▼This medicinal product is subject to additional monitoring in Australia. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected adverse events at www.tga.gov.au/reporting-problems.

AUSTRALIAN PI – RYDAPT® (MIDOSTAURIN) CAPSULES

1 NAME OF THE MEDICINE

midostaurin

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each capsule contains 25 mg of midostaurin.

Excipients with known effect: May contain traces of sulfites in gelatin and 6.5% m/m alcohol.

For the full list of excipients, see Section 6.1 List of excipients.

3 PHARMACEUTICAL FORM

Soft gelatin capsule.

Pale orange oblong capsules with red imprint “PKC NVR”.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

Rydapt® is indicated:

- in combination with standard anthracycline and cytarabine induction and cytarabine consolidation chemotherapy, followed in patients in complete response by single agent maintenance therapy for adult patients with newly diagnosed acute myeloid leukemia (AML) who are FLT3 mutation-positive
- for the treatment of adult patients with aggressive systemic mastocytosis (ASM), systemic mastocytosis with associated haematological neoplasms (SM-AHN), or mast cell leukaemia (MCL).

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Rydapt should be taken orally, twice daily at approximately 12 hour intervals. Rydapt should be taken with food to help prevent nausea (see section 5.2 “Pharmacokinetic Properties”).

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 should not be opened, crushed or chewed.

If a dose is missed, the dose should not be made up and the patient should only take the next scheduled 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.

Monitoring during treatment with Rydapt

Consider interval assessments of QT by ECG if RYDAPT is taken concurrently with medications that can prolong the QT interval.

Dosage regimen

Target Population

Recommended dose in AML

The recommended dose of Rydapt is 50 mg twice daily. Rydapt is dosed on days 8-21 of induction and consolidation chemotherapy cycles and then twice daily as single agent maintenance therapy until relapse for up to 12 cycles of 28 days each. Midostaurin should not be used as a single agent for induction or consolidation. In patients receiving haematopoietic stem cell transplant (SCT), Rydapt should be discontinued prior to the conditioning regimen for SCT.

Recommended dose in advanced SM

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

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

Dose modifications

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

Criteria	Rydapt dosing
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-hematological toxicities	Interrupt Rydapt until toxicities considered at least possibly related to Rydapt have resolved to Grade ≤2, then resume Rydapt.
During maintenance: Grade 4 neutropenia (ANC <0.5 x10^9/L)	Interrupt Rydapt until ANC ≥1.0 x 10^9/L, then resume Rydapt at 50 mg twice daily. If neutropenia (ANC <1.0 x 10^9/L) persists >2 weeks and is suspected to be related to Rydapt, discontinue Rydapt.

ANC: Absolute Neutrophil Count

Dose modifications in advanced SM

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

Table 2: Rydapt dose interruption, reduction, and discontinuation recommendations in patients with advanced SM

Criteria	Rydapt dosing
ANC <1.0 x 10^9/L in patients who did not have severe neutropenia at baseline	Interrupt Rydapt until ANC ≥1.5 x10^9/L, then resume Rydapt at 50 mg twice daily, and if tolerated, gradually increase to 100 mg twice daily. In the event of recurrence of ANC <1.0 x 10^9/L that is suspected to be related to Rydapt, discontinue Rydapt.
Hemoglobin less than 8 g/dL attributed to Rydapt in patients without MCL, or lifethreatening anemia attributed to Rydapt in patients with baseline hemoglobin value of 8 -10 g/L	Interrupt Rydapt until hemoglobin 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 if low hemoglobin 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 Rydapt at 50 mg twice daily, and if tolerated, gradually increase to 100 mg twice daily.
Other Grade 3/4 non-hematological 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.

ANC: Absolute Neutrophil Count

CTCAE severity: Grade 1 = mild symptoms; 2 = moderate symptoms; 3 = severe symptoms; 4 = life-threatening symptoms.

Special Populations

Patients with 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. No data are available in patients with end-stage renal disease (see section 5.2 “Pharmacokinetic Properties”).

Patients with Hepatic Impairment

No dose adjustment is required in patients with mild or moderate (Child-Pugh A or B) hepatic impairment (see section 5.2 “Pharmacokinetic Properties”). 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.

Elderly Patients

No dosage regimen adjustment is required in patients over 65 years of age (see section 4.4 “Special Warnings and Precautions for Use”).

Paediatric Patients

Rydapt should not be used in combination with intensive paediatric AML combination chemotherapy regimens including anthracyclines, fludarabine and cytarabine (see sections 4.4 Special Warnings and Precautions for Use and 5.1 Clinical Trials).

4.3 CONTRAINDICATIONS

Rydapt is contraindicated in patients with hypersensitivity to midostaurin or to any of the excipients.

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/Infections

Neutropenia has occurred in patients receiving Rydapt as monotherapy and in combination with chemotherapy (see section 4.8 "Adverse Effects"). Severe neutropenia (ANC less than 0.5 x 10^9/L) was generally reversible by withholding Rydapt until recovery or discontinuation in the advanced SM studies. White blood cells (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 greater than or equal to 1.0 x 10^9/L in patients with AML or 1.5 x 10^9/L in patients with advanced SM, as recommended in Tables 8 and 9. 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 "Dose and Method of Administration").

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

Cardiac dysfunction

In the advanced SM studies with Rydapt, cardiac dysfunction such as congestive heart failure (CHF), some of which were fatal, and transient decreases in left ventricular ejection fraction (LVEF) occurred. No difference in CHF was observed between the Rydapt + chemotherapy and placebo + chemotherapy arms in the randomized AML study. In patients at risk, Rydapt should be used with caution and patients should be closely monitored (at baseline and during treatment).

Pulmonary toxicity

Interstitial lung disease (ILD) and pneumonitis, 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 should be discontinued in patients who experience pulmonary symptoms indicative of ILD/pneumonitis without an infectious etiology which are ≥Grade 3 (NCI CTCAE).

Use in the Elderly

No dosage regimen adjustment is required in patients over 65 years of age (see section 5.2 "Pharmacokinetic Properties"). There is limited experience with midostaurin in AML patients aged 60-70 years (46 patients in supportive study) and no experience in AML patients above 70 years. No patients aged ≥60 years were included in the pivotal study. 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.

Paediatric Use

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 section 5.1 Clinical Trials).

Effects on laboratory tests

No data available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Midostaurin undergoes extensive hepatic metabolism through CYP3A4 enzymes which are either induced or inhibited by a number of concomitant drugs. Based on *in vitro* data, midostaurin and/or its metabolites have the potential to inhibit and induce CYP enzymes and inhibit transporters (see section 5.2 "Pharmacokinetic Properties"). Therefore, Rydapt may be a victim or a perpetrator of drug-drug interactions *in vivo.*

Effect of other drugs on Rydapt

Drugs 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 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 Rydapt led to a significant increase in midostaurin exposure (1.8-fold C_{max} increase and 10-fold AUC_{inf} increase) while the peak concentrations of the active metabolites, CGP62221 and CGP52421, decreased by half (see section 5.2 "Pharmacokinetic Properties"). Another study evaluated the concomitant administration of multiple dose midostaurin 50 mg twice daily with the strong CYP3A4 inhibitor itraconazole at steady-state in a subset of patients (N=7), and showed that itraconazole increased midostaurin steady-state exposure (C_{min}) by only 2.09-fold. During the induction phase of the AML study, up to 62% of patients received midostaurin concomitantly with strong inhibitors of CYP3A4. Upon co-administration with CYP3A4 inhibitors, a 1.44-fold increase in midostaurin exposure (C_{min}) was observed. No impact was observed for CGP62221 and CGP52421. Caution should be

advised when concomitantly administering 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), and macrolide antibiotics (e.g., clarithromycin). Alternative therapeutics 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 toxicity.

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 50mg single dose of midostaurin decreased midostaurin C_{max} by 73% and AUC_{inf} by 96% on average, respectively. Both metabolites, CGP62221 and CGP52421, exhibited a similar pattern.

Effect of Rydapt on other drugs

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 AUCinf and AUClast by 48% and 49% respectively and Cmax 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 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 considered as inhibitors of CYP1A2 and CYP2E1 and inducers of CYP1A2. Therefore, medicinal products with a narrow therapeutic range that are substrates of CYP1A2 and CYP2E1 should be used with caution when administered concomitantly with midostaurin, and may need dose adjustment to maintain optimal exposure.

In healthy subjects, co-administration of a single dose of midazolam (CYP3A substrate) with multiple doses of midostaurin (50 mg twice daily) at steady-state decreased midazolam AUCinf and AUClast by 3% and 4% respectively and increased Cmax by 10% compared to administration of midazolam alone. Therefore, midostaurin has neither inhibitory nor inducing effect on CYP3A substrates.

In healthy subjects, co-administration of a single dose of pioglitazone (CYP2C8 substrate) with multiple doses of midostaurin (50 mg twice daily) at steady-state did not cause any clinically significant decrease in pioglitazone exposure (6% decrease in AUCinf and AUClast respectively, and 10% decrease in Cmax) compared to the administration of pioglitazone alone. Clinically relevant drug-drug interactions between midostaurin and CYP2C8 substrates are unlikely to occur.

In healthy subjects, co-administration of a single dose of dextromethorphan (CYP2D6 substrate) with a single dose of midostaurin (100 mg) did not cause any increase in dextromethorphan exposure (13% decrease in AUCs and 28% decrease in Cmax) compared to administration of dextromethorphan alone. Therefore, midostaurin has no inhibitory effect on CYP2D6 and clinically relevant drug-drug interactions between midostaurin and CYP2D6 substrates are unlikely to occur.

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 AUCinf and AUClast by 37% and 48% respectively; Cmax 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 should be used with caution when administered concomitantly with midostaurin, and may need dose adjustment to maintain optimal exposure.

In healthy subjects, co-administration of a single dose of digoxin (P-gp substrate) with a single dose of midostaurin (100 mg) increased digoxin AUCinf and AUClast by 23% and 21% respectively, and Cmax by 20% compared to administration of digoxin alone. This indicates that midostaurin has a minor inhibitory effect on P-gp substrates. Clinically relevant drug-drug interactions between midostaurin and P-gp substrates are unlikely to occur.

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.

***In vitro* evaluation of drug interaction potential**

Based on in-vitro data, midostaurin and its active metabolites, CGP52421 and CGP62221, are considered as inhibitors of CYP1A2 and CYP2E1 and inducers of CYP2B6 (induction mediated by CAR) and CYP1A2 (induction mediated by AhR). Based on in-vitro data midostaurin and its active metabolites may inhibit BCRP and BSEP. Simulations using physiologically based pharmacokinetic (PBPK) models predicted that midostaurin given at a dose of 50 mg twice daily at steady-state is unlikely to cause clinically relevant inhibition of OATP1B

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on Fertility

Rydapt may impair fertility in humans. Oral administration of midostaurin at 10, 30 and 60 mg/kg/day was associated with reproductive toxicity in male and female rats. In males, testicular degeneration and atrophy were observed at all doses, and alterations in epididymides (aspermia, epididymal spermatid stasis, epididymal oligospermia) and sperm motility, a decrease in sperm counts, and a decrease in reproductive organ weights were observed at 60

mg/kg/day. In females, increased resorptions, decreased pregnancy rate, number of implants and live embryos were observed at 60 mg/kg/day. Inhibition of spermatogenesis was also seen in dogs at doses ≥3 mg/kg/day. The plasma midostaurin concentrations in rats at 60 mg/kg/day and dogs at 3 mg/kg/day are approximately 8- and 100-fold below the human therapeutic exposures at the recommended doses of 50 or 100 mg twice daily based on AUC.

Use in Pregnancy (Category D)

Based on mechanism of action and findings in animal reproduction studies, Rydapt can cause fetal harm when administered to a pregnant woman.

There are no adequate and well-controlled studies in pregnant women. Pregnant women should be advised of the potential risk to the fetus. Midostaurin is not recommended during pregnancy or in women of childbearing potential not using contraception.

In embryo-fetal development studies in rats and rabbits, pregnant animals received oral doses of midostaurin at 3, 10, and 30 mg/kg/day and at 2, 10 and 20 mg/kg/day, respectively, during the period of organogenesis. An increase in number of late resorptions and in the incidence of dilated lateral brain ventricles in low weight fetuses was observed at all dose levels and a reduction in fetal weight, associated for some of them with an increase in the incidence of renal pelvic cavitation and delayed skeletal ossification was observed in rats at the high dose of 30 mg/kg/day; no maternal toxicity was observed. In rabbits, maternal toxicity was observed at all dose levels. Mortality in dams, reduced fetal weight and delayed ossification was observed at 10 and 20 mg/kg/day, and abortions secondary to maternal toxicity at all doses. The plasma midostaurin concentrations at the lowest embryofetal toxicity dose in both species are 200-300 fold below the human therapeutic exposures at the recommended doses of 50 and 100 mg twice daily based on AUC comparisons across species.

In a pre- and post-natal developmental study, rats were given oral doses of 5, 15, and 30 mg/kg/day during gestation through lactation up to weaning. Maternal toxicity including excessive salivation, signs of dystocia and reduced litter size were observed at 30 mg/kg/day. Lower body weights, accelerated complete eye opening and delayed auricular startle ontogeny were noted in the rat pups (F1 generation) at 30 mg/kg/day. Maternal systemic exposure at 30 mg/kg (based on AUC) was 10-fold below the human therapeutic exposures at the human doses of 50 and 100 mg twice daily.

Use in Lactation

It is unknown whether midostaurin or its active metabolites are excreted in human milk. There are no data on the effects of Rydapt on the breastfed child or the effects of Rydapt on milk production. Studies show that orally administered midostaurin and its active metabolites pass into the milk of lactating rats (milk:plasma midostaurin AUC ratio ~7). Because many drugs are excreted in human milk and because of the potential for serious adverse reactions in nursing infants from Rydapt, a nursing woman should be advised on the potential risks to the child and breast-feeding should be discontinued during treatment with Rydapt and for at least 4 months after stopping treatment.

Women of child-bearing potential and sexually active men
Sexually-active females of reproductive potential are advised to have a pregnancy test within seven days prior to starting treatment with Rydapt.

Females of reproductive potential should be advised that animal studies show Rydapt to be harmful to the developing fetus. Sexually-active females of reproductive potential 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.

Sexually-active males taking Rydapt should use a condom during intercourse with females of reproductive potential or pregnant women and for at least 4 months after stopping treatment with Rydapt to avoid conception or embryo-fetal harm.

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 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Reporting suspected adverse effects
Reporting suspected adverse reactions after registration 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 at www.tga.gov.au/reporting-problems.

AML - Summary of the safety profile

The safety evaluation of Rydapt (50 mg twice daily) in patients with newly diagnosed FLT3 mutated AML is based on a phase III, randomized, double-blind, placebo-controlled study. A total of 717 patients were randomized (1:1) to receive Rydapt or placebo sequentially (on days 8 to 21) in combination with standard daunorubicin (60 mg/m^2 on days 1 to 3) / cytarabine (200 mg/m^2 on days 1 to 7) induction and high dose cytarabine (3 g/m^2 on days 1, 3, 5) consolidation, followed by maintenance with continuous Rydapt or placebo treatment according to initial assignment for up to 12 cycles (28 days/cycle). 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 (incidence ≥30%) adverse drug reactions (ADRs) in the Rydapt plus standard chemotherapy arm were febrile neutropenia, nausea, exfoliative dermatitis, vomiting, headache, petechiae and pyrexia. The most frequent Grade 3/4 ADRs (incidence ≥10%) were febrile neutropenia, lymphopenia, device related infection, exfoliative dermatitis, and nausea.

Serious AEs occurred in 46.3 % of patients in the Rydapt plus standard chemotherapy arm versus 51.8 % in the placebo plus standard chemotherapy arm. The most frequent serious AE in patients in the Rydapt plus standard chemotherapy arm was febrile neutropenia (16.2%) and this occurred at a similar rate in the placebo arm (15.9%).

Discontinuation due to any adverse event occurred in 9.2% of patients in the Rydapt arm versus 6.2% in the placebo arm. The most frequent Grade 3/4 adverse event leading to discontinuation in the Rydapt arm was exfoliative dermatitis (1.2%).

Deaths occurred in 4.3% of patients in the Rydapt plus standard chemotherapy arm versus 6.3% in the placebo plus standard chemotherapy arm. The most frequent cause of death in the Rydapt plus standard chemotherapy arm was sepsis (1.2%) and occurred at a similar rate in the placebo arm (1.8%).

Tabulated summary of adverse drug reactions from clinical trials in AML

Table 3 presents the frequency category of ADRs reported in the phase-III study in patients with newly diagnosed FLT3 mutated AML. 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. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each ADR: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Table 4 presents the key laboratory abnormalities from the same phase-III study in patients with newly diagnosed FLT3 mutated AML.

Table 3: Adverse drug reactions reported in AML clinical study

Adverse drug reactions	All grades		Grades 3/4		Frequency category
	Rydapt + chemo n=229[1] %	Placebo + chemo n=226[1] %	Rydapt + chemo N345[1] %	Placebo + chemo n=335[1] %	
Infections and infestations					
Device related infection	24	17.3	15.7	9.9	very common
Upper respiratory tract infection	5.2	3.1	0.6	0.9	common
Neutropenic sepsis	0.9	0.4	3.5	0.3	uncommon
Blood and lymphatic system disorders					
Febrile neutropenia	83.4	80.5	83.5	83.0	very common
Petechiae	35.8	27	1.2	0.6	very common
Lymphopenia[2]	16.6	18.6	20	22.7	very common

Adverse drug reactions	All grades		Grades 3/4		Frequency category
	Rydapt + chemo n=229[1] %	Placebo + chemo n=226[1] %	Rydapt + chemo N345[1] %	Placebo + chemo n=335[1] %	
Immune system disorders					
Hypersensitivity	15.7	14.2	0.6	1.2	very common
Metabolism and nutrition disorders					
Hyperuricaemia	8.3	6.2	0.6	0.6	common
Psychiatric disorders					
Insomnia	12.2	8	0	0.3	very common
Nervous system disorders					
Headache	45.9	38.1	2.6	3	very common
Syncope	5.2	4.9	4.6	3	common
Tremor	3.9	1.8	0	0	common
Eye disorders					
Eyelid oedema	3.1	0.4	0	0	common
Cardiac disorders					
Hypotension	14.4	15	5.5	3	very common
Sinus tachycardia	9.6	8	1.2	0	common
Hypertension	7.9	5.8	2.3	0.9	common
Pericardial effusion	3.5	1.3	0.6	0	common
Respiratory, thoracic and mediastinal disorders					
Epistaxis	27.5	23.5	2.6	0.6	very common
Laryngeal pain	11.8	9.7	0.6	0.9	very common
Pneumonitis [3]	11.4	12.8	4.9	6.6	very common
Dyspnoea	10.9	12.4	5.5	3.9	very common
Pleural effusion	5.7	3.5	0.9	0.9	common
Nasopharyngitis	8.7	6.6	0	0	common
Acute respiratory distress syndrome	2.2	0.4	2.3	0.9	common
Gastrointestinal disorders					
Nausea	83.4	70.4	5.8	10.1	very common

Adverse drug reactions	All grades		Grades 3/4		Frequency category
	Rydapt + chemo n=229[1] %	Placebo + chemo n=226[1] %	Rydapt + chemo N345[1] %	Placebo + chemo n=335[1] %	
Vomiting	60.7	52.7	2.9	4.5	very common
Stomatitis	21.8	14.2	3.5	2.7	very common
Abdominal pain upper	16.6	14.6	0	0.3	very common
Haemorrhoids	15.3	10.6	1.4	0	very common
Anorectal discomfort	7	4	0.9	0	common
Abdominal discomfort	3.5	0.9	0	0	common
Skin and subcutaneous tissue disorders					
Dermatitis exfoliative	61.6	60.6	13.6	7.5	very common
Hyperhidrosis	14.4	8	0	0	very common
Dry skin	7	5.3	0	0	common
Keratitis	6.6	4.9	0.3	0.6	common
Musculoskeletal and connective tissue disorders					
Back pain	21.8	15.5	1.4	0.6	very common
Arthralgia	14	8	0.3	0.3	very common
Bone pain	9.6	9.7	1.4	0.3	common
Pain in extremity	9.6	8.8	1.4	0.6	common
Neck pain	7.9	4	0.6	0	common
General disorders and administration site conditions					
Pyrexia	34.5	35.4	3.2	2.7	very common
Catheter-related thrombosis	3.5	1.3	2	1.8	common
Investigations					
Hyperglycaemia	20.1	16.8	7	5.4	very common
Electrocardiogram QT prolonged[3]	19.7	16.8	5.8	5.4	very common
Activated partial thromboplastin time prolonged	12.7	8.4	2.6	1.8	very common
Weight increased	6.6	3.1	0.6	0.3	common

Adverse drug reactions	All grades		Grades 3/4		Frequency category
	Rydapt + chemo n=229[1] %	Placebo + chemo n=226[1] %	Rydapt + chemo N345[1] %	Placebo + chemo n=335[1] %	

[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 summarized only on patients in Non North American trial sites whereas grade 3 and 4 are summarized on patients in all trial sites.

[2] Higher frequency with Rydapt observed during maintenance phase, please see paragraph below "Safety profile during maintenance phase" .

[3]These ADRs were detected during the AML clinical study and were included after identification in the post-marketing setting.

Table 4: Percentage of patients with key Grade 3 and 4 laboratory abnormalities

Key laboratory abnormality	Rydapt 50 mg twice daily (N=345) Grade 3/4 %	Placebo (N=335) Grade 3/4 %	Frequency category (based on all grades)
Absolute neutrophils decreased	85.8	86.9	very common
Haemoglobin decreased	78.6	77.6	very common
Aspartate aminotransferase (AST) increased	6.4	6.0	very common
Alanine aminotransferase (ALT) increased	19.4	14.9	very common
Hypercalcaemia	0.6	0.3	common
Hypokalaemia	13.9	14.3	very common
Hypernatraemia	1.2	1.8	very common

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 also generally lower. Adverse drug reactions during the maintenance phase with at least ≥5% difference between the Rydapt and placebo arms were: nausea (46.4% vs 17.9%), hyperglycaemia (20.2% vs 12.5%), vomiting (19% vs 5.4%) and lymphopenia (16.7% vs 8.9%).

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 absolute neutrophil count decrease (20.8% vs 18.9%) and leukopenia (7.5% vs 5.9%).

Overall, ADRs reported during the maintenance phase were of mild to moderate intensity and led to very few discontinuations (1.2% in Rydapt arm vs 0% in placebo arm).

Description of selected adverse drug reactions

Gastrointestinal disorders

In AML patients during the maintenance phase, low grade nausea and vomiting were observed. These were well managed with supportive prophylactic medication and led to treatment discontinuation in 2 patients, one in each treatment group.

Advanced SM - Summary of the safety profile

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, multicenter studies. The median duration of exposure to Rydapt was 11.4 months (range: 0 to 81 months).

The most frequent ADRs (incidence ≥30%) were nausea, vomiting, diarrhoea, peripheral oedema, and fatigue. The most frequent Grade 3/4 ADRs (incidence ≥6%) were fatigue, sepsis, pneumonia, febrile neutropenia, and diarrhoea. The most frequent non-haematologic laboratory abnormalities (incidence ≥30%) were glucose increased, total bilirubin increased, lipase increased, AST increased, and ALT increased while the most frequent haematologic laboratory abnormalities (incidence ≥25%) were absolute lymphocyte decreased and neutrophils decreased. The most frequent Grade 3/4 laboratory abnormalities (incidence ≥10%) were absolute lymphocyte decreased, absolute neutrophils decreased, glucose increased, and lipase increased.

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.

Adverse events that led to treatment discontinuation occurred in 23.9% of patients. The most common AEs leading to discontinuation were GI related events (5.6%).

Deaths occurred in 18.3% of patients. The most frequent causes of death were disease progression and sepsis.

Tabulated summary of adverse reactions from clinical trials in advanced SM

Table 5 presents the frequency category of ADRs based on pooled data from two studies in patients with advanced SM. 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. In addition, the corresponding frequency category using the following convention (CIOMS III) is also provided for each ADR: very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to <1/100); rare (≥1/10,000 to <1/1,000); very rare (<1/10,000); not known (cannot be estimated from the available data). Table 6 presents the key laboratory abnormalities based on pooled data from two studies in patients with advanced SM.

Table 5: Adverse drug reactions reported in advanced SM studies

Adverse drug reaction	Rydapt (100 mg twice daily) N=142 All grades %	Grade 3 %	Grade 4 %	Frequency category
Infections and infestations				
Urinary tract infection	13	2.1	0.7	very common
Upper respiratory tract infection	11	1.4	0	very common
Pneumonia	8.5	7.0	0	common
Sepsis	7.7	2.1	5.6	common
Bronchitis	5.6	0	0	common
Oral herpes	4.9	0	0	common
Cystitis	4.2	0	0	common
Sinusitis	4.2	0.7	0	common
Erysipelas	3.5	1.4	0	common
Herpes zoster	3.5	0.7	0	common
Blood and lymphatic system disorders				
Febrile neutropenia	7.7	6.3	0.7	common
Immune system disorders				
Hypersensitivity	2.1	0	0	common
Anaphylactic shock	0.7	0	0.7	uncommon
Nervous system disorders				
Nervous system disorders	26	1.4	0	very common
Headache	13	0	0	very common
Dizziness	7	0	0	common
Disturbance in attention	6.3	0	0	common
Ear and labyrinth disorders				
Vertigo	4.9	0	0	common
Vascular disorders				
Hypotension	9.2	2.1	0	common
Haematoma	6.3	0.7	0	common
Respiratory, thoracic and mediastinal disorders				
Dyspnoea	18	4.2	1.4	very common
Cough	16	0.7	0	very common
Pleural effusion	13	4.2	0	very common
Epistaxis	12	2.1	0.7	very common
Oropharyngeal pain	4.2	0	0	common
Interstitial lung disease*	1.4	0	0	Common
Pneumonitis*	0.7	0	0	Uncommon
Gastrointestinal disorders				
Nausea	82	4.9	0.7	very common
Vomiting	68	4.9	0.7	very common
Diarrhoea	51	6.3	0	very common
Constipation	29	0.7	0	very common

Adverse drug reaction	Rydapt (100 mg twice daily) N=142 All grades %	Grade 3 %	Grade 4 %	Frequency category
Dyspepsia	5.6	0	0	common
Gastrointestinal haemorrhage	4.2	2.8	0.7	common
General disorders and administration site conditions				
Oedema peripheral	35	3.5	0	very common
Fatigue	31	7.0	1.4	very common
Pyrexia	27	4.2	0	very common
Asthenia	4.9	0	0.7	common
Chills	4.9	0	0	common
Oedema	4.2	0.7	0	common
Investigations				
Electrocardiogram QT prolonged*	10.6	0.7	0	very common
Weight increased	5.6	2.8	0	common
Injury, poisoning and procedural complications				
Contusion	6.3	0	0	common
Fall	4.2	0.7	0	common

*These ADRs were detected during the Advanced SM studies and were included after identification in the post-marketing setting

Table 6 presents the frequency of laboratory abnormalities reported in the advanced SM trials.

Table 6: Percentage of patients with key laboratory abnormalities in the advanced SM studies

Key laboratory abnormality	Rydapt (100 mg twice daily) N=142 Grade 3 %	Grade 4 %	Frequency category (based on all grades)
Glucose increased*	18.3	0.7	very common
Absolute neutrophils decreased	15.5	11.3	very common
Absolute lymphocyte decreased	38.7	7.0	very common
Aspartate aminotransferase (AST) increased	2.1	0.7	very common
Alanine aminotransferase (ALT) increased	3.5	0	very common
Total bilirubin increased	4.9	0	very common
Amylase increased	4.2	2.8	very common
Lipase increased	14.8	2.8	very common

**non fasting*

Adverse drug reactions from spontaneous reports and literature cases (frequency not known

The following adverse drug reactions have been derived from post-marketing experience with Rydapt via spontaneous case reports and literature cases. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency.

Table 7: ADRs from spontaneous reports and literature cases

Adverse drug reaction	**Frequency category**
Respiratory, thoracic and mediastinal disorders	
Interstitial lung disease*	Not known
Skin and subcutaneous tissue disorders	
Acute febrile neutrophilic dermatosis (Sweet syndrome)*	Not known

**Applicable only for AML indication*

Description of selected adverse drug reactions

Gastrointestinal disorders

In the advanced SM patient population 17 (12%) patients had a dose adjustment or interruption for nausea, 13 (9.2%) for vomiting, and 7 (4.9%) for diarrhoea. The treatment discontinuation rate was low with 3 (2.1%) patients discontinued for nausea, 2 (1.4%) patients for vomiting, and 1 (0.7%) patient for diarrhoea. Most of the events occurred within the first 6 months of treatment and were well managed with supportive prophylactic medication.

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.

General supportive measures should be initiated in all cases of overdose.

For information on the management of overdose, contact the Poisons Information Centre on 13 11 26 (Australia).

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: Antineoplastic agents, protein kinase inhibitors, ATC code: L01XE39

Mechanism of action

Midostaurin inhibits multiple receptor tyrosine kinases, including FLT3 and KIT kinase. Midostaurin inhibits FLT3 receptor signaling and induces cell cycle arrest and apoptosis in leukemic cells expressing ITD and TKD mutant receptors or overexpressing wild type receptors. Midostaurin inhibits both the wild type and D816V mutant KIT, leading to interference with the aberrant signaling of KIT and inhibits mast cell proliferation and survival, and histamine release.

In addition, it inhibits several other tyrosine kinases such as PDGFR or VEGFR2, as well as members of the serine/threonine kinase families, such as the isoforms of PKC (protein kinase C). Midostaurin binds to the catalytic domain of these kinases and inhibits the mitogenic signaling of the respective growth factors in cells, resulting in growth arrest.

Pharmacodynamics

Midostaurin is a high affinity inhibitor for the receptor tyrosine kinase of FLT3 (Kd of 11 nM) and is equally active against ITD- and TKD-mutated FLT3.

The affinity constant of midostaurin to the receptor tyrosine kinase KIT D816V mutant has been determined as 7.7 nM.

Two major metabolites have been identified in murine models and humans.

In proliferation assays with FLT3-ITD expressing cells, CGP62221 showed similar potency compared to the parent compound, whereas CGP52421 was approximately 10 fold less potent.

Interactions with conventional chemotherapeutic drugs

In cell proliferation assays, midostaurin displayed complex interactions with conventional antileukemic drugs in neoplastic cells of different genotype. In human leukemia cell lines bearing FLT3 mutations and MLL rearrangements, midostaurin displayed additive to synergistic activity with cytarabine, doxorubicin, idarubicin, mitoxantrone, etoposide, 4-hydroperoxy cyclophosphamide and vincristine, but antagonistic with methotrexate. In leukemia cell lines that did not bear FLT3 mutations but had MLL rearrangements, midostaurin displayed antagonistic effects with cytarabine, doxorubicin, etoposide and methotrexate but displayed additive or synergistic effects with vincristine, 4-hydroperoxy cyclophosphamide, mitoxantrone and idarubicin. In human leukemia cell lines that lacked both FLT3 mutations and MLL rearrangements, midostaurin mostly displayed antagonistic interactions with conventional chemotherapeutic agents (except vincristine and 4 hydroperoxy cyclophosphamide). Careful evaluation of the patient's leukemia genotype should be undertaken before using midostaurin in combination with conventional chemotherapeutic agents.

Cardiac Electrophysiology

A dedicated QT study in 192 healthy subjects with a dose of 75mg twice daily did not reveal clinically significant prolongation of QT by midostaurin and CGP62221 and 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 Cmin 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 10msecs with 6.3, 2.4, and 4.7 msecs, respectively.

The risk of hERG related-QT prolongation appears to be low. In the repeat dose studies in dogs, a decrease in heart rate and a prolongation of the P-Q interval was seen in individual animals at 10 and 30 mg/kg; there were no morphological changes in the heart.

Clinical trials

Acute Myeloid Leukaemia (AML)

The efficacy and safety of Rydapt in combination with chemotherapy versus placebo pluschemotherapy and as single agent maintenance therapy was investigated in 717 patients (18 to 60 years of age) in a randomized, double-blind, phase III study. Patients with newly diagnosed FLT3 mutated AML as determined by a clinical trial assay were randomized (1:1) to receive Rydapt 50 mg twice daily (n=360) or placebo (n=357) (dosed on days 8-21 of induction and consolidation chemotherapy cycles) sequentially in combination with daunorubicin (60 mg/m^2 daily on days 1 to 3) / cytarabine (200 mg/m^2 daily on days 1 to 7) induction (1 – 2 cycles) and high dose cytarabine (3 g/m^2 every 12 hours on days 1, 3, 5)

consolidation (3-4 cycles), followed by continuous Rydapt 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 leukemia (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 and details are shown in Table 8.

Table 8: Study: Demographics and baseline characteristics

Baseline characteristics	MIDOSTAURIN N=360	PLACEBO N=357
Age (Years)		
Median	47.0	48.0
Range	19 - 59	18 - 60
Gender -n (%)		
Female	186 (51.7)	212 (59.4)
Male	174 (48.3)	145 (40.6)
ECOG/Zubrod performance status –n (%)		
0 to 2	352 (97.8)	346 (96.9)
3 to 4	8 (2.2)	11 (3.1)
Race -n (%)		
Unknown / Not Reported	195 (54.2)	213 (59.7)
White	147 (40.8)	128 (35.9)
Black or African American	8 (2.2)	9 (2.5)
Other	10 (2.8)	7 (2.0)
FLT3 mutation status -n (%)		
ITD <0.7	171 (47.5)	170 (47.6)
ITD ≥0.7	108 (30.0)	106 (29.7)
TKD	81 (22.5)	81 (22.7)

ITD: Internal Tandem Duplication. TKD: Tyrosine Kinase Domain.

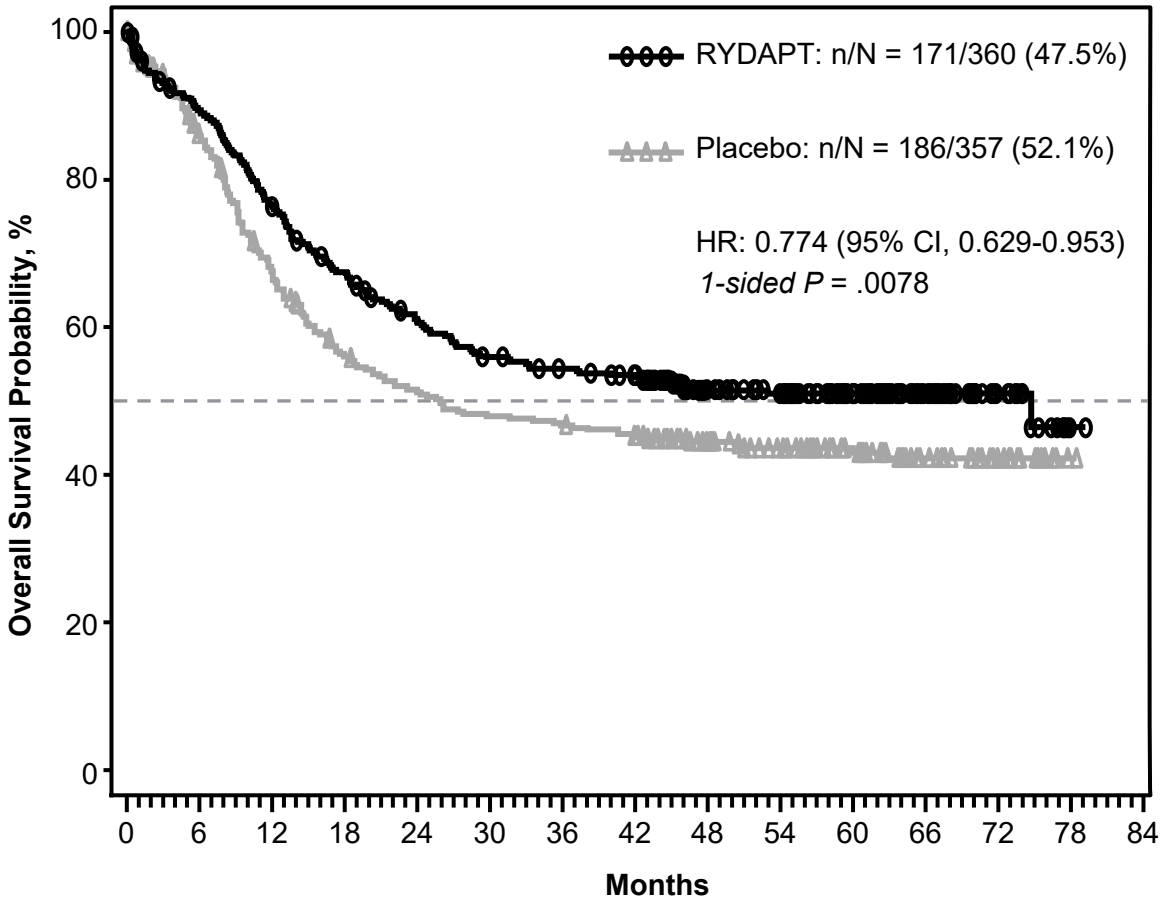
Note: ITD <0.7, ITD ≥0.7 and TKD are the randomization strata.

Patients who proceeded to hematopoietic stem cell transplant (SCT) stopped receiving study treatment on or before the time of stem cell infusion. The overall rate of SCT was 59.4% (214/360) of patient in the Rydapt 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 randomization until death by any cause. The primary analysis was conducted after a minimum follow-up of approximately 3.5 years after the randomization of the last patient. The study demonstrated a statistically significant improvement in OS for Rydapt plus chemotherapy over placebo plus chemotherapy (HR = 0.774 [95% CI: 0.629, 0.935]; p = 0.0078, 1-sided log-rank test stratified by FLT3 mutation status). The median survival times could not be reliably

estimated in Rydapt arm because the survival curves plateaued before reaching the median (see Table 9, Figure 1).

Figure 1: Kaplan-Meier curve for overall survival, non-censored at the time of stem cell transplantation



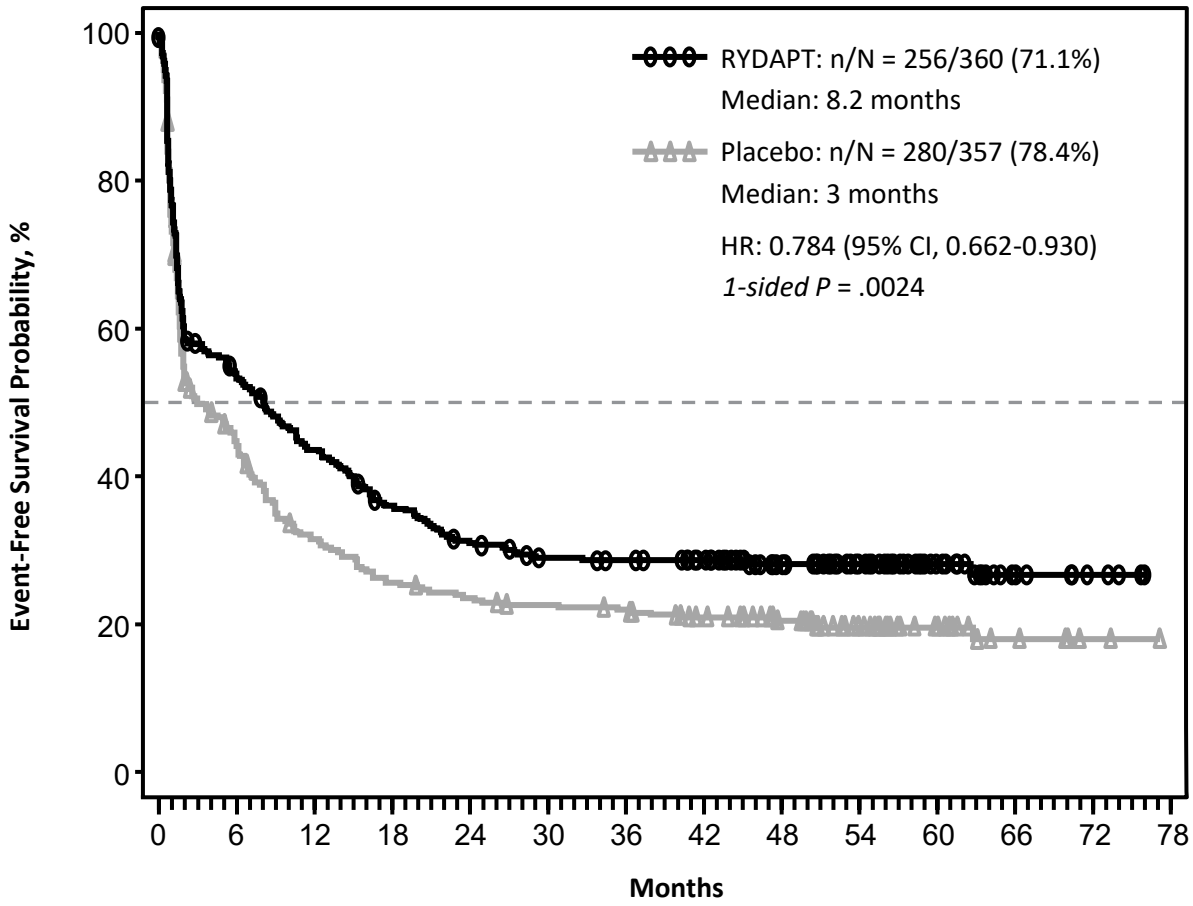
Patients at risk

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

P value is based on 1-sided log-rank test stratified by FLT3 mutation status

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 Rydapt plus standard chemotherapy over placebo plus standard chemotherapy (see Table 8, Figure 2).

Figure 2: Kaplan-Meier curve for event-free survival, non-censored for SCT



Patients at risk

Months	**0**	**6**	**12**	**18**	**24**	**30**	**36**	**42**	**48**	**54**	**60**	**66**	**72**	**78**
Midostaurin	360	190	153	124	106	95	92	83	65	51	27	9	4	0
Placebo	357	153	106	86	78	73	70	60	49	32	18	8	2	0

P value is based on 1-sided log-rank test stratified by FLT3 mutation status

Sensitivity analyses for both OS and EFS when censored at the time of SCT also supported the clinical benefit with Rydapt plus standard chemotherapy over placebo. There was a trend favoring Rydapt 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 in induction, the cumulative incidence of relapse (CIR) at 12 months was 26% in the midostaurin arm vs. 41% in the placebo arm based on an exploratory analysis.

Table 9: Efficacy of Rydapt in AML

Efficacy Parameter	Rydapt n=360	Placebo n=357	HR* (95% CI)	P-value¥
Overall Survival (OS)[1]				
Number of events (%)	171 (47.5)	186 (52.1)		
Estimated OS (%) at 1 year (95% CI)	76 (72, 81)	68 (62, 72)	0.77 (0.63, 0.95)	0.0078
Event Free Survival (EFS)[2]				
Number of events (%), considering CRs within 60 days of treatment start	256 (71.1)	280 (78.4)		
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)	0.002
Number of event (%), considering CRs anytime during induction	244 (67.8)	277 (77.6)		
Median EFS in months, considering CRs anytime during induction (95% CI)	10.2 (8.1-13.9)	5.6 (2.9-6.7)	0.73 (0.61, 0.87)	0.001
Disease Free Survival (DFS)				
Number of event (%), in patients with CR within 60 days of treatment start	109 (51.4)	114 (59.7)		
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§
anytime during induction (%)	234 (65.0)	207 (58.0)	NE	0.027§

[1]primary endpoint. [2]key secondary endpoint; NE: Not Estimated,

*Hazard ratio (HR) estimated using Cox regression model stratified according to the randomization FLT3 mutation factor.

¥1-sided p-value calculated using log-rank test stratified according to the randomization FLT3 mutation factor.

§Not Significant (1-sided, CMH test)

EFS event = failure to obtain a CR within 60 days of treatment start, or relapse, or death from any cause.

DFS event = relapse or death from any cause (in patients with CR within 60 days of treatment start)

CR = <5% blasts in bone marrow, no extramedullary disease, no leukemic blasts in peripheral blood, absolute neutrophil count ≥1 $x10^9$/L, platelets ≥100 $x10^9$/L.

In a subgroup analysis, a gender imbalance was observed for OS benefit, however, a gender imbalance was not observed for all secondary efficacy endpoints (EFS, CR, DFS and CIR), where female patients demonstrated a benefit from midostaurin.

Efficacy and safety in patients 18-70 years old were evaluated in a phase II, single-arm, investigator-initiated study of midostaurin in combination with intensive induction, consolidation including allogeneic SCT and single-agent maintenance in patients with FLT3-ITD mutated AML. Based on the interim analysis conducted in the first 145 patients enrolled (99 patients were ≤ 60 years of age; 46 were > 60 years of age), the EFS rate – as per protocol-defined EFS definition - at 2 years (primary endpoint) was 34.6 % (95% CI: 27.4, 43.6) in all

patients, 38.2% (95% CI: 29.5, 49.6) in patients aged 60 years or younger and 27.1% (95% CI: 16.6, 44.1), in patients older than 60 years of age.

Paediatric Patients with Acute Myeloid Leukaemia (AML)

In a phase 2 study, midostaurin was investigated in combination with chemotherapy in newly diagnosed pediatric 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 to 5; fludarabine 30 mg/m^2/day, day 1 to 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.

Advanced Systemic Mastocytosis (ASM)

The efficacy of Rydapt in patients with aggressive systemic mastocytosis (ASM) or mast cell leukemia (MCL), with or without an associated hematologic non-mast cell lineage disorder (AHNMD), collectively referred to as Advanced SM, was evaluated in two open-label, single-arm, multicenter studies (142 patients in total).

The pivotal study was a multicenter, single-arm phase II study in 116 patients with advanced SM (Study CPKC412D2201). Rydapt 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 (PEP). Of these, 73 patients had ASM (57 with an AHNMD), and 16 patients had MCL (6 with an AHNMD). The median age in the PEP was 64 years with approximately half of the patients ≥65 years). Approximately one-third (36%) received prior anti-neoplastic therapy for advanced SM. At baseline in the PEP, 65% of the patients had > 1 measurable C-finding. 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 Rydapt are shown in Table 10. Activity was observed regardless of KIT D816V status, number of prior therapies, and presence or absence of an AHNMD. Forty-six percent of patients had a decrease in bone marrow infiltration exceeded 50% and 58% had a decrease in serum tryptase levels 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 10: Efficacy of Rydapt 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 (%)	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)

Major response included patients with incomplete remission, pure clinical response and unspecified response. Partial response included patients with good partial response and minor response

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 11).

Table 11 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, months (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.

Patient-reported outcome assessments were evaluated using the Memorial Symptom Assessment Scale (MSAS) and SF-12 questionnaires. The most commonly reported baseline symptoms (>65% of prevalence) on the MSAS were “lack of energy”, “feeling drowsy”, and “difficulty sleeping”. The prevalence of all symptoms had decreased at Cycle 12, with the exception of nausea and vomiting. The results from the SF-12 indicated that patients had a worse status at baseline for both the physical and mental component scales as compared to a healthy population. During the study, the status of these components improved and approached that of a healthy population, especially among responders.

The supportive study was a single arm, multicenter, open-label phase II study of 26 patients with advanced SM (CPKC412A2213). Rydapt was administered orally at 100 mg twice daily. Lack of a major response (MR) or partial response (PR) by the end of the second cycle resulted in discontinuation from the study treatment. Twenty (76.9%) patients had ASM (17 [85%] with AHNMD) and 6 patients (23.1%) had MCL (2 [33.3%] with AHNMD). 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 for up one year after treatment discontinuation for survival).

5.2 PHARMACOKINETIC PROPERTIES

Absorption

In humans, the absorption of midostaurin is rapid after oral administration, with T_{max} of total radioactivity observed at 1 to 3 hours post dose. In healthy subjects, the extent of 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. Time to peak concentration was also delayed in presence of a standard meal or a high-fat meal (median T_{max} = 2.5 hrs to 3 hrs). In clinical studies, midostaurin was administered with a light meal, in order to decrease potential nausea and vomiting events and it is recommended that midostaurin is administered to patients with food.

Distribution

Midostaurin has a high tissue distribution of geometric mean Vz/F= 98.9 L. Midostaurin and its metabolites are distributed mainly in plasma rather than red blood cells. *In vitro* data showed midostaurin and its metabolites CGP62221 and CGP52421 are greater than 99.8% bound to plasma protein.

Metabolism

Midostaurin is metabolized by CYP3A4 mainly via oxidative pathways and the major plasma components included midostaurin and two major active metabolites; CGP62221 and CGP52421 accounting for 27.7± 2.7% and 37.97± 6.6% respectively of the total plasma exposure. O-demethylation, oxidation at benzene ring, oxidation at pyrrolidinine ring, amide bond hydrolysis, and N-demethylation were the major pathways of metabolism in man, leading to formation of 16 metabolites. CYP1A1, CYP3A4, and CYP3A5 were found capable of metabolizing both CGP62221 and CGP52421, with CYP3A4 being the main contributor to the clearance of these active metabolites.

Excretion

Based on a single-dose study, the median terminal half-lives of midostaurin, CGP62221 and CGP52421 in plasma are approximately 20.3, 33.4 and 495 hours. The Human Mass Balance study results indicate that fecal 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. At least 16 radiolabeled metabolites werecharacterized and quantitated in the excreta. In feces, the predominant metabolite was P29.6B (26.7%). In urine, the predominant metabolite was P6B (hippuric acid).

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. While the exact mechanism for the declining concentration of midostaurin is unclear, it may be possibly due to CYP3A4 enzyme auto-induction. The pharmacokinetics of the CGP62221 metabolite showed a similar trend. However, CGP52421 concentrations increased up to 2.5 fold with advanced SM to and up to 9-fold for AML, compared to midostaurin after one month of treatment.

Pharmacokinetics in special patient groups

Patients with hepatic impairment

A dedicated hepatic impairment study assessed the systemic exposure of midostaurin in subjects with baseline mild, moderate and severe hepatic impairment (Child-Pugh Class A, B and C, respectively) and control subjects with normal hepatic function. 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 dosage 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.

Patients with renal impairment

No dedicated renal impairment study was conducted for midostaurin. Population pharmacokinetic (popPK) analyses were conducted using data from clinical trials 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 PK 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.

Paediatric

The pharmacokinetics of midostaurin in pediatric patients were explored in phase 1 dose escalation monotherapy study with 22 patients (ages 3 months to 18 years of age) with AML or MLL-rearranged ALL using a population PK approach. After adjusting for body weight, exposures of midostaurin and its two metabolites in pediatrics fell within the ranges predicted by modeling data from adults.

Elderly (65 years or above)

Based on population PK model analyses of the effect of age on clearance of midostaurin and its active metabolites, there was no statistically significant finding and the anticipated changes in exposure were not deemed to be clinically relevant. In adult patients with advanced SM or AML, no midostaurin dose adjustment is required based on age.

Effect of Gender

Based on population PK 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 were not deemed to be clinically relevant. No midostaurin dose adjustment is required based on gender.

Effect of Ethnicity

There are no differences in the pharmacokinetic profile between Caucasian and Black subjects. Based on the phase 1 study in healthy Japanese volunteers, pharmacokinetic profiles of midostaurin and its metabolites (CGP62221 and CGP52421) are similar compared to those observed in other PK studies conducted in Caucasians and Blacks. No midostaurin dose adjustment is required based on ethnicity.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

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

Midostaurin was not mutagenic in vitro in the bacterial reverse mutation assay (Ames test), did not induce forward mutations in Chinese hamster V79 cells, did not induce chromosomal aberrations in Chinese hamster ovary cells and was not clastogenic in an in vivo rat bone marrow micronucleus assay when tested to the maximum tolerated dose of 200 mg/kg (approximately 2 fold below the human therapeutic exposures at the human doses of 50 and 100 mg twice daily based on AUC). Based on the available data midostaurin has no mutagenic potential.

Carcinogenicity

No carcinogenicity studies have been performed.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Corn oil PEG-6 esters, PEG-40 hydrogenated castor oil, macrogol 400, ethanol, di-alpha-tocopherol.

Capsule shell: gelatin, purified water, iron oxide yellow, titanium dioxide, glycerol and iron oxide red.

Proprietary Ingredient: Edible ink Red (PI No 3115).

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

In Australia, information on the shelf life can be found on the public summary of the Australian Register of Therapeutic Goods (ARTG). The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C, protect from moisture. Store in the original package to protect from moisture.

6.5 NATURE AND CONTENTS OF CONTAINER

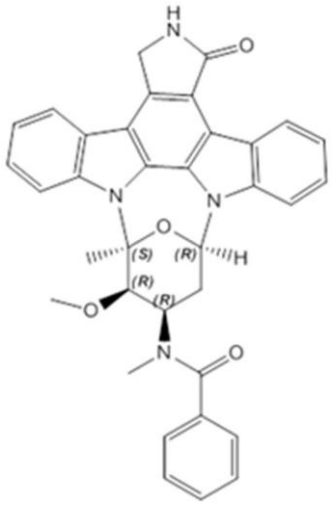
Al/Al blister packs containing 112 and 56 capsules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

In Australia, any unused medicine or waste material should be disposed of by taking to your local pharmacy.

6.7 PHYSICOCHEMICAL PROPERTIES

Structural formula:



Chemical name (IUPAC):
N-[(2*S*,3*R*,4*R*,6*R*)-3-Methoxy-2-methyl-16-oxo-29-oxa-1,7,17-triazaoctacyclo [12.12.2.1^{2,6}.0^{7,28}.0^{8,13}.0^{15,19}.0^{20,27}.0^{21,26}]nonacosa-8,10,12,14,19,21,23,25,27-nonaen-4-yl]-*N*methylbenzamide

INN: midostaurin

CAS name:

N-[(9*S*,10*R*,11*R*,13*R*)-2,3,10,11,12,13-Hexahydro-10-methoxy-9-methyl-1-oxo-9,13-epoxy-1*H*,9*H*-diindolo[1,2,3-*gh*:3′,2′,1′-*lm*]pyrrolo[3,4-*j*][1,7]benzodiazonin-11-yl]-*N*methylbenzamide

CAS no.: 120685-11-2

Molecular formula:

$C_{35}H_{30}N_4O_4$

Molecular weight:

570.65

Description:

The drug substance is a white to light yellow or light green powder. The drug substance is poorly soluble in water (< 0.001 mg/mL). The compound is slightly hygroscopic. Midostaurin is a highly permeable compound, has four chiral centers and is optically active.

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription Only Medicine

8 SPONSOR

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10 DATE OF REVISION

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Summary of Changes

Section changed	Summary of new information
8	Sponsor address change

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