 0.49)		
Event-free survival (EFS)[2]				
Median EFS in months, considering CRs within 60 days of treatment start (95% CI)	8.2 (5.4, 10.7)	3.0 (1.9, 5.9)	0.78 (0.66, 0.93)	0.0024
Median EFS in months, considering CRs any time during induction (95% CI)	10.2 (8.1, 13.9)	5.6 (2.9, 6.7)	0.73 (0.61, 0.87)	0.0001
Disease-free survival (DFS)				
Median DFS in months (95% CI)	26.7 (19.4, NE)	15.5 (11.3, 23.5)	0.71 (0.55, 0.92)	0.0051
Complete remission (CR)				
within 60 days of treatment start (%)	212 (58.9)	191 (53.5)	NE	0.073§
any time during induction (%)	234 (65.0)	207 (58.0)	NE	0.027§
Cumulative incidence of relapse (CIR)				
Median (95% CI)	NE (25.7, NE)	17.6 (12.7, 46.3)	0.68 (0.52, 0.89)	0.0023

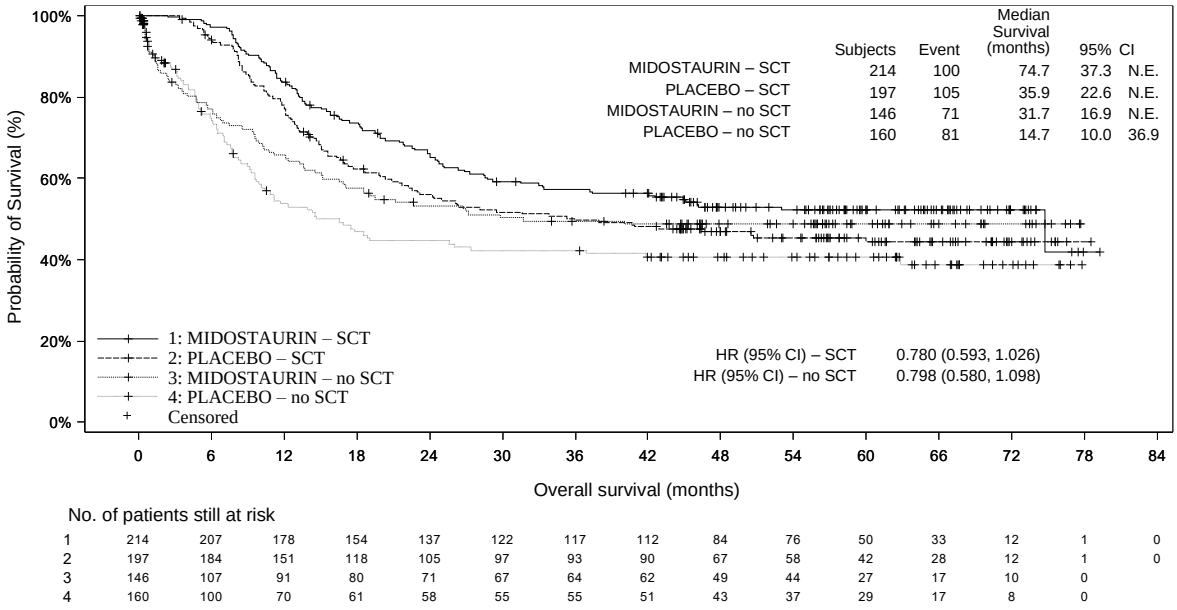
[1]primary endpoint; [2]key secondary endpoint; NE: Not Estimated
*Hazard ratio (HR) estimated using Cox regression model stratified according to the randomisation FLT3 mutation factor.
¥1-sided p-value calculated using log-rank test stratified according to the randomisation FLT3 mutation factor.
§Not significant

There was a trend favouring midostaurin for CR rate by day 60 for the midostaurin arm (58.9% versus 53.5%; p = 0.073) that continued when considering all CRs during induction (65.0% versus 58.0%; p = 0.027). In addition, in patients who achieved complete remission during induction, the cumulative incidence of relapse at 12 months was 26% in the midostaurin arm versus 41% in the placebo arm.

Sensitivity analyses for both OS and EFS when censored at the time of SCT also supported the clinical benefit with midostaurin plus standard chemotherapy over placebo.

Results for OS by SCT status are shown in Figure 2. For EFS, considering complete remissions within 60 days of study treatment start, the HR was 0.602 (95% CI: 0.372, 0.974) for patients with SCT and 0.827 (95% CI: 0.689, 0.993) for patients without SCT, favouring midostaurin.

Figure 2 Kaplan Meier curve for overall survival by SCT status in AML



In a subgroup analysis, no apparent OS benefit was observed in females, however, a treatment benefit was observed in females in all secondary efficacy endpoints (see Table 6).

Table 6 Overview of OS, EFS, CR, DFS and CIR by gender in AML

Endpoint	**Overall 95% CI**	**Males 95% CI**	**Females 95% CI**
OS (HR)	0.774 (0.629, 0.953)	0.533 (0.392, 0.725)	1.007 (0.757, 1.338)
EFS (CR induction) (HR)	0.728 (0.613, 0.866)	0.660 (0.506, 0.861)	0.825 (0.656, 1.037)
CR induction (OR)	0.743* (0.550, 1.005)	0.675* (0.425, 1.072)	0.824* (0.552, 1.230)
DFS (CR induction) (HR)	0.663 (0.516, 0.853)	0.594 (0.408, 0.865)	0.778 (0.554, 1.093)
CIR (CR induction) (HR)	0.676 (0.515, 0.888)	0.662 (0.436, 1.006)	0.742 (0.516, 1.069)
*Odds ratio calculated as (No complete remission in treatment/Complete remission in treatment) / (No complete remission in placebo/complete remission in placebo) HR= Hazard ratio; OR=odds ratio			

Efficacy and safety in patients >60-70 years old were evaluated as part of a phase II, single-arm, investigator-initiated study of midostaurin in combination with intensive induction, consolidation including allogenic SCT and single-agent maintenance in patients with FLT3-ITD mutated AML. Based on the final analysis, the EFS rate at 2 years (primary endpoint) was 34% (95% CI: 27, 44) and the median OS was 22.7 months in patients older than 60 years of age (128 out of 440 patients).

ASM, SM-AHN and MCL

The efficacy of midostaurin in patients with ASM, SM-AHN and MCL, collectively referred to as advanced systemic mastocytosis (SM), was evaluated in two open-label, single-arm, multicentre studies (142 patients in total).

The pivotal study was a multicentre, single-arm phase II study in 116 patients with advanced SM (Study CPKC412D2201). Midostaurin was administered orally at 100 mg twice daily until disease progression or intolerable toxicity. Of the 116 patients enrolled, 89 were considered eligible for

response assessment and constituted the primary efficacy population. Of these, 73 patients had ASM (57 with an AHN) and 16 patients had MCL (6 with an AHN). The median age in the primary efficacy population was 64 years with approximately half of the patients ≥65 years. Approximately one third (36%) received prior anti-neoplastic therapy for ASM, SM-AHN or MCL. At baseline in the primary efficacy population, 65% of the patients had >1 measurable C finding (thrombocytopenia, hypoalbuminaemia, anaemia, high total bilirubin, transfusion-dependent anaemia, weight loss, neutropenia, high ALT or high AST). The KIT D816V mutation was detected in 82% of patients.

The primary endpoint was overall response rate (ORR). Response rates were assessed based on the modified Valent and Cheson criteria and responses were adjudicated by a study steering committee. Secondary endpoints included duration of response, time to response, and overall survival. Responses to midostaurin are shown in Table 7. Activity was observed regardless of number of prior therapies, and presence or absence of an AHN. Confirmed responses were observed in both KIT D816V mutation positive patients (ORR=63%) and KIT D816V wild type or unknown patients (ORR=43.8%). However, the median survival for KIT D816V positive patients was longer, i.e. 33.9 months (95% CI: 20.7, 42), than for KIT D816V wild type or unknown patients, i.e. 10 months (95% CI: 6.9, 17.4). Forty-six percent of patients had a decrease in bone marrow infiltration that exceeded 50% and 58% had a decrease in serum tryptase levels that exceeded 50%. Spleen volume decreased by ≥10% in 68.9% of patients with at least 1 post-baseline assessment (26.7% of patients had a reduction of ≥35%, which correlates with a 50% decrease by palpation).

The median time to response was 0.3 months (range: 0.1 to 3.7 months). The median duration of follow-up was 43 months.

Table 7 Efficacy of midostaurin in ASM, SM-AHN and MCL: primary efficacy population

	All N=89	**ASM N=16**	**SM-AHN N=57**	**MCL N=16**
Primary endpoint				
Overall response, n (%) (95% CI)	53 (59.6) (48.6, 69.8)	12 (75.0) (47.6, 92.7)	33 (57.9) (44.1, 70.9)	8 (50.0) (24.7, 75.3)
Major response, n (%)	40 (44.9)	10 (62.5)	23 (40.4)	7 (43.8)
Partial response, n (%)	13 (14.6)	2 (12.5)	10 (17.5)	1 (6.3)
Stable disease, n (%)	11 (12.4)	1 (6.3)	7 (12.3)	3 (18.8)
Progressive disease, n (%)	10 (11.2)	1 (6.3)	6 (10.5)	3 (18.8)
Secondary endpoints				
Median duration of response, months (95% CI)	18.6 (9.9, 34.7)	36.8 (5.5, NE)	10.7 (7.4, 22.8)	NR (3.6, NE)
Median overall survival, months (95% CI)	26.8 (17.6, 34.7)	51.1 (28.7, NE)	20.7 (16.3, 33.9)	9.4 (7.5, NE)
Kaplan-Meier estimates at 5 years (95% CI)	26.1 (14.6, 39.2)	34.8 (1.7, 76.2)	19.9 (8.6, 34.5)	33.7 (12.3, 56.8)

NE: Not Estimated, NR: Not Reached
Patients who received non-study anti-neoplastic therapy were considered as having progressed at the time of the new therapy.

Although the study was designed to be assessed with the modified Valent and Cheson criteria, as a *post-hoc* exploratory analysis, efficacy was also assessed per the 2013 International Working Group - Myeloproliferative Neoplasms Research and Treatment - European Competence Network on Mastocytosis (IWG-MRT-ECNM) consensus criteria. Response to Rydapt was determined using a computational algorithm applied without any adjudication. Out of 116 patients, 113 had a C-finding as defined by IWG response criteria (excluding ascites as a C-finding). All responses were considered and required a 12-week confirmation (see Table 8).

Table 8 Efficacy of midostaurin in ASM, SM-AHN and MCL per IWG-MRT-ECNM consensus criteria using an algorithmic approach

	All patients evaluated	ASM	SM-AHN	MCL	Subtype unknown
	N=113	N=15	N=72	N=21	N=5
Overall response rate, n (%)	32 (28.3)	9 (60.0)	15 (20.8)	7 (33.3)	1 (20.0)
(95% CI)	(20.2, 37.6)	(32.3, 83.7)	(12.2, 32.0)	(14.6, 57.0)	(0.5, 71.6)
Best overall response, n (%)					
Complete remission	1 (0.9)	0	0	1 (4.8)	0
Partial remission	17 (15.0)	5 (33.3)	8 (11.1)	3 (14.3)	1 (20.0)
Clinical improvement	14 (12.4)	4 (26.7)	7 (9.7)	3 (14.3)	0
Duration of response*					
n/N (%)	11/32 (34.4)	4/9 (44.4)	4/15 (26.7)	3/7 (42.9)	0/1 (0.0)
median (95% CI)	NE (27.0, NE)	36.8 (10.3, 36.8)	NE (17.3, NE)	NE (4.1, NE)	NE
Overall survival					
n/N (%)	65/113 (57.5)	4/15 (26.7)	49/72 (68.1)	12/21 (57.1)	0/5 (0.0)
median (95% CI)	29.9 (20.3, 42.0)	51.1 (34.7, NE)	22.1 (16.8, 32.2)	22.6 (8.3, NE)	NE

*Confirmation period for responses: 12 weeks
Analysis excludes ascites as a C-finding.
Patients who received non-study anti-neoplastic therapy were considered as having progressed at the time of the new therapy.

The supportive study was a single-arm, multicentre, open-label phase II study of 26 patients with ASM, SM-AHN and MCL (CPKC412A2213). Midostaurin was administered orally at 100 mg twice daily in cycles of 28 days. Lack of a major response (MR) or partial response (PR) by the end of the second cycle required discontinuation from the study treatment. Twenty (76.9%) patients had ASM (17 [85%] with AHN) and 6 patients (23.1%) had MCL (2 [33.3%] with AHN). The median age was 64.5 years with half of the patients ≥65 years). At baseline, 88.5% had >1 C finding and 69.2% had received at least one prior anti-neoplastic regimen.

The primary endpoint was ORR evaluated by the Valent criteria during the first two cycles of treatment. Nineteen patients (73.1%; 95% CI = [52.2, 88.4]) achieved a response during the first two cycles of treatment (13 MR; 6 PR). The median duration of follow-up was 73 months, and the median duration of response has not been reached. Median overall survival was 40.0 months (patients were only followed up for one year after treatment discontinuation for survival).

Paediatric population

In a phase II study, midostaurin was investigated in combination with chemotherapy in newly diagnosed paediatric patients with FLT3-mutated AML. Among the three FLT3-mutated AML patients enrolled in the study, two patients (10 and 14 years old) experienced dose limiting toxicities (DLTs) following the second induction cycle with midostaurin (at 30 mg/m^2 twice daily) in combination with chemotherapy (containing cytarabine 2 g/m^2/day, day 1-5; fludarabine 30 mg/m^2/day, day 1-5 and idarubicin 12 mg/m^2/day, day 2, 4 and 6). Both patients showed markedly delayed haematological recoveries (i.e. prolonged grade 4 thrombocytopenia lasting for 44 days in the first patient and 51 days in the second patient and grade 4 neutropenia lasting for 46 days in the second patient). In the first induction cycle both patients received midostaurin in combination with cytarabine, etoposide and idarubicin.

The European Medicines Agency has waived the obligation to submit the results of studies with Rydapt in all subsets of the paediatric population in the treatment of malignant mastocytosis and mast

cell leukaemia (see section 4.2 for information on paediatric use).

The European Medicines Agency has deferred the obligation to submit the results of studies with Rydapt in one or more subsets of the paediatric population in the treatment of acute myeloid leukaemia (see section 4.2 for information on paediatric use).

5.2 Pharmacokinetic properties

Midostaurin is a compound with good absorption and poor solubility. Two of its metabolites demonstrated pharmacological activities (CGP52421 and CGP62221). Following multiple doses, the pharmacokinetics of midostaurin and CGP62221 were time-dependent, with an initial increase observed in the first week followed by a decline of concentrations until reaching steady state on day 28. CGP52421 concentrations do not appear to decline as significantly as for midostaurin and CGP62221.

Absorption

The absolute bioavailability of midostaurin following oral administration is not known.

In humans, the absorption of midostaurin was rapid after oral administration, with T_{max} of total radioactivity observed at 1-3 hours post dose. The population pharmacokinetic analysis indicated that the absorption in patients was less than dose proportional at doses >50 mg twice daily.

In healthy subjects, after administration of a single dose of 50 mg midostaurin with food, AUC of midostaurin was increased to 20 800 ng*h/ml and C_{max} was decreased to 963 ng/ml (see section 4.5). Similarly, for CGP52421 and CGP62221 AUC increased to 19 000 and 29 200 ng*h/ml and C_{max} decreased to 172 and 455 ng/ml, respectively. Time to peak concentration was also delayed in the presence of a high-fat meal. T_{max} was delayed for all entities, midostaurin median T_{max} was 3 h, and for CGP52421 and CGP62221 T_{max} was delayed to 6 and 7 hours respectively.

In clinical studies, the efficacy and safety of Rydapt were investigated following administration with a light meal. After oral administration of a single 100 mg dose of midostaurin under fed conditions in ASM, SM-AHN and MCL patients, AUC_{inf}, C_{max} and T_{max} were 49 600 ng*h/ml, 2 940 ng/ml and 3 h, respectively, for midostaurin. For CGP52421, AUC_{0-12h} and C_{max} were 2 770 ng*h/ml and 299 ng/ml, respectively. AUC_{0-12h} and C_{max} for CGP62221 were 8 700 ng*h/ml and 931 ng/ml, respectively. After 100 mg bid multiple oral doses of midostaurin the $C_{min,ss}$ plasma midostaurin in AML and ASM, SM-AHN, MCL patients were 919 and 1 060 ng/ml, respectively. The CGP62221 $C_{min,\ ss}$ in the AML and the ASM, SM-AHN, MCL population were 1 610 ng/ml and 2 020 ng/ml, respectively. The CGP52421, $C_{min,ss}$ in the AML and the ASM, SM-AHN, MCL population were 8 630 ng/ml and 2 860 ng/ml, respectively.

Distribution

Midostaurin has a tissue distribution of geometric mean of 95.2 l (Vz/F). Midostaurin and its metabolites are distributed mainly in plasma rather than red blood cells. *In vitro* data showed midostaurin is more than 98% bound to plasma proteins, such as albumin, α1-acid glycoprotein (AGP) and lipoprotein.

Biotransformation

Midostaurin is metabolised by CYP3A4 mainly via oxidative pathways. The major plasma components included midostaurin and two major active metabolites, CGP62221 (via O-demethylation) and CGP52421 (via hydroxylation), accounting for 27.7±2.7% and 38.0±6.6%, respectively, of the total plasma exposure at 96 hours after a single 50 mg dose of midostaurin.

Elimination

The median terminal half-lives of midostaurin, CGP62221 and CGP52421 in plasma are approximately 20.9, 32.3 and 471 hours. The mean apparent plasma clearance (CL/F) was 2.4-3.1 l/h in healthy subjects. In AML and ASM, SM-AHN and MCL patients, population pharmacokinetic estimates for clearance of midostaurin at steady state were 5.9 l/h and 4.4 l/h, respectively. The Human Mass Balance study results indicated that faecal excretion is the major route of excretion (78% of the dose), and mostly as metabolites (73% of the dose), while unchanged midostaurin accounts for 3% of the dose. Only 4% of the dose is recovered in urine.

Linearity/non-linearity

In general, midostaurin and its metabolites showed no major deviation from dose-proportionality after a single dose in the range of 25 mg to 100 mg. However, there was a less than dose-proportional increase in exposure after multiple doses within the dose range of 50 mg to 225 mg daily.

Following multiple oral doses, midostaurin displayed time-dependent pharmacokinetics with an initial increase in plasma concentrations during the first week (peak C_{min}) followed by a decline with time to a steady state after approximately 28 days (2.5-fold decrease). While the exact mechanism for the declining concentration of midostaurin is unclear, it is likely due to the auto-induction properties of midostaurin and its two active metabolite CGP52421 and CGP62221 on CYP3A4. The pharmacokinetics of the CGP62221 metabolite showed a similar trend. However, CGP52421 concentrations increased up to 2.5-fold for ASM, SM-AHN and MCL and up to 9-fold for AML, compared to midostaurin after one month of treatment.

In vitro evaluation of drug-drug interaction potential
Based on *in vitro* data, midostaurin and its active metabolites, CGP52421 and CGP62221, are considered inhibitors of CYP1A2 and CYP2E1 and inducers of CYP2B6 (induction mediated by CAR) and CYP1A2 (induction mediated by AhR).

In vitro experiments demonstrated that midostaurin, CGP52421 and CPG62221 can potentially inhibit BCRP and BSEP. Simulations using physiologically-based pharmacokinetic (PBPK) models predicted that midostaurin given at a dose of 50 mg or 100 mg twice daily at steady state is unlikely to cause clinically relevant inhibition of OATP1B.

Special populations

Elderly patients
Based on population pharmacokinetic analyses no significant impact of age on the pharmacokinetics of midostaurin and its two active metabolites was identified for patients aged between 65 and 85 years. In adult patients with ASM, SM-AHN and MCL or AML, no midostaurin dose adjustment is required based on age.

Paediatric patients
Rydapt is not recommended to be used in children and adolescents (see section 4.2).
The pharmacokinetics of midostaurin in paediatric patients were explored in a phase I dose escalation monotherapy study with 22 patients (12 aged 0-2 years and 10 aged 10-17 years) with AML or MLL-rearranged ALL using a population pharmacokinetic approach. The pharmacokinetics of midostaurin were less than dose proportional with the doses of 30 mg/m^2 and 60 mg/m^2 after single and multiple doses. Due to the limited pharmacokinetic data in paediatric patients, no comparison with midostaurin pharmacokinetics in adults can be made.

Gender
Based on population pharmacokinetic model analyses of the effect of gender on clearance of midostaurin and its active metabolites, there was no statistically significant finding and the anticipated changes in exposure (<20%) were not deemed to be clinically relevant. No midostaurin dose adjustment is required based on gender.

Race/ethnicity
There are no differences in the pharmacokinetic profile between Caucasian and Black subjects. Based on a phase I study in healthy Japanese volunteers, pharmacokinetic profiles of midostaurin and its metabolites (CGP62221 and CGP52421) are similar compared to those observed in other pharmacokinetic studies conducted in Caucasians and Blacks. No midostaurin dose adjustment is required based on ethnicity.

Hepatic impairment
A dedicated hepatic impairment study assessed the systemic exposure of midostaurin after oral administration of 50 mg twice daily for 6 days and a single 50 mg dose on day 7 in subjects with baseline mild or moderate (Child-Pugh Class A or B, respectively) and following a single dose administration of 50 mg in subjects with severe hepatic impairment (Child-Pugh Class C) in comparison to control subjects with normal hepatic function. The maximum concentration of midostaurin was reached between 2 and 3 hours after administration after single or repeated doses for all groups. On day 1, the AUC_{0-12} and C_{max} were 8 130 ng*h/ml and 1 206 ng/ml, respectively, for healthy subjects. AUC_{0-12} was decreased by 39% and 36% in subjects with mild and moderate hepatic impairment, respectively. On day 7, $AUC_{Ctrough}$ (exposure under the curve of C_{trough} from day 1 to day 7) was 5 410 ng*h/ml in healthy subjects and was decreased by 35% and 20% in subjects with mild and moderate hepatic impairment, respectively. AUC_{tau} was decreased by 28% and 20% on day 7, respectively.

The subjects with severe hepatic impairment had a lower geometric mean C_{max} and AUC_{inf} of midostaurin compared to the control group (C_{max}: 1 360 ng/ml, AUC_{inf}: 30 100 ng.h/ml). C_{max} and AUC_{inf} of midostaurin decreased on average by 78% and 59% respectively in subjects with severe hepatic impairment.

Finally, the long-term data from patients were analysed using a population pharmacokinetic approach. No impact of hepatic impairment could be identified in patients with mild or moderate hepatic impairment in the ASM, SM-AHN, MCL and AML populations.

Overall, there was no increase in exposure (AUC) to plasma midostaurin and its metabolites (CGP62221 and CGP52421) in subjects with mild, moderate or severe hepatic impairment compared to subjects with normal hepatic function. No dose adjustment is necessary for patients with baseline mild or moderate hepatic impairment. Exposure to midostaurin and its active metabolite CGP62221 is substantially lower in patients with severe hepatic impairment than that in patients with normal hepatic function (see section 4.2). However, there are insufficient efficacy data in patients with severe hepatic impairment to suggest a dose adjustment is required.

Renal impairment
Renal elimination is a minor route of elimination for midostaurin. No dedicated renal impairment study was conducted for midostaurin. Population pharmacokinetic analyses were conducted using data from clinical studies in patients with AML (n=180) and ASM, SM-AHN and MCL (n=141). Out of the 321 patients included, 177 patients showed pre-existing mild (n=113), moderate (n=60) or severe (n=4) renal impairment (15 ml/min ≤ creatinine clearance [CrCL] <90 ml/min). 144 patients showed normal renal function (CrCL >90 ml/min) at baseline. Based on the population pharmacokinetic analyses, midostaurin clearance was not significantly impacted by renal impairment and therefore no dose adjustment is necessary for patients with mild or moderate renal impairment.

5.3 Preclinical safety data

Due to dose-limiting toxicity, clinical therapeutic exposure levels could not be reached in animals. All animal findings described below were observed at midostaurin exposure significantly lower than therapeutic levels.

Safety pharmacology and single/repeated dose toxicity

Safety pharmacology studies indicate that midostaurin is unlikely to interfere with vital functions of the central nervous system. *In vitro*, midostaurin did not inhibit hERG channel activity up to the limit of solubility of 12 µM. The two major human metabolites GGP52421 and CGP62221 (also tested at the limit of solubility) inhibited hERG current with moderate safety margins. In the repeat-dose studies in dogs, a decrease in heart rate, prolongation of the P-Q interval, and sporadically occurring atrioventricular blocks were seen in individual animals.

In the repeat-dose studies, target organs for toxicity were the gastrointestinal tract (emesis in dogs and monkeys, diarrhoea and mucosal alteration), testes (decreased spermatogenesis), bone marrow (hypocellularity) and lymphoid organs (depletion/atrophy). The effect on the bone marrow and lymphoid organs was accompanied by haematological changes of decreased white blood cells, lymphocytes and erythrocytic parameters. An increase in liver enzymes (ALT and AST) was seen consistently in rats, and in dogs and monkeys in long-term studies of ≥3 months duration, without histopathological correlates.

Reproductive toxicity

In a fertility study in rats, midostaurin was associated with reduced fertility, testicular degeneration and atrophy, reduced sperm motility, oligo- and aspermia, increased resorptions, decreased pregnancy rate, number of implants and live embryos.

In embryo-foetal development studies in rats and rabbits, increased numbers of late resorptions, reduced foetal weight and reduced skeletal ossification were observed.

In a pre- and post-natal developmental study, maternal dystocia and reduced litter size, lower pup body weights, accelerated complete eye opening and delayed auricular startle ontogeny were noted.

Juvenile animal studies

In a toxicity study in juvenile rats, midostaurin was administered from days 7 to 70 postpartum. A reduction in body weight, haemorrhage and mixed cell infiltration in the lungs, and erythrocytosis/erythrophagocytosis in the mesenteric lymph nodes were seen. There were no effects on physical development, sensory function or behavioural function. Mating index, fertility index and conception rates were reduced at 0, 5 and 15 mg/kg/day, but not at 2 mg/kg/day.

Genotoxicity

In vitro and *in vivo* genotoxicity studies covering relevant genotoxicity endpoints showed no evidence of mutagenic or clastogenic activity. No carcinogenicity studies have been performed.

Environmental risk assessment (ERA)

ERA studies have shown that midostaurin has the potential to be persistent, bioaccumulative and toxic to the environment.

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Capsule content

Macrogolglycerol hydroxystearate
Macrogol
Ethanol anhydrous
Maize oil mono-di-triglycerides
All-rac-alpha-tocopherol

Capsule shell

Gelatin
Glycerol
Titanium dioxide (E171)
Iron oxide yellow (E172)
Iron oxide red (E172)
Purified water

Printing ink

Carmine (E120)
Hypromellose
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years.

6.4 Special precautions for storage

This medicinal product does not require any special temperature storage conditions.

Store in the original container in order to protect from moisture.

6.5 Nature and contents of container

PA/alu/PVC/alu blisters. One blister contains 4 soft capsules.

Packs containing 56 (2 packs of 28) or 112 (4 packs of 28) soft capsules.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal

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

7. MARKETING AUTHORISATION HOLDER

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1218/001-002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 18 September 2017
Date of latest renewal: 30 May 2022

10. DATE OF REVISION OF THE TEXT

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

ANNEX II

A. MANUFACTURERS 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. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturers responsible for batch release

Novartis Pharma GmbH
Roonstrasse 25
90429 Nuremberg
Germany

Novartis Farmacéutica S.A.
Gran Via de les Corts Catalanes, 764
08013 Barcelona
Spain

Novartis Pharma GmbH
Sophie-Germain-Strasse 10
90443 Nuremberg
Germany

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (see Annex I: Summary of Product Characteristics, section 4.2).

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.

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.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rydapt 25 mg soft capsules
midostaurin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each soft capsule contains 25 mg midostaurin.

3. LIST OF EXCIPIENTS

Contains macrogolglycerol hydroxystearate and ethanol anhydrous. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Soft capsule

56 (2 packs of 28) capsules
112 (4 packs of 28) capsules

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 the original container 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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1218/001	112 (4 packs of 28) capsules
EU/1/17/1218/002	56 (2 packs of 28) capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rydapt 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 OUTER PACKAGING

INTERMEDIATE CARTON

1. NAME OF THE MEDICINAL PRODUCT

Rydapt 25 mg soft capsules
midostaurin

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each soft capsule contains 25 mg midostaurin.

3. LIST OF EXCIPIENTS

Contains macrogolglycerol hydroxystearate and ethanol anhydrous. See leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Soft capsule

28 capsules. Not to be sold separately.

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 the original container 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

Novartis Europharm Limited
Vista Building
Elm Park, Merrion Road
Dublin 4
Ireland

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/17/1218/001	112 (4 packs of 28) capsules
EU/1/17/1218/002	56 (2 packs of 28) capsules

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Rydapt 25 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS

1. NAME OF THE MEDICINAL PRODUCT

Rydapt 25 mg capsules
midostaurin

2. NAME OF THE MARKETING AUTHORISATION HOLDER

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

B. PACKAGE LEAFLET

Package leaflet: Information for the patient

Rydapt 25 mg soft capsules
midostaurin

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- 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, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Rydapt is and what it is used for

What Rydapt is
Rydapt contains the active substance midostaurin. It belongs to a class of medicines called protein kinase inhibitors.

What Rydapt is used for
Rydapt is used to treat acute myeloid leukaemia (AML) in adults who have a defect in a gene called FLT3. Acute myeloid leukaemia is a form of cancer of certain white blood cells (called myeloid cells) in which the body over-produces an abnormal type of these cells.

Rydapt is also used in adults to treat aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasm (SM-AHN), or mast cell leukaemia (MCL). These are disorders in which the body produces too many mast cells, a type of white blood cell. Symptoms are caused when too many mast cells enter organs such as the liver, bone marrow or spleen, and release substances such as histamine into the blood.

How Rydapt works
Midostaurin blocks the action of some enzymes (kinases) in the abnormal cells and stops their division and growth.

At the start of treatment in AML Rydapt is always used together with chemotherapy (medicines for treating cancer).

If you have any questions about how Rydapt works or why this medicine has been prescribed for you, ask your doctor, pharmacist or nurse.

2. What you need to know before you take Rydapt

Follow the doctor's instructions carefully. They may differ from the general information in this leaflet.

Do not take Rydapt
- if you are allergic to midostaurin or to any of the other ingredients of this medicine (listed in section 6). If you think you may be allergic, ask your doctor for advice.
- if you are already taking any of the following medicines:
  - medicines used to treat tuberculosis, such as rifampicin;
  - medicines used to treat epilepsy, such as carbamazepine or phenytoin;
  - enzalutamide, a medicine used to treat prostate cancer;
  - St. John's Wort (also known as *Hypericum perforatum*), a herbal medicine used to treat depression.

  These medicines must be avoided during treatment with Rydapt. Talk to your doctor if you are told that you have to start taking one of them during Rydapt treatment.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before taking Rydapt:
- if you have any infections.
- if you have a heart disorder.
- if you have problems with your lungs or problems breathing.
- if you have problems with your kidneys.

Tell your doctor, pharmacist or nurse straight away if you get any of these symptoms during treatment with Rydapt:
- if you have fever, sore throat or mouth ulcers, because these may indicate that your white blood cell count is low.
- if you have new or worsening symptoms such as fever, cough with or without mucous, chest pain, trouble breathing or shortness of breath, because these may be signs of lung problems.
- if you have or experience chest pain or discomfort, light-headedness, fainting, dizziness, blue discolouration of your lips, hands or feet, shortness of breath, or swelling of your lower limbs (oedema) or skin, because these may be signs of heart problems.

Your doctor may need to adjust, temporarily stop or completely discontinue your treatment with Rydapt.

<u>Monitoring during treatment with Rydapt</u>
Your doctor will perform regular blood tests during treatment with Rydapt in order to monitor the amount of blood cells (white blood cells, red blood cells and platelets) and electrolytes (e.g. calcium, potassium, magnesium) in your body. Your heart and lung function will also be checked regularly.

Children and adolescents
Rydapt should not be used in children and adolescents below 18 years of age who are also receiving other chemotherapy, because it could cause a severe reduction of certain types of blood cells.

Other medicines and Rydapt
Tell your doctor or pharmacist if you are taking, have recently taken or might take any other medicines. This is because Rydapt can affect the way some medicines work. Some other medicines can also affect how Rydapt works.

The following medicines must be avoided during treatment with Rydapt:
- medicines used to treat tuberculosis, such as rifampicin;
- medicines used to treat epilepsy, such as carbamazepine or phenytoin;
- enzalutamide, a medicine used to treat prostate cancer;
- St. John's Wort (also known as *Hypericum perforatum*), a herbal medicine used to treat depression.

Tell your doctor or pharmacist if you are taking any of the following medicines:
- some medicines used to treat infections, such as ketoconazole or clarithromycin;
- some medicines used to treat HIV, such as ritonavir or efavirenz;
- some medicines used to treat depression, such as nefazodone or bupropion;
- some medicines used to control levels of fat in your blood, such as atorvastatin or rosuvastatin;
- tizanidine, a medicine used to relax muscles;
- chlorzoxazone, a medicine used for treating discomfort caused by muscle spasms.

If you are taking any of these medicines, your doctor might prescribe a different medicine for you during your treatment with Rydapt.

You should also tell your doctor if you are already taking Rydapt and you are prescribed a new medicine that you have not previously taken during treatment with Rydapt.

Ask your doctor or pharmacist if you are not sure whether your medicine is one of the medicines listed above.

Pregnancy and breast-feeding
Rydapt may harm your unborn baby and is not recommended during pregnancy. If you are pregnant, think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine.

Rydapt could harm your baby. You should not breast-feed during treatment with Rydapt and for at least 4 months after stopping the treatment.

Contraception in women
If you become pregnant while taking Rydapt, it may harm your baby. Your doctor will ask you to take a pregnancy test before you start treatment with Rydapt to make sure you are not pregnant. You must use an effective method of contraception while taking Rydapt and for at least 4 months after you have stopped taking it. Your doctor will discuss with you the most suitable method of contraception for you to use.

If you become pregnant or think you are pregnant, tell your doctor right away.

Fertility
Rydapt may reduce fertility in men and women. You should discuss this with your doctor before starting treatment.

Driving and using machines
Take special care when driving and using machines as you may develop dizziness and vertigo while you are taking Rydapt.

Rydapt contains ethanol anhydrous (alcohol)
This medicine contains 666 mg of alcohol (ethanol) in each 200 mg dose (maximum daily dose) which is equivalent to 14 vol. % ethanol anhydrous. The amount in a 200 mg dose of this medicine is equivalent to 17 ml beer or 7 ml wine. The small amount of alcohol in this medicine will not have any noticeable effects. Alcohol may be harmful if you have alcohol-related problems, epilepsy or liver problems, or if you are pregnant or breast-feeding.

Rydapt contains macrogolglycerol hydroxystearate (castor oil)
This medicine contains macrogolglycerol hydroxystearate, which may cause stomach discomfort and diarrhoea.

3. How to take Rydapt

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

Do not exceed the dose prescribed by your doctor.

How much Rydapt to take
Your doctor will tell you exactly how many capsules to take.
- *Patients with AML*
  The usual daily dose is 50 mg (2 capsules) twice daily.
- *Patients with ASM, SM-AHN or MCL*
  The usual daily dose is 100 mg (4 capsules) twice daily.

Depending on how you respond to Rydapt, your doctor may lower your dose or temporarily interrupt the treatment.

Taking this medicine
- Taking Rydapt at the same time each day will help you to remember to take your medicine.
- Take Rydapt twice a day at about 12-hour intervals (for example, with breakfast and with your evening meal).
- Take Rydapt with food.
- Swallow the capsules whole with a glass of water. Do not open, crush or chew them to ensure proper dosing and avoid the unpleasant taste of the capsule content.
- For patients with AML, Rydapt is taken with chemotherapy medicines. It is very important to follow your doctor's recommendations.
- If you vomit after you swallow the capsules, do not take any more capsules until your next scheduled dose.

How long to take Rydapt
- Continue taking Rydapt for as long as your doctor tells you. Your doctor will regularly monitor your condition to check that the treatment is having the desired effect.
- If you are being treated for AML, after you finish taking Rydapt with chemotherapy medicines, you will receive Rydapt alone for up to 12 months.
- If you are being treated for ASM, SM-AHN or MCL, you will receive Rydapt as a long-term treatment, possibly lasting for months or years.

If you have any questions about how long to take Rydapt, talk to your doctor or pharmacist.

If you take more Rydapt than you should
If you take more capsules than you should, or if someone else takes your medicine, talk to a doctor or go to a hospital straight away, taking the pack with you, as medical treatment may be necessary.

If you forget to take Rydapt
If you forget to take Rydapt, skip the missed dose and take your next dose at the usual time. Do not take a double dose to make up for a forgotten dose. Instead, wait until it is time for your next dose.

If you stop taking Rydapt
Stopping your treatment with Rydapt may cause your condition to become worse. Do not stop taking your medicine unless your doctor tells you to do so.

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.

Stop taking Rydapt and tell your doctor straight away if you notice any of the following as these could be signs of an allergic reaction:
- difficulty breathing or swallowing
- dizziness
- swelling of the face, lips, tongue or throat
- severe itching of the skin, with a red rash or raised bumps

Some side effects in patients with AML could be serious.
Tell your doctor, pharmacist or nurse straight away if you notice any of the following:
- weakness, spontaneous bleeding or bruising, frequent infections with signs such as fever, chills, sore throat or mouth ulcers (signs of a low level of blood cells)
- fever, cough with or without mucus, chest pain, trouble breathing or shortness of breath (signs of non-infectious interstitial lung disease or pneumonitis)
- severe shortness of breath, laboured and unusually rapid breathing, dizziness, light-headedness, confusion and extreme tiredness (signs of acute respiratory distress syndrome)
- infections, fever, low blood pressure, decreased urination, rapid pulse, rapid breathing (signs of sepsis or neutropenic sepsis)

Other possible side effects in patients with AML
Other side effects include those listed below. If any of these side effects become severe, tell your doctor or pharmacist.

Most of the side effects are mild to moderate and will generally disappear after a few weeks of treatment.

Very common (may affect more than 1 in 10 people)
- infection at catheter site
- red or purple, flat, pinhead spots under the skin (petechiae)
- problems falling asleep (insomnia)
- headache
- shortness of breath, laboured breathing (dyspnoea)
- abnormal electrocardiogram results which can indicate to your doctor that you have an abnormality of the electrical activity of your heart known as QT prolongation
- dizziness, light-headedness (low blood pressure)
- nose bleeds
- throat pain (laryngeal pain)
- mouth sores (stomatitis)
- nausea, vomiting
- upper abdominal pain
- haemorrhoids (piles)
- excessive sweating
- skin rash with flaking or peeling (exfoliative dermatitis)
- back pain
- joint pain (arthralgia)
- fever
- thirst, high urine output, dark urine, dry flushed skin (signs of high levels of sugar in the blood, known as hyperglycaemia)
- muscle weakness, drowsiness, confusion, convulsions, impaired consciousness (signs of high level of sodium in the blood, known as hypernatraemia)
- muscle weakness, muscle spasms, abnormal heart rhythm (signs of low levels of potassium in the blood, known as hypokalaemia)
- bruising and bleeding (defect in blood clotting)
- abnormal blood test results which can indicate to your doctor how well certain parts of your

body are functioning: high levels of alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST) (indicative of liver function)

Common (may affect up to 1 in every 10 people)
- upper respiratory tract infection
- nausea, vomiting, constipation, stomach pain, frequent urination, thirst, muscle weakness and twitching (signs of high levels of calcium in the blood, known as hypercalcaemia)
- fainting
- involuntary shaking of the body
- headache, dizziness (high blood pressure)
- fast heart beat (sinus tachycardia)
- collection of fluid around the heart, which, if severe, can decrease the heart's ability to pump blood (pericardial effusion)
- fluid collection in the lungs/chest cavity, which, if severe, could make you breathless (pleural effusion)
- sore throat and a runny nose
- swelling of the eyelid
- discomfort in the anus and rectum
- abdominal pain, nausea, vomiting, constipation (abdominal discomfort)
- dry skin
- eye pain, blurred vision, intolerance to light (keratitis)
- neck pain
- bone pain
- pain in limbs
- increased weight
- blood clotted in the catheter
- abnormal blood test results which can indicate to your doctor how well certain parts of your body are functioning: high levels of uric acid

Not known (frequency cannot be estimated from the available data)
- Raised, painful, red to dark reddish-purple skin patches or sores that appear mainly on the arms, legs, face and neck, with a fever (signs of acute febrile neutrophilic dermatosis)

Some side effects in patients with ASM, SM-AHN and MCL could be serious.
Tell your doctor, pharmacist or nurse straight away if you notice any of the following:
- weakness, spontaneous bleeding or bruising, frequent infections with signs such as fever, chills, sore throat or mouth ulcers (signs of a low level of blood cells)
- fever, cough, difficult or painful breathing, wheezing, chest in pain when breathing (signs of pneumonia)
- fever, cough with or without mucus, chest pain, trouble breathing or shortness of breath (signs of non-infectious interstitial lung disease or pneumonitis)
- infections, fever, dizziness, light-headedness, decreased urination, rapid pulse, rapid breathing (signs of sepsis or neutropenic sepsis)
- vomiting of blood, black or bloody stools (signs of gastrointestinal bleeding)

Other possible side effects in patients with ASM, SM-AHN and MCL
Other side effects include those listed below. If any of these side effects become severe, tell your doctor or pharmacist.

Most of the side effects are mild to moderate and will generally disappear after a few weeks of treatment.

Very common (may affect more than 1 in 10 people)
- urinary tract infection
- upper respiratory tract infection
- headache
- dizziness

- shortness of breath, laboured breathing (dyspnoea)
- cough
- fluid collection in the lungs/chest cavity, which, if severe, could make you breathless (pleural effusion)
- abnormal electrocardiogram results which can indicate to your doctor that you have an abnormality of the electrical activity of your heart known as QT prolongation
- nose bleeds
- nausea, vomiting
- diarrhoea
- constipation
- swelling of the limbs (calves, ankles)
- feeling very tired (fatigue)
- fever
- thirst, high urine output, dark urine, dry flushed skin (signs of high levels of sugar in the blood, known as hyperglycaemia)
- yellow skin and eyes (sign of high bilirubin in the blood)
- abnormal blood test results which indicate possible problems with the pancreas (high levels of lipase or amylase) and liver (high levels of alanine aminotransferase (ALT) or aspartate aminotransferase (AST))

Common (may affect up to 1 in every 10 people)
- involuntary shaking of the body
- cough with phlegm, chest pain, fever (bronchitis)
- cold sores in the mouth due to viral infection (oral herpes)
- painful and frequent urination (cystitis)
- feeling of pressure or pain in the cheeks and forehead (sinusitis)
- red, swollen painful rash on any part of the skin (erysipelas)
- shingles (herpes zoster)
- disturbance in attention
- feeling dizzy with spinning sensation (vertigo)
- bruising (haematoma)
- upset stomach, indigestion
- feeling weak (asthenia)
- chills
- generalised swelling (oedema)
- increased weight
- contusion (bruises)
- falls
- dizziness, light-headedness (low blood pressure)
- sore throat
- rapid weight gain

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 Rydapt

- 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 the blister foil after EXP. The expiry date refers to the last day of that month.
- This medicine does not require any special temperature storage conditions. Store in the original container in order to protect from moisture.
- Do not use this medicine if you notice any damage to the packaging or if there are any signs of

tampering.
- 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 Rydapt contains
- The active substance is midostaurin. Each soft capsule contains 25 mg midostaurin.
- The other ingredients are: macrogolglycerol hydroxystearate (see "Rydapt contains macrogolglycerol hydroxystearate (castor oil)" in section 2), gelatin, macrogol, glycerol, ethanol anhydrous (see "Rydapt contains ethanol anhydrous (alcohol)" in section 2), maize oil mono-di-triglycerides, titanium dioxide (E171), all-rac-alpha-tocopherol, iron oxide yellow (E172), iron oxide red (E172), carmine (E120), hypromellose, propylene glycol, purified water.

What Rydapt looks like and contents of the pack
Rydapt 25 mg soft capsules (capsules) are pale orange, oblong capsules with red imprint "PKC NVR".

The capsules are provided in blisters and are available in packs containing 56 capsules (2 packs of 28 capsules) or 112 capsules (4 packs of 28 capsules). Not all pack sizes may be marketed in your country.

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: http://www.ema.europa.eu