Attachment 1: Product information for AusPAR - XOSPATA – gilteritinib (as fumarate) – Astellas Pharma Australia – PM-2019-03406-1-6 Final 8 September 2020. This is the Product Information that was approved with the submission described in this AusPAR. It may have been superseded. For the most recent PI, please refer to the TGA website at <https://www.tga.gov.au/product-information-pi>

▼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 PRODUCT INFORMATION – XOSPATA® (GILTERITINIB FUMARATE) FILM-COATED TABLETS

1 NAME OF THE MEDICINE

gilteritinib fumarate

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains 44.2 mg gilteritinib fumarate (corresponding to 40 mg gilteritinib).

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

3 PHARMACEUTICAL FORM

Film-coated tablets.

Round, light yellow film-coated tablet, debossed with the Astellas logo and '235' on the same side.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

XOSPATA is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with a FLT3 mutation.

4.2 DOSE AND METHOD OF ADMINISTRATION

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

Before taking XOSPATA, relapsed or refractory AML patients must have confirmation of FMS-like tyrosine kinase 3 (FLT3) mutation (internal tandem duplication [ITD] or tyrosine kinase domain [TKD]).

Dosage

The recommended starting dose of XOSPATA is 120 mg (three 40 mg tablets) once daily.

Blood chemistries, including creatine phosphokinase, should be assessed prior to initiation of treatment, on day 15 and monthly for the duration of treatment.

An electrocardiogram (ECG) should be performed before initiation of XOSPATA treatment, on day 8 and 15 and prior to the start of the next three subsequent months of treatment. In addition, an ECG should be performed following the same schedule in case of dose increase (see section 4.4 Special warnings and precautions for use and section 4.8 Adverse effects (Undesirable effects)).

Treatment should continue until the patient is no longer clinically benefiting from XOSPATA or until unacceptable toxicity occurs. Response may be delayed; therefore, continuation of treatment at the prescribed dose for up to 6 months should be considered to allow time for a clinical response.

In the absence of a response (patient did not achieve a CRc) after 4 weeks of treatment, the dose can be increased to 200 mg (five 40 mg tablets) once daily, if tolerated or clinically warranted.

Dose modifications

For dose interruption, reduction and discontinuation recommendations, see Table 1.

Table 1. XOSPATA dose interruption, reduction and discontinuation recommendations in patients with relapsed or refractory AML

Criteria	**XOSPATA dosing**
Differentiation syndrome	• If differentiation syndrome is suspected, administer systemic corticosteroids and initiate hemodynamic monitoring until symptom resolution and for a minimum of 3 days (see section 4.4 Special warnings and precautions for use). • Interrupt XOSPATA if severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids (see section 4.4 Special warnings and precautions for use). • Resume XOSPATA at the same dose when signs and symptoms improve to Grade 2[a] or lower.
Posterior reversible encephalopathy syndrome	• XOSPATA should be discontinued.
QTc interval >500 msec	• XOSPATA should be interrupted. • Treatment with XOSPATA can be resumed at a reduced dose (80 mg or 120 mg[b]) when QTc interval returns to within 30 msec of baseline or ≤480 msec.
QTc interval increased by >30 msec on ECG on day 8 of cycle 1	• Confirm with ECG on day 9. • If confirmed, consider dose reduction to 80 mg or 120 mg[b].
Symptoms of pancreatitis	• XOSPATA should be interrupted until pancreatitis is resolved. • Treatment with XOSPATA can be resumed at a reduced dose (80 mg or 120 mg[b]).
Other Grade 3a or higher toxicity considered related to treatment.	• XOSPATA should be interrupted until toxicity resolves or improves to Grade 1[a].

	• Treatment with XOSPATA can be resumed at a reduced dose (80 mg or 120 mg[b]).
Planned haematopoietic stem cell transplantation (HSCT)	• Interrupt treatment with XOSPATA one week prior to administration of the conditioning regimen for HSCT. • Treatment can be resumed 30 days after HSCT if engraftment was successful, the patient did not have grade ≥2 acute graft versus host disease and was in CRc.[c]

a. Grade 1 is mild, Grade 2 is moderate, Grade 3 is serious, Grade 4 is life-threatening.
b. The daily dose can be reduced from 120 mg to 80 mg or from 200 mg to 120 mg.
c. Composite complete remission (CRc) is defined as the remission rate of all CR (see section 5.1 for definition of CR), CRp [achieved CR except for incomplete platelet recovery (<100 x 10^9/L)] and CRi (achieved all criteria for CR except for incomplete haematological recovery with residual neutropenia <1 x 10^9/L with or without complete platelet recovery).

Missed dose

Administer XOSPATA at about the same time each day. If a dose is missed or not taken at the usual time, administer the dose as soon as possible on the same day, and return to the normal schedule the following day. If vomiting occurs after dosing, patients should not take another dose but should return to the normal schedule the following day.

Method of administration

For oral use.

XOSPATA can be taken with or without food. The tablets should be swallowed whole with water and should not be broken or crushed.

4.3 CONTRAINDICATIONS

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

Anaphylactic reactions have been observed in clinical trials (see section 4.8 Adverse effects (Undesirable effects)).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Differentiation syndrome

XOSPATA has been associated with differentiation syndrome (see section 4.8 Adverse effects (Undesirable effects)). Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms and other clinical findings of differentiation syndrome include fever, dyspnoea, pleural effusion, pericardial effusion, pulmonary oedema, hypotension, rapid weight gain, peripheral oedema, rash, and renal dysfunction. If differentiation syndrome is suspected, corticosteroid therapy should be initiated along with hemodynamic monitoring until symptom resolution. Corticosteroids can be

tapered after resolution of symptoms and should be administered for a minimum of 3 days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. If severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids, Xospata should be interrupted until signs and symptoms are no longer severe (see sections 4.2 Dose and method of administration and 4.8 Adverse effects (Undesirable effects)).

Posterior Reversible Encephalopathy Syndrome

There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving XOSPATA (see section 4.8 Adverse effects (Undesirable effects)). PRES is a rare, reversible, neurological disorder with which can present with rapidly evolving symptoms including seizure, headache, confusion, visual and neurological disturbances, with or without associated hypertension and altered mental status. If PRES is suspected, it should be confirmed by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of XOSPATA in patients who develop PRES is recommended. (see sections 4.2 Dose and method of administration and 4.8 Adverse effects (Undesirable effects)).

Prolonged QT interval

Gilteritinib has been associated with prolonged cardiac ventricular repolarisation (QT Interval) (see sections 4.8 Adverse effects (Undesirable effects) and 5.1 Pharmacodynamic properties). QT prolongation can be observed in the first three months of treatment with XOSPATA. Therefore, electrocardiogram (ECG) should be performed prior to initiation of treatment, on day 8 and 15 of cycle 1, and prior to the start of the next three subsequent months of treatment. In addition, an ECG should be performed in case of dose increase, following the same schedule. Hypokalaemia or hypomagnesaemia may increase the QT prolongation risk. Hypokalaemia or hypomagnesaemia should therefore be corrected prior to and during XOSPATA treatment.

XOSPATA should be interrupted in patients who have a QTcF >500 msec (see section 4.2 Dose and method of administration).

Pancreatitis

There have been reports of pancreatitis. Patients who develop signs and symptoms suggestive of pancreatitis should be evaluated and monitored. XOSPATA should be interrupted and can be resumed at a reduced dose when the signs and symptoms of pancreatitis have resolved (see section 4.2 Dose and method of administration).

Interactions

Coadministration of CYP3A/P-gp inducers may lead to decreased gilteritinib exposure and consequently a risk for lack of efficacy. Therefore, concomitant use of XOSPATA with strong CYP3A4/P-gp inducers should be avoided (see section 4.5 Interactions with other medicines and other forms of interactions).

Caution is required when concomitantly prescribing XOSPATA with medicinal products that are strong inhibitors of CYP3A and/or P-gp (such as, but not limited to, voriconazole, itraconazole, posaconazole and clarithromycin) because they can increase gilteritinib exposure. Alternative

medicinal products that do not strongly inhibit CYP3A and/or P-gp activity should be considered. In situations where satisfactory therapeutic alternatives do not exist, patients should be closely monitored for toxicities during administration of XOSPATA (see section 4.5 Interactions with other medicines and other forms of interactions).

XOSPATA may reduce the effects of medicinal products that target $5HT_{2B}$ receptor or sigma nonspecific receptors. Therefore, concomitant use of XOSPATA with these products should be avoided unless use is considered essential for the care of the patient (see section 4.5 Interactions with other medicines and other forms of interactions).

Embryofetal toxicity and contraception

Pregnant women should be informed of the potential risk to a fetus (see section 4.6 Fertility, pregnancy and lactation). Females of reproductive potential should be advised to have a pregnancy test within seven days prior to starting treatment with XOSPATA and to use effective contraception during treatment with XOSPATA and for at least 6 months after stopping treatment. Women using hormonal contraceptives should add a barrier method of contraception. Males with female partners of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose of XOSPATA.

Use in hepatic impairment

No dose adjustment is required for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. XOSPATA has not been studied in patients with severe hepatic impairment (Child-Pugh Class C) (see section 5.2 Pharmacokinetic properties).

Use in renal impairment

No dose adjustment is necessary in patients with renal impairment. There is no clinical experience in patients with severe renal impairment (see section 5.2 Pharmacokinetic properties).

Use in the elderly

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

Paediatric use

The safety and efficacy of XOSPATA in children aged below 18 years has not yet been established.

No data are available. XOSPATA should not be used in children from birth to less than 6 months of age because of potential safety concerns. Due to *in vitro* binding to $5HT_{2B}$ (see section 4.5 Interactions with other medicines and other forms of interactions), there is a potential impact on cardiac development in patients less than 6 months of age.

Effects on laboratory tests

No data are available.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

Gilteritinib is primarily metabolised by CYP3A enzymes, which can be induced or inhibited by a number of concomitant medications.

Effects of Other Medicinal Products on XOSPATA

CYP3A/P-gp Inducers

Concomitant use of XOSPATA with strong CYP3A/P-gp inducers (e.g., phenytoin, rifampin and St. John's Wort) should be avoided because they can decrease gilteritinib plasma concentrations. In healthy subjects, co-administration of rifampicin (600 mg), a strong CYP3A/P-gp inducer, to steady state with a single 20 mg dose of gilteritinib decreased gilteritinib mean C_{max} by 27% and mean AUC_{inf} by 70%, respectively, compared to subjects administered a single dose of gilteritinib alone. (see section 4.4 Special warnings and precautions for use).

CYP3A Inhibitors and/or P-gp inhibitors

Strong inhibitors of CYP3A (e.g., voriconazole, itraconazole, posaconazole, clarithromycin, erythromycin, captopril, carvedilol, ritonavir, azithromycin) should be used with caution during XOSPATA treatment because they can increase gilteritinib plasma concentrations. A single, 10 mg dose of gilteritinib co-administered with itraconazole (200 mg once daily for 28 days), a strong CYP3A and/or P-gp inhibitor, to healthy subjects resulted in an approximate 20% increase in mean C_{max} and 2.2-fold increase in mean AUC_{inf} relative to subjects administered a single dose of gilteritinib alone. Gilteritinib exposure increased approximately 1.5-fold in patients with relapsed or refractory AML when co-administered with a strong CYP3A and/or P-gp inhibitor. (see section 4.4 Special warnings and precautions for use).

Gilteritinib as an inhibitor or inducer

Gilteritinib is not an inhibitor or inducer of CYP3A4 or an inhibitor of MATE1 in vivo. The pharmacokinetics of midazolam (a sensitive CYP3A4 substrate) were not significantly (Cmax and AUC increased approximately 10%) affected after once-daily administration of gilteritinib (300 mg) for 15 days in patients with FLT3-mutated relapsed or refractory AML. Additionally, the pharmacokinetics of cephalexin (a sensitive MATE1 substrate) were not significantly (Cmax and AUC decreased by less than 10%) affected after once daily administration of gilteritinib (200 mg) for 15 days in patients with FLT3-mutated relapsed or refractory AML.

Effects of XOSPATA on Other Medicinal Products

$5HT_{2B}$ receptor or sigma nonspecific receptor

Based on *in vitro* data, gilteritinib may reduce the effects of medicinal products that target $5HT_{2B}$ receptor or sigma nonspecific receptor (e.g., escitalopram, fluoxetine, sertraline). Avoid concomitant use of these medicinal products with XOSPATA unless use is considered essential for the care of the patient.

Transporter drug-drug interactions

In vitro experiments demonstrated that gilteritinib is a P-gp substrate and may potentially inhibit BCRP and P-gp in the small intestine, OCT1 in the liver at clinically relevant concentrations.

4.6 FERTILITY, PREGNANCY AND LACTATION

Pregnancy testing is recommended for females of reproductive potential seven days prior to initiating XOSPATA treatment. Women of childbearing potential are recommended to use effective contraception (methods that result in less than 1% pregnancy rates) during and up to 6 months after treatment. It is unknown whether XOSPATA may reduce the effectiveness of hormonal contraceptives, and therefore women using hormonal contraceptives should add a barrier method of contraception. Males of reproductive potential should be advised to use effective contraception during treatment and for at least 4 months after the last dose of XOSPATA (see section 4.4 Special warnings and precautions for use).

Effects on fertility

There are no data on the effect of gilterinitib on human fertility.

Use in pregnancy – Pregnancy Category D

XOSPATA can cause fetal harm when administered to pregnant women. There are no or limited amount of data from the use of XOSPATA in pregnant women. Gilteritinib crossed the placenta in rats (fetal tissue levels were similar to maternal plasma levels), causing embryofetal lethality and teratogenicity at doses resulting in subclinical exposures (≥20 mg/kg/day PO). XOSPATA should not be used during pregnancy or in women of childbearing potential not using effective contraception. For more information regarding contraception and appropriate wash-out periods see section 4.4 Special warnings and precautions for use — Embryofetal toxicity and contraception.

Use in lactation

It is unknown whether gilteritinib or its metabolites are excreted in human milk. Available animal data have shown excretion of gilteritinib and/or its metabolites in the animal milk of lactating rats with levels higher than maternal plasma levels. Distribution to the tissues in infant rats via the milk was evident.

A risk to breast-fed children cannot be excluded. Breastfeeding should be discontinued during treatment with XOSPATA and for at least two months after the last dose.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

Gilteritinib has minor influence on the ability to drive and use machines. Dizziness has been reported in patients taking XOSPATA and should be considered when assessing a patient's ability to drive or use machines (see section 4.8 Adverse effects (Undesirable effects)).

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

Summary of the safety profile

The safety of XOSPATA was evaluated in 319 patients with relapsed or refractory AML who received at least one dose of 120 mg gilteritinib.

The most frequent adverse drug reactions with gilteritinib were alanine aminotransferase (ALT) increased (82.1%), aspartate aminotransferase (AST) increased (80.6%), blood alkaline phosphatase

increased (68.7%), blood creatine phosphokinase increased (52.9%), diarrhoea (35.1%), fatigue (30.4%), nausea (29.8%), constipation (28.2%), cough (28.2%), peripheral oedema (24.1%), dyspnea (24.1%), dizziness (20.4%), hypotension (17.2%), pain in extremity (14.7%), asthenia (13.8%), arthralgia (12.5%) and myalgia (12.5%).

The most frequent serious adverse reactions were acute kidney injury (6.6%), diarrhoea (4.7%), ALT increased (4.1%), dyspnea (3.4%), AST increased (3.1%) and hypotension (2.8%). Other clinically significant serious adverse reactions included differentiation syndrome (2.2%), electrocardiogram QT prolonged (0.9%) and posterior reversible encephalopathy syndrome (0.6%).

Tabulated list of adverse reactions

Adverse reactions observed during clinical studies are listed below by frequency category. Frequency categories are defined as follows: 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 order of decreasing seriousness.

Table 2: Adverse reactions

Adverse drug reactions	All Grades %	Grades ≥3 %	Frequency category
Immune system disorders			
Anaphylactic reaction	1.3	1.3	Common
Nervous system disorders			
Dizziness	20.4	0.3	Very common
Posterior reversible encephalopathy syndrome	0.6	0.6	Uncommon
Cardiac disorders			
Electrocardiogram QT prolonged	8.8	2.5	Common
Pericardial effusion	4.1	0.9	Common
Pericarditis	1.6	0	Common
Cardiac failure	1.3	1.3	Common
Vascular disorders			
Hypotension	17.2	7.2	Very common
Respiratory, thoracic and mediastinal disorders			
Cough	28.2	0.3	Very common
Dyspnoea	24.1	4.4	Very common
Differentiation syndrome	3.4	2.2	Common
Gastrointestinal disorders			
Diarrhoea	35.1	4.1	Very common
Nausea	29.8	1.9	Very common
Constipation	28.2	0.6	Very common
Hepatobiliary disorders			
Alanine aminotransferase increased*	82.1	12.9	Very common
Aspartate aminotransferase increased*	80.6	10.3	Very common
Musculoskeletal and connective tissue disorders			
Blood creatine phosphokinase increased*	53.9	6.3	Very common

Blood alkaline phosphatase increased*	68.7	1.6	Very common
Pain in extremity	14.7	0.6	Very common
Arthralgia	12.5	1.3	Very common
Myalgia	12.5	0.3	Very common
Musculoskeletal pain	4.1	0.3	Common
Renal and urinary disorders			
Acute kidney injury	6.6	2.2	Common
General disorders and administration site conditions			
Fatigue	30.4	3.1	Very common
Peripheral oedema	24.1	0.3	Very common
Asthenia	13.8	2.5	Very common
Malaise	4.4	0	Common

* Frequency is based on central laboratory values.

Description of selected adverse reactions

Differentiation syndrome

Of 319 patients treated with XOSPATA in the clinical trials, 11 (3%) experienced differentiation syndrome. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells and may be life-threatening or fatal if not treated. Symptoms of differentiation syndrome in patients treated with XOSPATA included fever, dyspnoea, pleural effusion, pericardial effusion, pulmonary oedema, hypotension, rapid weight gain, peripheral oedema, rash, and renal dysfunction. Some cases had concomitant acute febrile neutrophilic dermatosis. Differentiation syndrome occurred as early as one day and up to 82 days after XOSPATA initiation and has been observed with or without concomitant leukocytosis. Of the 11 patients who experienced differentiation syndrome, 9 (82%) recovered after treatment or after dose interruption of XOSPATA. For recommendations in case of suspected differentiation syndrome see sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use.

PRES

Of the 319 patients treated with XOSPATA in the clinical trials, 0.6% experienced posterior reversible encephalopathy syndrome (PRES). PRES is a rare, reversible, neurological disorder, which can present with rapidly evolving symptoms including seizure, headache, confusion, visual and neurological disturbances, with or without associated hypertension. Symptoms have resolved after discontinuation of treatment (see sections 4.2 Dose and method of administration and 4.4 Special warnings and precautions for use).

QT prolongation

Of the 317 patients treated with XOSPATA at 120 mg with a post-baseline QTC value in clinical trials, 4 patients (1%) experienced a QTcF >500 msec. Additionally, across all doses, 12 patients (2.3%) with relapsed/refractory AML had a maximum post-baseline QTcF interval >500 msec (see sections 4.2 Dose and method of administration, 4.4 Special warnings and precautions for use and 5.1 Pharmacodynamic properties).

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.

4.9 OVERDOSE

There is no known specific antidote for XOSPATA. 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, taking into consideration the long half-life estimated at 113 hours.

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: protein kinase inhibitors, ATC code: L01XE54

Pharmacodynamic effects

In patients with relapsed or refractory AML receiving gilteritinib 120 mg, substantial (> 90%) inhibition of FLT3 phosphorylation was rapid (within 24 hours after first dose) and sustained, as characterised by an *ex vivo* plasma inhibitory activity (PIA) assay.

Prolonged QT interval

A concentration-related increase in change from baseline of QTcF was observed across gilteritinib doses ranging from 20 to 450 mg. The predicted mean change from baseline of QTcF at the mean steady-state C_{max} (282.0 ng/mL) at the 120 mg daily dose was 4.96 msec with an upper 1-sided 95% CI = 6.20 msec.

Mechanism of action

Gilteritinib fumarate is a FMS-like tyrosine kinase 3 (FLT3) and AXL (as well as other kinases) inhibitor.

Gilteritinib inhibits FLT3 receptor signalling and proliferation in cells expressing FLT3 including FLT3-ITD, FLT3-D835Y, and FLT3-ITD-D835Y, and it induced apoptosis in leukaemic cells expressing FLT3-ITD.

Clinical trials

Relapsed or refractory AML

Efficacy and safety was evaluated in the active-controlled, phase 3 trial (2215-CL-0301).

ADMIRAL Trial (2215-CL-0301)

The ADMIRAL trial is a Phase 3, open-label, multicentre, randomised clinical trial of adult patients with relapsed or refractory AML with a FLT3 mutation as determined by the LeukoStrat® CDx FLT3

Mutation Assay. In this trial, 371 patients were randomized in a 2:1 ratio to receive gilteritinib or one of the following salvage chemotherapies (247 in the gilteritinib arm and 124 in the salvage chemotherapy arm):

- cytarabine 20 mg twice daily by subcutaneous (SC) or intravenous (IV) for 10 days (days 1 through 10) (LoDAC)
- azacitidine 75 mg/m^2 once daily by SC or IV for 7 days (days 1 through 7)
- mitoxantrone 8 mg/m^2, etoposide 100 mg/m^2 and cytarabine 1000 mg/m^2 once daily by IV for 5 days (days 1 through 5) (MEC)
- granulocyte colony-stimulating factor 300 mcg/m^2 once daily by SC for 5 days (days 1 to 5), fludarabine 30 mg/m^2 once daily by IV for 5 days (days 2 through 6), cytarabine 2000 mg/m^2 once daily by IV for 5 days (days 2 through 6), idarubicin 10 mg/m^2 once daily by IV for 3 days (days 2 through 4) (FLAG-Ida).

Gilteritinib was given orally at a starting dose of 120 mg daily until unacceptable toxicity or lack of clinical benefit. Dose reductions were allowed, to manage adverse reactions, and dose increases were allowed, for those patients who did not respond at the starting dose of 120 mg.

MEC and FLAG-Ida were given for up to two cycles depending on response to first cycle. LoDAC and azacitidine were given in continuous 4-week cycles until unacceptable toxicity or lack of clinical benefit.

The demographic and baseline characteristics were well-balanced between the two treatment arms. The median age at randomisation was 62 years (range 20 to 84 years) in the gilteritinib arm and 62 years (range 19 to 85 years) in the salvage chemotherapy arm. Fifty-four percent of the patients were female. Most patients in the study were Caucasian (59.3%); 27.5% Asian, 5.7% Black, 4% other races and 3.5% unknown. The majority of patients (83.8%) had an ECOG performance status score of 0 or 1. Patients had the following confirmed mutations: FLT3-ITD alone (88.4%), FLT3-TKD alone (8.4%) or both FLT3-ITD and -TKD (1.9%). Prior to treatment with gilteritinib, 39.4% of patients had primary refractory AML, 19.7% had relapsed AML after an allogeneic haematopoietic stem cell transplant (HSCT) and 41% had relapsed AML with no allogenic HSCT. Majority of patients had AML with intermediate risk cytogenetics (73%), 10% had unfavourable, 1.3% had favourable and 15.6% had unclassified cytogenetics.

The primary efficacy endpoint for the final analysis was OS in the intent-to-treat (ITT) population, measured from the date of randomisation until death by any cause (number of events analysed was 261). Patients randomised to the gilteritinib arm had significantly longer survival compared to the chemotherapy arm (HR 0.637; 95% CI 0.490 – 0.830; 1 sided p-value: 0.0004). The median OS was 9.3 months for patients receiving gilteritinib and 5.6 months for those receiving chemotherapy. Efficacy was further supported by the rate of complete remission (CR)/complete remission with partial haematologic recovery (CRh), the duration of CR/CRh (DOR) and a modified analysis of event free survival (EFS) (**Table 3**, **Figure 1**).

Table 3: ADMIRAL trial overall survival, complete remission and event free survival in patients with relapsed or refractory AML

	Gilteritinib (N=247)	Chemotherapy (N=124)
Overall survival		
Deaths, n (%)	171 (69.2)	90 (72.6)
Median in months (95% CI)	9.3 (7.7, 10.7)	5.6 (4.7, 7.3)
Hazard Ratio (95% CI)	0.637 (0.490, 0.830)	
p-value (1-sided)[g]	0.0004	
1 year survival rate, % (95% CI)	37.1 (30.7, 43.6)	16.7 (9.9, 25)
Complete remission		
CR[a] (95% CI[b])	21.1% (16.1, 26.7)	10.5% (5.7, 17.3)
Median DOR[c] in months (95% CI[e])	NR (11, NR)	1.8 (NE, NE)
CRh[d] (95% CI[b])	13% (9, 17.8)	4.8% (1.8, 10.2)
Median DOR[c] in months (95% CI[e])	4 (2.1, 5.3)	NE (NE, NE)
CR/CRh (95% CI[b])	34% (28.1, 40.3)	15.3% (9.5, 22.9)
Median DOR[c] in months (95% CI[e])	11 (4.6, NR)	1.8 (NE, NE)
Event free survival[f]		
Median in months (95% CI)	2.3 (1.4, 3.6)	0.7 (0.1, 1.3)
Hazard Ratio (95% CI)	0.499 (0.387, 0.643)	
p-value (1-sided)[g]	<0.0001	

CI: confidence interval; NE: not estimable

a. CR was defined as an absolute neutrophil count ≥1.0 x 10^9/L, platelets ≥100 x 10^9/L, normal marrow differential with <5% blasts, must have been red blood cells, platelet transfusion independent and no evidence of extramedullary leukaemia.
b. The 95% CI rate was calculated using the exact method based on binomial distribution.
c. DOR was defined as the time from the date of either first CR or CRh until the date of a documented relapse of any type.
d. CRh was defined as marrow blasts <5%, partial haematologic recovery absolute neutrophil count ≥0.5 x 10^9/L and platelets ≥50 x 10^9/L, no evidence of extramedullary leukaemia and could not have been classified as CR.
e. Based on Kaplan-Meier estimates.
f. Modified analysis of event free survival (EFS), defined as a failure to obtain a composite complete remission (CRc) with failures assigned as an event on date of randomization, relapse, or death from any cause, including events and initiation of new anti-leukaemia treatments reported in long-term follow up.
g. Based on log-rank test from stratified analysis.

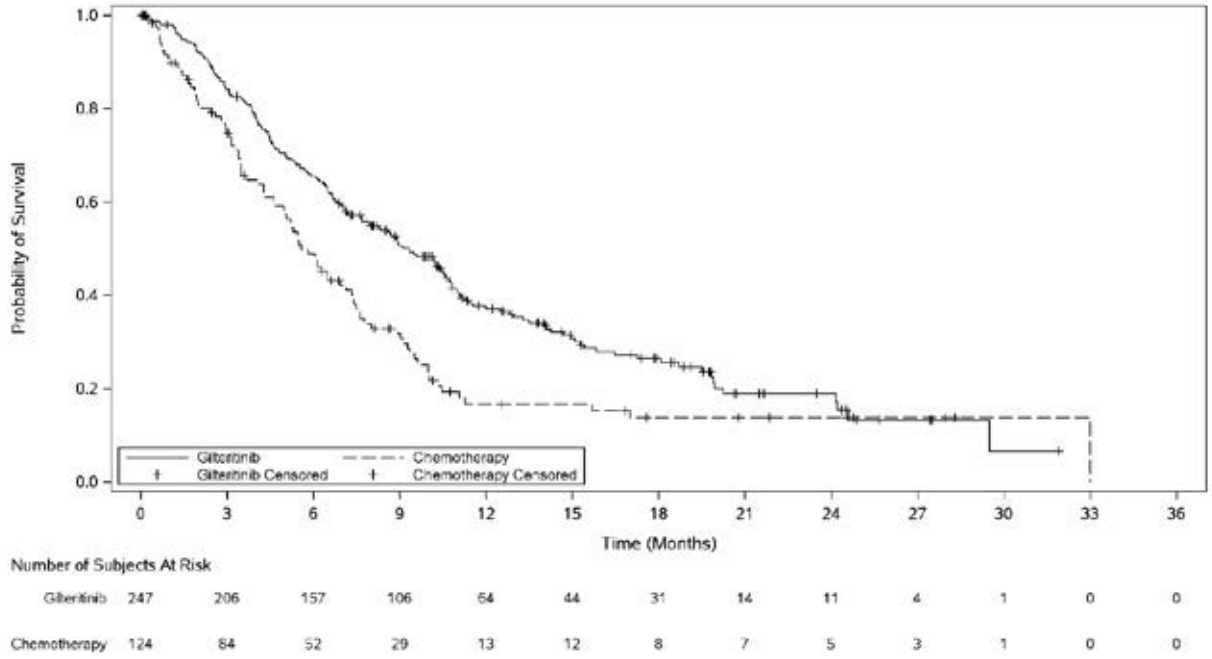


Figure 1: Kaplan-Meier Plot of Overall Survival in ADMIRAL Trial

For patients who achieved a CR/CRh, the median time to first response was 3.7 months (range, 0.9 to 10.6 months) in the gilteritinib arm and 1.2 months (range: 1 to 2.6 months) in the salvage chemotherapy arm. The median time to best response of CR/CRh was 3.8 months (range, 0.9 to 16 months) in the gilteritinib arm and 1.2 months (range: 1 to 2.6 months) in the salvage chemotherapy arm.

Among the 197 patients who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline, 68 (34.5%) became independent of RBC and platelet transfusions during any 56-day post-baseline period. For the 49 patients who were independent of both RBC and platelet transfusions at baseline, 29 (59.2%) remained transfusion-independent during any 56-day post-baseline period.

5.2 PHARMACOKINETIC PROPERTIES

Absorption

Following oral administration of gilteritinib, peak plasma concentrations are observed at a median t_{max} approximately between 4 and 6 hours in healthy volunteers and patients with relapsed or refractory AML. Gilteritinib undergoes first-order absorption with an estimated absorption rate (k_a) of 0.43 h-1 with a lag time of 0.34 hours based on population PK modelling. Median steady-state maximum concentration (C_{max}) is 282.0 ng/mL (CV% = 50.8), and area under the plasma concentration curve during 24-hour dosing interval (AUC_{0-24}) is 6180 ng·h/mL (CV% = 46.4) after once-daily dosing of 120 mg gilteritinib. Steady-state plasma levels are reached within 15 days of once-daily dosing with an approximate 10-fold accumulation.

Effect of Food

In healthy adults, gilteritinib C_{max} and AUC decreased by approximately 26% and less than 10%, respectively, when a single 40 mg dose of gilteritinib was co-administered with a high fat meal compared to gilteritinib exposure in fasted state. Median t_{max} was delayed 2 hours when gilteritinib was administered with a high-fat meal.

Distribution

The population estimate of central and peripheral volume of distribution were 1092 L and 1100 L, respectively. These data indicate gilteritinib distributes extensively outside of plasma, which may indicate extensive tissue distribution. *In vivo* plasma protein binding in humans is approximately 90% and gilteritinib is primarily bound to albumin.

Metabolism

Based on *in vitro* data, gilteritinib is primarily metabolised via CYP3A4. The primary metabolites in humans include M17 (formed via N-dealkylation and oxidation), M16 and M10 (both formed via N-dealkylation) and were observed in animals. None of these three metabolites exceeded 10% of overall parent exposure. The pharmacological activity of the metabolites against FLT3 and AXL receptors is unknown.

Excretion

After a single dose of [^{14}C]-gilteritinib, gilteritinib is primarily excreted in faeces with 64.5% of the total administered dose recovered in faeces. Renal excretion is a minor elimination pathway with 16.4% of the total dose recovered in urine as unchanged drug and metabolites. Gilteritinib plasma concentrations declined in a bi-exponential manner with a population mean estimated half-life of 113 hours. The estimated apparent clearance (CL/F) based on the population PK model is 14.85 L/h.

Linearity/Non-linearity

In general, gilteritinib exhibited linear, dose-proportional pharmacokinetics after single and multiple dose administration at doses ranging from 20 to 450 mg in patients with relapsed or refractory AML.

Special Populations

Based on population pharmacokinetic analyses, no clinically meaningful effect on the pharmacokinetics of gilteritinib was observed for the following covariates: age (20 years to 90 years), race (Caucasian, Black, Asian or Other), sex, body weight (36 kg to 157 kg), and body surface area (1.29 to 2.96 m^2).

Hepatic impairment

The effect of hepatic impairment on gilteritinib pharmacokinetics was studied in subjects with mild (Child-Pugh Class A) and moderate (Child-Pugh Class B) hepatic impairment. Results indicate unbound gilteritinib exposure in subjects with mild or moderate hepatic impairment is comparable to that observed in subjects with normal hepatic function. The effect of mild hepatic impairment [as defined by NCI-ODWG] on gilteritinib exposure was also assessed using the population PK model and the results demonstrate little difference in predicted steady-state gilteritinib exposure relative to a typical patient with relapsed or refractory AML and normal liver function.

Gilteritinib has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).

Renal impairment
A dedicated renal impairment study has not been conducted to assess of the effect of renal function on gilteritinib pharmacokinetics. In the population pharmacokinetic analysis serum creatinine, a marker of renal function, was identified as a statistically significant covariate. Estimated impact on gilteritinib exposure was less than 2-fold.

5.3 PRECLINICAL SAFETY DATA

Genotoxicity

Gilteritinib did not induce gene mutation in an *in vitro* bacterial reverse mutation assay and chromosome aberration in an *in vitro* chromosome aberration assay with Chinese hamster lung cells. However, the *in vivo* micronucleus test showed that gilteritinib induced micronuclei in mouse bone marrow cells at oral doses ≥65 mg/kg/day (resulting in subclinical exposures.

Carcinogenicity

Carcinogenicity studies have not been performed with gilteritinib.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Tablet Core:
Mannitol
Hyprolose
Magnesium Stearate

Coating:
Hypromellose
Purified talc
Macrogol 8000
Titanium dioxide
Iron oxide yellow

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 in the original container.

Store below 25ºC.

This medicinal product does not require any special storage conditions.

6.5 NATURE AND CONTENTS OF CONTAINER

OPA/aluminium/PVC/aluminium blisters containing 21 film coated tablets.

Each pack contains 84 film-coated tablets.

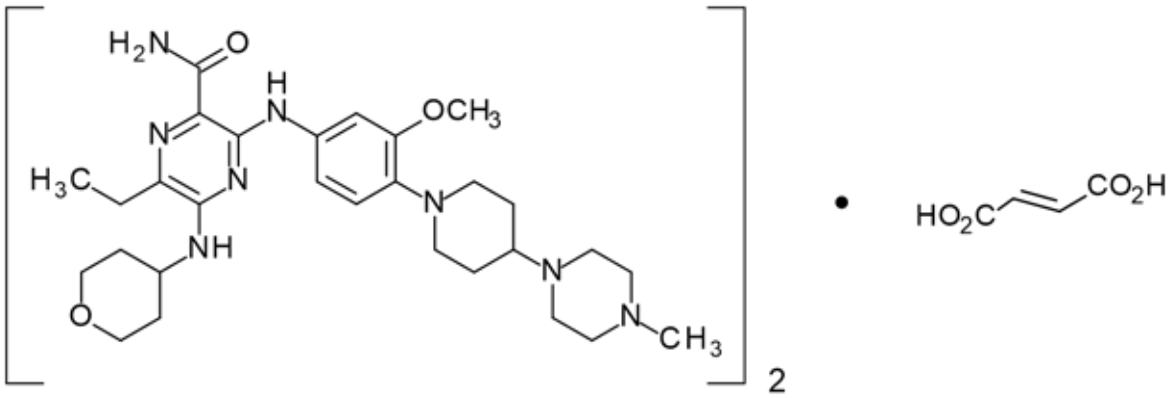
6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

Chemical structure

Gilteritinib is a tyrosine kinase inhibitor. The chemical name is 2-Pyrazinecarboxamide, 6-ethyl-3-[[3-methoxy-4-[4-(4 methyl-1-piperazinyl)-1-piperidinyl] phenyl] amino]-5-[(tetrahydro-2*H*-pyran-4-yl) amino]-, (2E)-2-butenedioate (2:1). The molecular weight is 1221.50 and the molecular formula is $(C_{29}H_{44}N_8O_3)_2{\cdot}C_4H_4O_4$. The structural formula is:



Gilteritinib fumarate is a light yellow to yellow powder or crystals that is sparingly soluble in water and very slightly soluble in anhydrous ethanol.

CAS number

1254053-84-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 – Prescription only medicine

8 SPONSOR

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Macquarie Park NSW 2113

Tel: 1800 751 755 (Medical Information)
Email: aaumedinfo@astellas.com (Medical Information)
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9 DATE OF FIRST APPROVAL

2 April 2020

10 DATE OF REVISION

Not applicable

SUMMARY TABLE OF CHANGES

Section Changed	Summary of new information
all	New product information