1. NAME OF THE MEDICINAL PRODUCT

Rydapt® 25 mg

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".

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Acute myeloid leukaemia (AML)
Rydapt is indicated in combination with standard induction and consolidation chemotherapy followed by single-agent maintenance therapy for adults with newly diagnosed acute myeloid leukaemia (AML) who have an FLT3 mutation.

Advanced systemic mastocytosis (advanced SM)
Rydapt is indicated for the treatment of adult patients with advanced systemic mastocytosis (advanced SM).

4.2 Posology and method of administration

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

Dosage for AML

Usual dosage

The recommended dose of Rydapt is 50 mg twice daily (see Table 1.1).

Initiation of therapy

Rydapt is dosed on days 8 to 21 of induction and consolidation chemotherapy cycles.

Maintenance therapy

Thereafter, Rydapt is administered twice daily as single-agent maintenance therapy for 12 months.

Table 1.1 Dosage for AML

	Induction chemotherapy (1 to 2 cycles, 21 days per cycle)	**Consolidation chemotherapy (up to 4 cycles, 21 days per cycle)**	**Single-agent maintenance therapy (12 cycles, 28 days per cycle)**
Use of midostaurin	On days 8 to 21, 50 mg twice daily	On days 8 to 21, 50 mg twice daily	On days 1 to 28, 50 mg twice daily

Dose modification due to adverse effects/interactions

Recommendations for dose modifications of Rydapt in patients with AML are shown in Table 1.2.

Table 1.2 Rydapt dose interruption, reduction, and discontinuation – recommendations for patients with AML

Criteria	**Rydapt dosing**
During maintenance therapy: Grade 4 neutropenia (ANC <0.5 × 10^9/liter)	Interrupt Rydapt until ANC ≥1.0 × 10^9/liter, then resume Rydapt at 50 mg twice daily. If neutropenia (ANC <1.0 × 10^9/liter) persists >2 weeks and is suspected to be related to Rydapt, discontinue Rydapt.

ANC: absolute neutrophil count

Dosing for advanced SM

Usual dosage

The recommended starting dose of Rydapt is 100 mg twice daily.

Treatment duration

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

Dose modification due to adverse effects/interactions

Recommendations for dose modifications of Rydapt in patients with advanced SM are shown in Table 2.

Table 2 Rydapt dose interruption, reduction, and discontinuation – recommendations for patients with advanced SM

Criteria	Rydapt dosing
ANC <1.0 × 10^9/liter in patients who did not have severe neutropenia at baseline.	Interrupt Rydapt until ANC ≥1.5 × 10^9/liter, then resume Rydapt at 50 mg twice daily. If well tolerated, gradually increase to 100 mg twice daily. If ANC <1.0 × 10^9/liter recurs and is suspected to be related to Rydapt, discontinue Rydapt.
Grade 3/4 nausea and/or vomiting despite optimal anti-emetic therapy	Interrupt Rydapt for 3 days (6 doses), then resume Rydapt at 50 mg per day and, if well tolerated, gradually increase dose to 100 mg twice daily

ANC: absolute neutrophil count

Common Terminology Criteria for Adverse Events (CTCAE) severity: grade 1 = mild symptoms; grade 2 = moderate symptoms; grade 3 = severe symptoms; grade 4 = life-threatening symptoms.

Special dosage instructions

Patients with hepatic impairment

No dose adjustment is required in patients with mild or moderate (Child-Pugh A or B) hepatic impairment. No studies have been conducted in patients with severe (Child-Pugh C) hepatic impairment (see section 5.2).

Patients with renal impairment

No dose adjustment is required in patients with mild or moderate renal impairment. Clinical experience in patients with severe renal impairment is limited. No data are available on patients with end-stage renal disease (see section 5.2).

Elderly patients

No dose adjustment is required in patients over 65 years of age (see section 5.2).

Children and adolescents

Rydapt is not indicated for children and adolescent under 18 years old.

Method of administration

Rydapt should be taken orally, twice daily at approximately 12-hour intervals. Rydapt should be taken with food to prevent nausea (see section 4.5 or 5.2)

Prophylactic anti-emetics should be administered in accordance with local medical practice as per patient tolerance.

Rydapt capsules should be swallowed whole with a glass of water. Rydapt capsules must not be opened, crushed or chewed.

If a dose is missed, the forgotten dose should not be taken and the patient should wait and take the next scheduled dose at the scheduled time.

If vomiting occurs during treatment, the patient should not take an additional dose before taking the next scheduled dose.

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 advanced SM 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 $\geq 1.0 \times 10^9$/l, as recommended in Tables 1.2 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 advanced SM 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).

Severe hepatic impairment

Caution is warranted when considering the administration of midostaurin in patients with severe hepatic impairment and patients should be carefully monitored for toxicity (see section 5.2).

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 drug reactions (ADRs) 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 ADRs 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 ADRs occurred at similar rates in patients in the Rydapt versus the placebo arm. The most frequent serious ADR 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 ADRs 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 ADRs was observed. The overall incidence of ADRs during the maintenance phase was generally lower than during the induction and consolidation phase. Incidences of ADRs were, however, higher in the Rydapt arm than in the placebo arm during the maintenance phase. ADRs 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%).

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

Advanced SM
The safety of Rydapt (100 mg twice daily) as a single agent in patients with advanced SM 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 ADRs were nausea (82%), vomiting (68%), diarrhoea (51%), peripheral oedema (35%) and fatigue (31%). The most frequent Grade 3/4 ADRs 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 ADRs occurred in 31% of patients. The most frequent ADRs that led to dose modification (incidence ≥5%) were nausea and vomiting.

ADRs 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 drug reactions

ADRs are listed according to MedDRA system organ class. Within each system organ class, the ADRs 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 ADRs reported in the phase III study in patients with newly diagnosed FLT3-mutated AML and during post marketing experience.

Table 3 Adverse drug reactions observed in AML

Adverse drug reaction	**All grades** Rydapt + chemo n=229[1] %	**Grades 3/4** Rydapt + chemo n=345[1] %	**Frequency category**
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
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 ADR 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]This ADR was included after identification in the post-marketing setting.
* Frequency is based on laboratory values.

Advanced SM

Table 4 presents the frequency category of ADRs based on pooled data from two studies in patients with advanced SM.

Table 4 Adverse drug reactions observed in advanced SM

Adverse drug 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 ADRs were included after identification in the post-marketing setting.			

Description of selected adverse drug reactions

Gastrointestinal disorders
Nausea, vomiting and diarrhoea were observed in AML and advanced SM patients. In advanced SM 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.
Any suspected adverse events should be reported to the Ministry of Health according to the National Regulation by using an online form
http://sideeffects.health.gov.il

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 advanced SM. 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 advanced SM 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

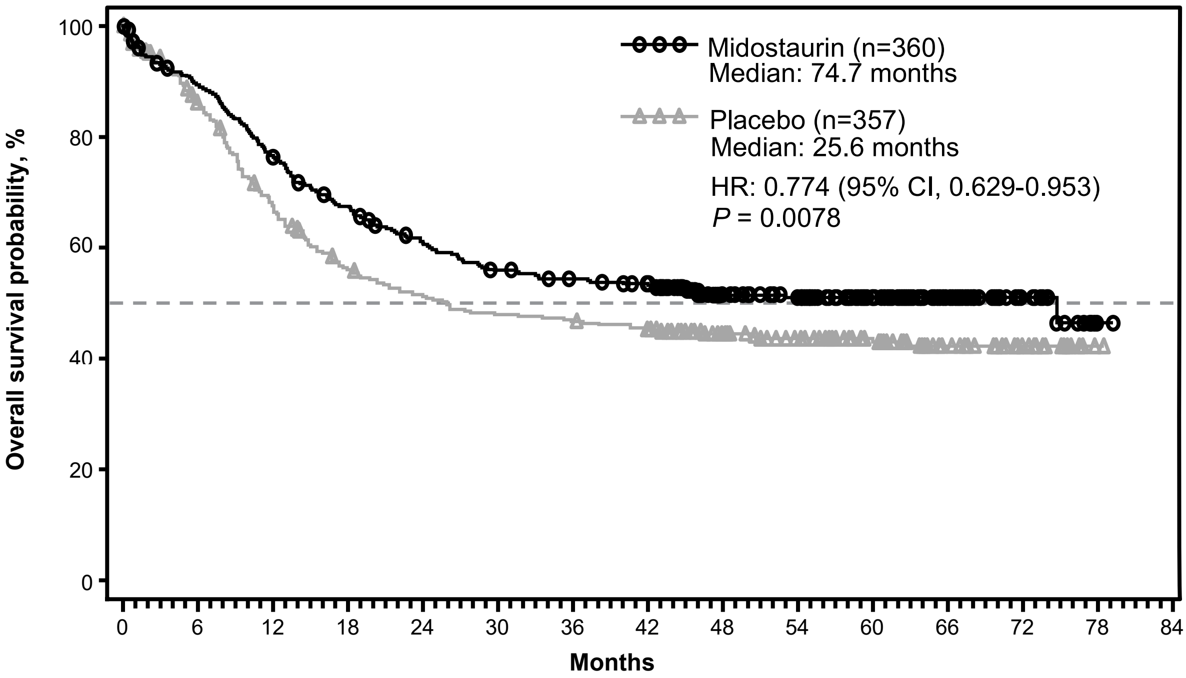
AML
The efficacy and safety of midostaurin in combination with standard chemotherapy versus placebo plus standard chemotherapy and as single agent maintenance therapy was investigated in 717 patients (18 to 60 years of age) in a randomised, double-blind, phase III study. Patients with newly diagnosed 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

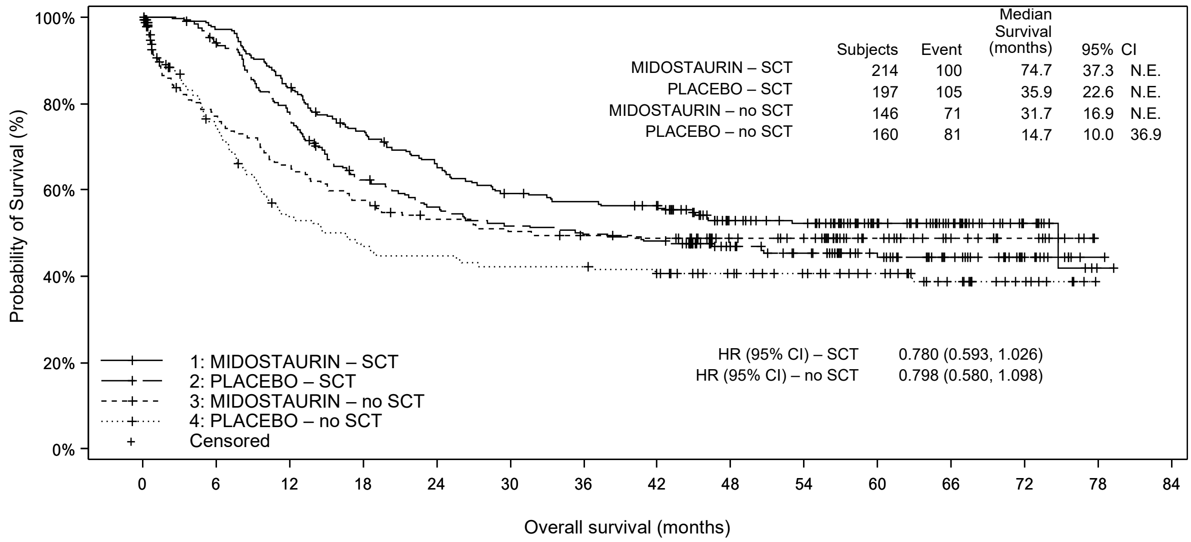
[1]primary endpoint; [2]key secondary endpoint; NE: Not Estimated
*Hazard ratio (HR) estimated using Cox regression model stratified according to the randomisation FLT3 mutation factor.
¥1-sided p-value calculated using log-rank test stratified according to the randomisation FLT3 mutation factor.
§Not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



No. of patients still at risk

	0	6	12	18	24	30	36	42	48	54	60	66	72	78	84
1	214	207	178	154	137	122	117	112	84	76	50	33	12	1	0
2	197	184	151	118	105	97	93	90	67	58	42	28	12	1	0
3	146	107	91	80	71	67	64	62	49	44	27	17	10	0	
4	160	100	70	61	58	55	55	51	43	37	29	17	8	0	

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).

Advanced SM.

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 advanced SM: primary efficacy population

	All **N=89**	**ASM** **N=16**	**SM-AHN** **N=57**	**MCL** **N=16**
Primary endpoint				
Overall response, n (%)	53 (59.6)	12 (75.0)	33 (57.9)	8 (50.0)
(95% CI)	(48.6, 69.8)	(47.6, 92.7)	(44.1, 70.9)	(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 advanced SM 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 advanced SM (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).

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 20800 ng*h/ml and C_{max} was decreased to 963 ng/ml (see section 4.5). Similarly, for CGP52421 and CGP62221 AUC increased to 19000 and 29200 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 advanced SM patients, AUC_{inf}, C_{max} and T_{max} were 49600 ng*h/ml, 2940 ng/ml and 3 h, respectively, for midostaurin. For CGP52421, AUC_{0-12h} and C_{max} were 2770 ng*h/ml and 299 ng/ml, respectively. AUC_{0-12h} and C_{max} for CGP62221 were 8700 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 advanced SM patients were 919 and 1060 ng/ml, respectively. The CGP62221 Cmin, ss in the AML and the advanced SM population were 1610 ng/ml and 2020 ng/ml, respectively. The CGP52421, $C_{min,ss}$ in the AML and the advanced SM population were 8630 ng/ml and 2860 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 advanced SM 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 advanced SM 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 advanced SM or AML, no midostaurin dose adjustment is required based on age.

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 hepatic impairment (Child-Pugh Class A or B, respectively) and 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 8130 ng*h/ml and 1206 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 5410 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.

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 advanced SM and AML populations.

Overall, there was noincrease in exposure (AUC) to plasma midostaurin and its metabolites (CGP62221 and CGP5242) in subjects with mild or moderate hepatic impairment compared to subjects with normal hepatic function. No dosage adjustment is necessary for patients with baseline mild or moderate hepatic impairment. The pharmacokinetics of midostaurin have not been assessed in patients with baseline severe hepatic impairment (Child-Pugh Class C) (see section 4.2).

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 advanced SM (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 dosage 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/repeat 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)

Environmental risk assessment 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 400
Ethanol anhydrous
Corn 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 2910
Propylene glycol

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

The expiry date of the product is indicated on the packaging materials.

6.4 Special precautions for storage

Do not store above 30˚C.
Store in original packaging to protect from moisture.

6.5 Nature and contents of container

PA/Al/PVC-Al blisters.

Multipacks 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. REGISTRATION HOLDER AND IMPORTER AND ITS ADDRESS

Novartis Israel Ltd.
POB 7126, Tel Aviv
Israel

8. REGISTRATION NUMBER

Rydapt 25 mg: 160-65-35320-00

Revised in April 2022 according to MOHs guidelines.