Date: 9 November 2020
Swissmedic, Swiss Agency for Therapeutic Products

Swiss Public Assessment Report

XOSPATA

International non-proprietary name: gilteritinib, gilteritinib hemifumarate
Pharmaceutical form: coated tablets
Dosage strength: 40 mg
Route(s) of administration: oral
Marketing Authorisation Holder: Astellas Pharma AG
Marketing Authorisation No.: 67211
Decision and Decision date: approved on 24 September 2020

Note:

Assessment Report as adopted by Swissmedic with all information of a commercially confidential nature deleted.

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About Swissmedic

Swissmedic is the Swiss authority responsible for the authorisation and supervision of therapeutic products. Swissmedic's activities are based on the Federal Act of 15 December 2000 (Status as of 1 January 2020) on Medicinal Products and Medical Devices (TPA, SR 812.21). The agency ensures that only high-quality, safe and effective drugs are available in Switzerland, thus making an important contribution to the protection of human health.

About the Swiss Public Assessment Report (SwissPAR)

- The SwissPAR is referred to in Article 67 para. 1 of the Therapeutic Products Act and the implementing provisions of Art. 68 para. 1 let. e of the Ordinance of 21 September 2018 on Therapeutic Products (TPO, SR 812.212.21).
- The SwissPAR provides information about the evaluation of a prescription medicine and the considerations that led Swissmedic to approve or not approve a prescription medicine submission. The report focuses on the transparent presentation of the benefit-risk profile of the medicinal product.
- A SwissPAR is produced for all human medicinal products with a new active substance and transplant products for which a decision to approve or reject an authorisation application has been issued.
- A supplementary report will be published for approved or rejected applications for an additional indication for a human medicinal product for which a SwissPAR has been published following the initial authorisation.
- The SwissPAR is written by Swissmedic and is published on the Swissmedic website. Information from the application documentation is not published if publication would disclose commercial or manufacturing secrets.
- The SwissPAR is a “final” document, which provides information relating to a submission at a particular point in time and will not be updated after publication.
- In addition to the actual SwissPAR, a concise version of SwissPAR that is more comprehensible to lay persons (Public Summary SwissPAR) is also published.

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1 Terms, Definitions, Abbreviations

ADA	Anti-drug antibody
ADME	Absorption, Distribution, Metabolism, Elimination
AE	Adverse event
ALT	Alanine aminotransferase
AML	Acute myeloid leukaemia
API	Active pharmaceutical ingredient
AST	Aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical Classification System
AUC	Area under the plasma concentration-time curve
AUC0-24h	Area under the plasma concentration-time curve for the 24-hour dosing interval
CI	Confidence interval
Cmax	Maximum observed plasma/serum concentration of drug
CR	Complete response
CRh	Complete response with partial haematological recovery
CRi	Incomplete count recovery
CYP	Cytochrome P450
ECOG	Eastern Cooperative Oncology Group
EFS	Event-free survival
ERA	Environmental Risk Assessment
FLAG-IDA	Fludarabine, cytarabine, idarubicin, and G-CSF
FLT3	FMS-like tyrosine kinase 3
G-CSF	Granulocyte colony-stimulating factor
GLP	Good Laboratory Practice
HR	Hazard ratio
HSCT	Haematopoietic stem cell transplantation
ICH	International Council for Harmonisation
Ig	Immunoglobulin
INN	International Nonproprietary Name
ITD	Internal tandem duplication
ITT	Intended to treat
LoQ	List of Questions
MAH	Marketing Authorisation Holder
Max	Maximum
MEC	Mitoxantrone and cytarabine
Min	Minimum
N/A	Not applicable
NO(A)EL	No Observed (Adverse) Effect Level
OS	Overall survival
PD	Pharmacodynamics
PIP	Paediatric Investigation Plan (EMA)
PK	Pharmacokinetics
PopPK	Population PK
PRES	Posterior reversible encephalopathy syndrome
PSP	Paediatric Study Plan (US-FDA)
RBC	Red blood cells
RMP	Risk Management Plan
R/R	Relapsed and/or Refractory
SAE	Serious adverse event
SwissPAR	Swiss Public Assessment Report
TEAE	Treatment-emergent adverse event
TKD	Tyrosine kinase domain

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TPA	Federal Act of 15 December 2000 (Status as of 1 January 2020 on Medicinal Products and Medical Devices (SR 812.21)
TPO	Ordinance of 21 September 2018 (Status as of 1 April 2020) on Therapeutic Products (SR 812.212.21)

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2 Background Information on the Procedure

2.1 Applicant's Request(s)

New Active Substance status
The applicant requested the status of a new active entity for the active substance gilteritinib of the medicinal product mentioned above.

Orphan drug status
The applicant requested the Orphan Drug Status in accordance with Article 4 a^{decies} no. 2 of the TPA. The Orphan Status was granted on 16 August 2018.

2.2 Indication and Dosage

2.2.1 Requested Indication

Xospata is indicated for the treatment of patients who have relapsed or refractory acute myeloid leukaemia (AML) with FMS-like tyrosine kinase 3 (FLT3) mutations.

2.2.2 Approved Indication

Xospata is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with FMS-like tyrosine kinase 3 (FLT3) mutations (see section Clinical efficacy).

2.2.3 Requested Dosage

The recommended starting dose of Xospata is 120 mg (three 40 mg tablets) once daily, with or without food. In the absence of a response after 4 weeks of treatment, the dose can be increased to 200 mg (five 40 mg tablets) once daily.

2.2.4 Approved Dosage

(see appendix)

2.3 Regulatory History (Milestones)

Application	23 May 2019
Formal control completed	12 July 2019
List of Questions (LoQ)	5 November 2019
Answers to LoQ	30 January 2020
Predecision	28 April 2020
Answers to Predecision	28 June 2020
Labelling corrections	3 August 2020
Answers to Labelling corrections:	23 August 2020
Final Decision	24 September 2020
Decision	approval

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3 Medical Context

Acute myeloid leukaemia (AML) is a biologically heterogeneous disease that is rapidly fatal if left untreated. Incidence of AML increases with age. The WHO classification of AML is based on microscopic, cytogenetic, and molecular characteristics. Therapy is individually tailored to each patient according to the biology of the disease and the age and comorbidities of the patient. For fit patients, the therapeutic intent is curative. FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) mutations have been associated with increased risk of relapse, while the prognostic relevance of FLT3-tyrosine kinase domain (TKD) mutations is controversial (Gale et al., Blood, 2008).

The majority of patients, who relapse after an initial complete response (CR), will relapse within 3 years after diagnosis (Dohner et al., NEJM, 2015). A short duration of remission (< 6 months), adverse genetic factors, prior haematopoietic stem cell transplantation (HSCT), older age, and poor general health status are major determinants of outcome after relapse. FLT3 also confers a poor prognosis in relapsed AML.

There is no standard treatment regimen defined for relapsed and/or refractory (R/R) AML. No clinical trial has shown superiority of any particular treatment combination. Salvage therapy aims at achieving a second CR in order to propose HSCT for fit candidates. Salvage regimens include intermediate-dose cytarabine, MEC (mitoxantrone, cytarabine) or, lastly, FLAG-IDA (fludarabine, cytarabine, idarubicin and G-CSF (granulocyte colony-stimulating factor)). The likelihood of achieving a second CR is best in patients with a long first remission, younger age and in those with favourable cytogenetics (Chevallier et al., Leukemia, 2011). Response rates for all these combinations lie between 32-79%, and median OS remains poor at 3-12 months. For patients who are not candidates for a new high-dose induction therapy, hypomethylating agents are an alternative.

4 Quality Aspects

4.1 Drug Substance

Xospata film-coated tablets contain the drug substance gilteritinib fumarate.

Chemical names:
There are the two following chemical names:

1. 2-Pyrazinecarboxamide, 6-ethyl-3-[[3-methoxy-4-[4-(4-methyl-1-piperazinyl)-1-piperidinyl]phenyl]amino]-5-[(tetrahydro-2H-pyran-4-yl]amino], (2E)-2-butenedioate (2:1) (Registered designation of USAN)
2. 6-Ethyl-3-[3-methoxy-4-[4-(4-methylpiperazin-1-yl)piperidin-1-yl]aniline]-5-(oxan-4-ylamino)pyrazine-2-carboxamide hemi-(2E)-but-2-enedioate.

Molecular formula:
The molecular formula of gilteritinib fumarate is $(C_{29}H_{44}N_8O_3)_2 \cdot C_4H_4O_4$ and the relative molecular mass is 1221.5 g/mol

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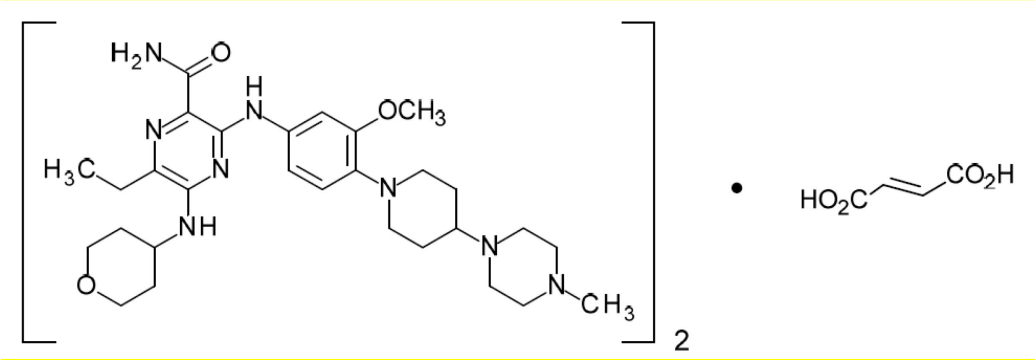
Molecular structure:



Physico-chemical properties:
Gilteritinib fumarate is a yellow crystal powder. It is not hygroscopic, and polymorphs have not been observed. The solubility in aqueous media ranges from sparingly to practically insoluble.

Attribute	Results	
Appearance	Yellow crystals	
Dissociation Constant (pKa)[1]	2.3, 5.0 and 7.9	
Partition Coefficient (Log P_{OW})	3.9	
Solubility Profile at 20 ± 5°C (JP)	Water	29 mg/mL (Sparingly soluble)
	Anhydrous ethanol	2.0×10^{-1} mg/mL (Very slightly soluble)
	Acetonitrile	less than 1.0×10^{-2} mg/mL (Practically insoluble)
	Tetrahydrofuran	2.2×10^{-1} mg/mL (Very slightly soluble)
	N,N-Dimethylacetamide	4.0 mg/mL (Slightly soluble)
	Aqueous solution (pH 1)[2] (After dissolution: pH 5.8)	1.9×10^{2} mg/mL (Freely soluble)
	Aqueous solution (pH 3)[3] (After dissolution: pH 5.2)	1.3×10^{2} mg/mL (Freely soluble)
	Aqueous solution (pH 5)[3] (After dissolution: pH 5.3)	82 mg/mL (Soluble)
	Aqueous solution (pH 7)[3] (After dissolution: pH 6.6)	8.7×10^{-2} mg/mL (Practically insoluble)
	Aqueous solution (pH 9)[3] (After dissolution: pH 8.3)	1.1×10^{-2} mg/mL (Practically insoluble)
	Aqueous solution (pH 11)[3] (After dissolution: pH 9.8)	3.8×10^{-3} mg/mL (Practically insoluble)
Hygroscopicity	Not hygroscopic	
Melting point (Ph. Eur. method 2.2.14)	Gilteritinib fumarate decomposes at approximately 239°C.	
Polymorphs	Polymorphs have not been observed.	

JP: Japanese Pharmacopoeia, Ph. Eur.: European Pharmacopoeia

[1] Obtained using AS2582215-HD

[2] 0.1 mol/L hydrochloric acid was used. This pH value was measured before sample dissolution.

[3] Carmody's buffer solutions were used. (A mixture of 0.2 mol/L boric acid, 0.05 mol/L citric acid and 0.1 mol/L trisodium phosphate) This pH value was measured before dissolution.

Synthesis: gilteritinib fumarate is a chemical compound synthesised in an 8-step synthesis employing five starting compounds. The route of synthesis is adequately described. Critical parameters are

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controlled by in-process controls. Intermediate compounds and starting materials are adequately specified and controlled. The process ensures a consistent drug substance quality.

Specification: The specification is established in accordance with guidance documents. It consists of description, purity, content, and microbiological properties.

Stability: The stability of the gilteritinib fumarate is evaluated in accordance with internationally acknowledged guidance documents. This is done in the proposed primary packaging system, which consists of double polyethylene bags, tightly closed and packed into a steel drum. A re-test of 30 months is justified.

4.2 Drug Product

The drug product is a film-coated tablet containing 44 mg of the drug substance gilteritinib fumarate (corresponding to 40 mg base). Excipients used in this formulation are mannitol (E421), high- and low-substituted hydroxypropylcellulose, magnesium stearate, and a film coating composed of hypromellose, talc, macrogol 8000, titanium dioxide, and iron oxide yellow (E172).

Description and composition: The drug product is a round light yellow film-coated tablet. It is debossed with the company logo and '235' on the same side. Common excipients are employed to produce this immediate-release film-coated tablet, containing 40 mg gilteritinib as fumarate.

Pharmaceutical development: Critical attributes and specifications (QCA) are presented. The aim is to manufacture an immediate-release oral dosage form via a robust and reproducible route.

Manufacture: The manufacture of the film coated tablets consists of a common and standard route of manufacture. Major steps are blending, granulation, compression to tablets, and film coating. The description consists of in-process controls and specifications for intermediate products.

Specification: The specification consists of identification, related substances, dissolution, assay, and microbiological purity. Control methods are described and validated. Assurance is provided to the effect that the specifications are controlled.

Container-Closure System: The film-coated tablets are packed into a blister consisting of an aluminium/aluminium material.

Stability: Shelf life and storage conditions are adequately verified. The data presented justify the shelf life of 48 months and the storage requirement as stated on the carton and the information for patients and healthcare professionals.

4.3 Quality Conclusions

Satisfactory and consistent quality of drug substance and drug product has been demonstrated.

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5 Nonclinical Aspects

Regarding the marketing authorisation application for Xospata, Swissmedic Preclinical Review conducted an abridged evaluation that was based on the FDA assessment report. In the USA, the indication of relapsed or refractory acute myeloid leukaemia (AML) with an FLT3 mutation was approved in 2018. Post-marketing studies, including two juvenile animal studies and the phototoxicity study, were reviewed.

Overall, the submitted nonclinical documentation is considered appropriate to support the approval of Xospata® in the proposed indication. The pharmaco-toxicological profile has been sufficiently characterised. The safety margins are negligible but acceptable taking into account the intended indication. However, juvenile animal studies have shown that juveniles may be more sensitive than adults.

All nonclinical data that are relevant for safety are adequately mentioned in the information for healthcare professionals.

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6 Clinical and Clinical Pharmacology Aspects

6.1 Clinical Pharmacology

The available assessment reports and respective product information from the US FDA were used as a basis for the clinical pharmacology evaluation. For further details concerning clinical pharmacology, see Chapter 8.1 of this report.

6.2 Dose Finding and Dose Recommendation

There is one dose-finding study. The 2215-CL-0101 study is a first in-human dose finding study with an included dose-expansion phase 2 study to determine safety, tolerability and pharmacokinetics of gilteritinib, as well as the maximum tolerated dose. As secondary endpoints, efficacy and drug-drug interaction studies were also planned. The study enrolled 265 patients, of whom 252 received at least one dose of study drug.

The study included AML patients with relapsed and/or refractory disease independent of FLT3 mutation status. However, a minimum number of FLT3-mutated patients was required by the protocol. Dose-escalation started at 20 mg as a once daily dose taken continuously. Accelerated dose-escalation was implemented up to 80 mg per day, and doses were further increased to 120 mg, 200 mg, 300 mg and 450 mg per day. There was evidence of increased response rates at 80 mg and above, as well as >90% inhibition of FLT3 phosphorylation, indicating target inhibition. Response rates did not increase further with doses above 120 mg/day.

The complete response rate was 37.2% in FLT3 mutation positive patients with relapsed/refractory AML. FLT3 mutation negative patients, however, do not seem to derive any benefit, with a complete response (CR) rate of 8.6%. Median time to first CR/CRh (complete response with partial haematological recovery) in FLT3 mutation positive patients was 57 days, indicating that a dose-escalation for non-response after one cycle, as requested by the applicant, is not established. In addition, as mentioned above response rates do not increase further with dosages > 120 mg.

For FLT3 mutation positive patients treated with ≥ 80 mg gilteritinib, median OS was approximately 7 months. For FLT3 mutation negative patients treated with any dose of gilteritinib, the median OS was approximately 4 months.

6.3 Efficacy

The application is based on one pivotal study 2215-CL-0301, the ADMIRAL trial. This trial included adult patients with FLT3-mutated AML that had relapsed after one prior line of treatment or that was refractory to first line treatment. Patients with secondary AML (treatment-induced; very poor prognosis) or with promyelocytic leukaemia (excellent outcome with treatment by retinoic acid and arsenic) were not eligible.

ADMIRAL was a phase 3 superiority trial comparing the efficacy of gilteritinib with standard salvage chemotherapy in relapsed/refractory AML patients presenting FLT3 mutations (FLT3-ITD, FLT3-TKD/D835 or FLT3-TKD/I836). Patients had to be eligible for rescue chemotherapy of the investigator's choice, have normal renal and liver function, no GVHD (graft-versus-host disease) and an ECOG (Eastern Cooperative Oncology Group) performance status of 0-2. The chemotherapy control arm was an investigator's choice between 4 different regimens (two low-dose [low-dose cytarabine and azacitidine] and two high-dose [MEC and [FLAG-IDA] regimens). No formal criteria were described on how patients were pre-selected for high-dose versus low-dose salvage therapy. Patients were stratified based on their response to first-line treatment and according to salvage chemotherapy (low-dose or high-dose) pre-determined by the investigator before randomisation. Sixty percent (60%) of patients were pre-determined for high-dose and 40% for low-dose chemotherapy

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(without specification of the exact regimen), and this was well balanced between the two treatment arms, as could be expected given the stratification for this variable.

The primary efficacy endpoint was overall survival. While the study was already recruiting, a co-primary endpoint of CR/CRh rate was added for the gilteritinib arm. At the same time an interim analysis was added when approximately 141 patients were randomised to the gilteritinib arm and were at least 112 days (4 treatment cycles) past the first dose of gilteritinib or randomisation (for patients who did not receive gilteritinib). This co-primary endpoint was only to be analysed during this new interim analysis and showed a CR/CRh rate that allowed for continuation of the study (lower bound of the 95% CI above 12% which corresponds to previously described response rates with chemotherapy in this indication). Alpha spending was correctly performed for the statistical analysis plan. Key secondary endpoints were event-free survival (EFS) and CR rate, as well as safety.

Gilteritinib was administered orally without food once a day continuously at 120 mg (3 tablets of 40 mg). Chemotherapy regimens were administered according to published standards. High-dose chemotherapy was assessed with bone marrow (BM) aspiration after one cycle (approximately day 15), and the treatment decision was based on response and BM cellularity. Low-dose chemotherapy and gilteritinib were continued until toxicity, progression, lack of efficacy (no response) or no more clinical benefit according to the investigator. Gilteritinib could be dose-reduced to 80 mg and then 40 mg. If 40 mg once daily was not tolerated, then no further dose-reduction was allowed, and treatment had to be discontinued. Dose-interruptions were allowed for a maximum of 14 days, after which treatment had to be definitively discontinued. No re-escalation was allowed.

For gilteritinib, azacitidine and LoDAC (low-dose cytarabine), treatment was continued until progression, intolerable toxicity or withdrawal of consent. For the higher dose chemotherapy regimens, treatment could also be interrupted due to lack of efficacy after one cycle, or if patients went on to HSCT. After treatment discontinuation, patients had an end of treatment visit within 7 days after treatment discontinuation, followed by a 30-day follow-up. After that, patients entered the long-term follow-up every 3 months for overall survival only.

The study planned to randomise 369 patients in a 2:1 ratio to receive gilteritinib or salvage chemotherapy. For the final analysis, the planned 258 death events provide about 90% power to detect a difference in OS between the gilteritinib arm with 7.7 months median survival time and salvage chemotherapy arm with 5 months median survival time (HR = 0.65) at the overall 1-sided 0.0245 significance level.

A total of 371 patients were randomised, 247 to the gilteritinib arm and 124 to salvage chemotherapy. In the salvage chemotherapy, fewer patients received treatment (87.9%) compared to the gilteritinib arm (99.6%). At the 30-day follow-up, there was a higher rate of patient withdrawals in the chemotherapy control arm (19 [15.3%]) versus 5 (2.0%) in the gilteritinib arm). In the long-term safety follow-up there were more patient withdrawals in the chemotherapy arm, with 18.5% compared to the gilteritinib arm with 2.8%. This withdrawal to follow-up has an even greater impact since follow-up time was short in the salvage chemotherapy arm that foresaw only one visit at 30 days after completion of treatment and then only a survival status check via telephone contact every 3 months. Given that the majority of patients were preselected for high-dose chemotherapy, which was administered for a maximum of two cycles, follow-up time was, at most, 3 months, and this in a population of patients with an expected median OS of 5 months (according to the statistical analysis plan). There were only 56.5% of patients in the salvage chemotherapy arm versus 87.9% in the gilteritinib arm who fell into the per protocol analysis set.

Overall, there were slightly more than 10% of patients with protocol deviations. These were balanced between the arms and should not therefore influence the interpretation of the study results. The baseline characteristics were well balanced. Most patients fall into the intermediate cytogenetic risk group (73%), but approximately 10% had unfavourable cytogenetics. About 16% of patients were not

classifiable into favourable, intermediate, or unfavourable risk. Approximately 40% of patients were ≥ 65 years old and > 80% had a baseline ECOG performance status of 0 or 1. There were no significant differences between the two arms regarding prior therapy and response to prior therapy, duration of response, and time since diagnosis. No information was provided on therapies received after study participation.

Treatment exposure was shorter in the chemotherapy arm, particularly since a majority of patients received high-dose chemotherapy that was pre-defined for one or two cycles only. Median duration of exposure to gilteritinib was 126 days.

OS was significantly longer in the gilteritinib arm in the ITT population, with a **median OS of 9.3 (95% CI: 7.7, 10.7) months** compared to the salvage chemotherapy arm with a **median of 5.6 (95% CI: 4.7, 7.3) months** using a Kaplan-Meier estimate (HR: 0.637; 95% CI: 0.490, 0.830; 1-sided P-value 0.0004). The survival probability was higher in the gilteritinib arm compared to the salvage chemotherapy arm at 6 months (65.5% versus 48.9%) and 12 months (37.1% versus 16.7%).

Regarding secondary endpoints, the study did not show a significant improvement in EFS (event-free survival). The other key secondary endpoint was CR/CRh rate, which was to be tested hierarchically after EFS. Given that EFS was not statistically significant, the CR/CRh rate is only exploratory, but shows a trend towards higher response rates in the gilteritinib arm compared to the chemotherapy arm. Median time to response in the gilteritinib arm was 3.7 months.

Patients who were eligible per the institutional guidelines and had a suitable donor were allowed to proceed to HSCT. While patients in the chemotherapy arm went off study at HSCT and were only followed for OS, patients in the gilteritinib arm were allowed to continue on study and could resume gilteritinib after successful HSCT. More patients in the gilteritinib group went on to receive HSCT (25.5% versus 15.3% in the gilteritinib and salvage chemotherapy arms, respectively).

Efficacy conclusion: **Gilteritinib increased median OS in the ITT population compared to salvage chemotherapy from 5.6 months to 9.3 months** with an HR of 0.637; 95% CI: 0.490, 0.830 and a 1-sided P-value of 0.0004. The survival probability was higher in the gilteritinib arm compared to the salvage chemotherapy arm at 6 months (65.5% versus 48.9%) and 12 months (37.1% versus 16.7%) when at 12 months 25% of the gilteritinib population and 10% of the chemotherapy population remained at risk. The secondary endpoint of improved EFS was not reached. CR/CRh rates were better in the gilteritinib arm, at 34.0% [84/247]) compared to the salvage chemotherapy arm (15.3% [19/124]). Transfusion-dependency was another secondary endpoint. Among the 197 patients in the gilteritinib arm who were dependent on RBC and/or platelet transfusions at baseline, 68 (34.5%) became independent of RBC and platelet transfusions during any 56-day postbaseline 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 postbaseline period.

6.4 Safety

The integrated R/R AML safety population included a total of 522 patients who received at least one dose of gilteritinib between 20 mg and 450 mg, comprised of 252 patients from Study 2215-CL-0101 (completed study), 24 patients from Study 2215-CL-0102 (completed study), and 246 patients from Study 2215 CL-0301 (data cut-off date: 17 Sep 2018). Of these 522 patients, 319 received a starting dose of gilteritinib 120 mg (including all 246 patients from study 2215-CL-0301).

The most frequent TEAEs (treatment-emergent adverse events) were ALT and AST elevations, anaemia, thrombocytopenia, febrile neutropenia, diarrhoea, nausea, blood alkaline phosphatase increased, fatigue, creatine phosphokinase elevation, constipation, neutropenia, dysgeusia, pyrexia, QT-prolongation, headache, vomiting, decreased appetite, myalgia, peripheral oedema, and rash.

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Overall, 96% of patients presented ≥ grade 3 toxicity, including 55% of patients with drug-related TEAEs. The most frequent were anaemia, thrombocytopenia, febrile neutropenia, ALT or AST elevation, blood creatine phosphokinase increased, fatigue, diarrhoea, and ECG QT prolonged (1.1%).

Deaths
Overall, 181 fatal TEAEs were observed in all 522 gilteritinib treated patients. Of these deaths, 18 were considered to be drug-related. Drug-related TEAEs leading to death were as follows: septic shock (3 patients), sepsis (1), pneumonia (3), respiratory failure (2), cerebral haemorrhage (1), large intestinal perforation (2), congestive heart failure (1), cellulitis (1), intracranial haemorrhage (1), intestinal ischaemia (1), neutropenia (1), pulmonary embolism (1), ventricular fibrillation (1), depressed level of consciousness (1), haemoptysis (1), and subdural haematoma (1).

Serious Adverse Events (SAEs)
SAEs were observed in 33% of patients treated with gilteritinib and comprised febrile neutropenia, pyrexia and pneumonia, but also transaminases increased, respiratory failure, syncope, and hypotension, all considered drug-related by the investigators.

TEAEs leading to withdrawal of treatment
Treatment withdrawal due to TEAEs was observed in 10% of patients, and the most frequent reasons were increased transaminases and pneumonia. Approximately 43% of patients had treatment interruptions due to adverse events (AEs) and 20% had dose-reductions.

AEs of special interest were defined by the applicant and comprised PRES (posterior reversible encephalopathy syndrome), cardiac failure, pericarditis, QT prolongation, creatine phosphokinase elevation and myopathy, liver transaminases elevation, differentiation syndrome, gastrointestinal obstruction, perforation and bleeding, pancreatitis, and drug hypersensitivity/anaphylaxis. All of these AEs were described in at least one patient and are considered safety risks. Most of these are rare events except for the transaminase increase that was observed in more than one third of patients, as well as creatine phosphokinase increase and QT prolongation that were also observed with frequencies of 10% and 7%, respectively.

Conclusion safety: Gilteritinib increased liver transaminases and caused hematologic toxicity, which is confounded by the underlying disease and previous treatments. The same is true for the high incidence of infectious complications under gilteritinib. Another safety issue is cardiac safety with several cardiac deaths in the gilteritinib-treated patients versus none in the chemotherapy control group and the documented QT prolongation under gilteritinib. Cases of PRES, pancreatitis and differentiation syndrome have been observed under gilteritinib and need to be monitored.

6.5 Final Clinical and Clinical Pharmacology Benefit Risk Assessment

Acute myeloid leukaemia (AML) is a biologically heterogeneous disease that is rapidly fatal if left untreated. Incidence of AML increases with age. The WHO classification of AML is based on microscopic, cytogenetic, and molecular characteristics. Therapy is individually tailored to each patient according to the biology of the disease and the age and comorbidities of the patient. For fit patients, the therapeutic intent is curative. FMS-like tyrosine kinase 3 internal tandem duplication (FLT3-ITD) mutations have been associated with increased risk of relapse, while the prognostic relevance of FLT3-tyrosine kinase domain (TKD) mutations is controversial.

The majority of patients, who relapse after initial complete response (CR), will relapse within 3 years after diagnosis. There is no standard treatment regimen defined for relapsed and/or refractory (R/R) AML. No clinical trial has shown superiority of any particular treatment combination. Salvage therapy aims at achieving a second CR in order to propose HSCT for fit candidates. The likelihood of achieving a second CR is best in patients with a long first remission, younger age, and in those with

favourable cytogenetics. For patients who are not candidates for a new high-dose induction therapy, hypomethylating agents are an alternative. Response rates for salvage chemotherapies lie between 32-79%, and median OS remains poor at 3-12 months.

There is a high unmet medical need.

Gilteritinib is a small molecule tyrosine kinase inhibitor targeting the FLT3 receptor tyrosine kinase. FLT3 is often mutated in AML and confers a poor prognosis. Gilteritinib is an oral medication, taken once a day without food in a continuous manner. In the phase 3 ADMIRAL trial, it was shown to improve overall survival in relapsed or refractory FLT3-mutated AML patients who had received one prior line of therapy compared to the investigator's choice chemotherapy from 5.6 months to 9.3 months with an HR of 0.637 (95% CI: 0.490- to 0.830, p=0.0004 one-sided log rank test). Overall, response rate was a key secondary endpoint and was in favour of gilteritinib compared to chemotherapy with 21.1% vs 10.5%, respectively, obtaining a CR. However, due to the hierarchical testing strategy to preserve the alpha-level, this difference cannot be considered statistically significant since event-free survival, which was ahead in the hierarchy, was not significant. Nevertheless, the difference is clinically important.

Median duration of CR in the gilteritinib arm was 14.8 months, and the overall OS analysis in the ITT population showed a survival benefit of nearly 4 months in favour of gilteritinib. The stress test performed to weigh the early censoring of patients in the chemotherapy arm was consistent with the primary analysis. In addition, in the gilteritinib arm 34% of transfusion dependent patients became transfusion independent, and 60% of transfusion independent patients remained so on gilteritinib.

Gilteritinib increases liver transaminases and creatine phosphokinase. One patient in the overall safety population experienced rhabdomyolysis. Gilteritinib induces a QT-prolongation. Gilteritinib has haematological toxicity with higher rates of cytopenia, particularly compared to low-dose chemotherapy. There were treatment-related deaths in the gilteritinib treatment arm, mostly due to infections but also to cardiac events including ventricular fibrillation and ventricular tachycardia. Cases of posterior reversible encephalopathy syndrome (PRES) were observed under gilteritinib. There were events of pancreatitis under gilteritinib. Differentiation syndrome was also described as an adverse event of gilteritinib.

To compare toxicity of gilteritinib to chemotherapy was challenging given the 2:1 randomisation with fewer patients in the chemotherapy arm and the heterogeneous treatments with four different regimens in the control arm. Separate analyses for toxicity of patients treated with gilteritinib compared to patients treated with low-dose chemotherapy exclusively in patients pre-selected for low-dose chemotherapy, showed higher incidences of TEAEs, grade 3/4 AEs and SAEs in patients treated with gilteritinib. When comparing patients pre-selected for high-dose chemotherapy and treated with gilteritinib with patients receiving high-dose chemotherapy, toxicity was similar. The difference is that high-dose chemotherapy was administered over a much shorter time period. Overall, comparative safety data are limited and safety data rely mostly on non-comparative observations.

Therefore, in view of the OS benefit, the higher ORR with a long duration of response and manageable toxicity the benefit-risk profile is evaluated as positive.

6.6 Approved Indication and Dosage

See information for healthcare professionals in the Appendix.

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7 Risk Management Plan Summary

The RMP summaries contain information on the medicinal products' safety profiles and explain the measures that are taken in order to further investigate and monitor the risks as well as to prevent or minimise them.
The RMP summaries are published separately on the Swissmedic website. Marketing Authorisation Holders are responsible for the accuracy and correctness of the content of the published RMP summaries. As the RMPs are international documents, their summaries might differ from the content in the information for healthcare professionals / product information approved and published in Switzerland, e.g. by mentioning risks occurring in populations or indications not included in the Swiss authorisations.

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8 Appendix

8.1 Approved Information for Healthcare Professionals

Please be aware that the following version of the information for healthcare professionals relating to Xospata was approved with the submission described in the SwissPAR. This information for healthcare professionals may have been updated since the SwissPAR was published.

Please note that the reference document, which is valid and relevant for the effective and safe use of medicinal products in Switzerland, is the information for healthcare professionals approved and authorised by Swissmedic (see www.swissmedicinfo.ch).

Note:
The following information for healthcare professionals has been translated by the MAH. The Authorisation Holder is responsible for the correct translation of the text. Only the information for healthcare professionals approved in one of the official Swiss languages is binding and legally valid.

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Placeholder for text approval stamp

▼ This medicine is subject to additional monitoring. This will allow quick identification of new safety information. Healthcare professionals are asked to report any suspected new or serious adverse reactions. See the "Undesirable effects" section for advice on the reporting of adverse reactions.

NAME OF THE MEDICINAL PRODUCT

XOSPATA™ 40 mg, film-coated tablets

Composition

Active substances

Gilteritinib as gilteritinib fumarate

Excipients

Mannitol (E421), hydroxypropyl cellulose, low-substituted hydroxypropyl cellulose, magnesium stearate, hypromellose, talc, macrogol 8000, titanium dioxide (E 171) and iron oxide yellow (E172).

Pharmaceutical form and active substance quantity per unit

Xospata 40 mg film-coated tablets are round, light yellow, film-coated tablets debossed with the Astellas logo and '235' on the same side. Each film-coated tablet contains 40 mg of gilteritinib (equivalent to 44.2 mg gilteritinib fumarate).

Indications/Uses

Xospata is indicated for the treatment of adult patients who have relapsed or refractory acute myeloid leukaemia (AML) with FMS-like tyrosine kinase 3 (FLT3) mutations (see section Clinical efficacy).

Dosage/Administration

The treatment must be initiated and monitored by a doctor experienced in cancer therapy.
The recommended starting dose is 120 mg gilteritinib (three 40 mg tablets) once-daily.
The treatment can be continued up to disease progression or intolerable toxicity.

Test phase

Before taking gilteritinib, 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]) using a validated test.

Blood chemistries, including creatine phosphokinase, have to be assessed prior to the initiation of treatment with Xospata, on day 15 of cycle 1 and monthly for the duration of therapy.
An electrocardiogram (ECG) has to be performed prior to initiation of treatment with Xospata, on day 8 and 15 of cycle 1, and prior to the start of the next two subsequent cycles.

Dose adjustment/titration

Response may be delayed; therefore, continuation of treatment at the prescribed dose for a period of 6 months should be considered to allow time for a clinical response.

Dose adjustment following undesirable effects/interactions

Xospata dose interruption, reduction and discontinuation recommendations in patients with relapsed or refractory AML:

Differentiation syndrome

- If differentiation syndrome is suspected, administer corticosteroids and initiate hemodynamic monitoring (see section Warnings and precautions).
- Interrupt gilteritinib if severe signs and/or symptoms persist for more than 48 hours after initiation of corticosteroids.
- Resume gilteritinib at the same dose when signs and symptoms improve to Grade 2[a] or lower.

Posterior reversible encephalopathy syndrome (PRES)

- Discontinue gilteritinib.

QTcF interval >500 msec

- Interrupt gilteritinib.
- Resume gilteritinib at a reduced dose (80 mg) when QTcF interval returns to ≤ 480 msec.

Other Grade 3[a] or higher toxicity considered related to treatment

- Interrupt gilteritinib until toxicity resolves or improves to Grade 1[a].
- Resume treatment with gilteritinib at a reduced dose (80 mg)[b].

[a.] Grade 1 is mild, Grade 2 is moderate, Grade 3 is serious, Grade 4 is life-threatening (grades are per CTCAE criteria).

[b.] The daily dose can be reduced from 120 mg to 80 mg.

Patients with impaired hepatic function

No dose adjustment is required for patients with mild (Child-Pugh Class A) or moderate (Child-Pugh Class B) hepatic impairment. Gilteritinib has not been studied in patients with severe hepatic impairment (Child-Pugh Class C). Refer to section Pharmacokinetics.

Patients with impaired renal function

No dose adjustment is required in patients with mild (creatinine clearance (CrCL) 60 - <90 ml/min) or moderate (CrCL 30 - <60 ml/min) renal impairment (estimated GFR [CrCL ml/min] according to

MDRD, refer to section Pharmacokinetics). There is no clinical experience in patients with severe renal impairment (CrCL <30 ml/min).

Elderly patients

No dose adjustment is required in patients ≥65 years of age (refer to section Pharmacokinetics)

Children and adolescents

There are no data to support the safety and efficacy of gilteritinib use in children. Therefore, gilteritinib is not recommended for use in children and adolescents.

Mode of administration

Xospata tablets should be taken orally once-daily with or without food. Do not break or crush the tablets. Administer Xospata tablets orally about the same time each day. If a dose of Xospata 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.

Contraindications

Hypersensitivity to the active substance or any excipients of the product. Anaphylactic reactions have been reported (refer to section Undesirable Effects).

Warnings and precautions

Differentiation syndrome

Gilteritinib has been associated with differentiation syndrome (see section 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 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. 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 Dosage/Administration and Undesirable Effects). Corticosteroids can be tapered after resolution of symptoms and should be administered for at least 3 further days. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment.

Posterior Reversible Encephalopathy Syndrome

There have been reports of posterior reversible encephalopathy syndrome (PRES) in patients receiving gilteritinib (see section Undesirable Effects). 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 and altered mental status. If PRES is suspected, the diagnosis is to be confirmed by brain imaging, preferably magnetic resonance imaging (MRI). Discontinuation of Xospata in patients who develop PRES is recommended.

Prolonged QT interval

Gilteritinib has been associated with prolonged cardiac ventricular repolarization (QT Interval). Refer to section Pharmacokinetics 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 two subsequent months of treatment.

Hypokalaemia or hypomagnesaemia may increase the QT prolongation risk. Correct hypokalaemia or hypomagnesemia prior to and during Xospata administration.

Xospata should be interrupted in patients who have a QTcF >500 msec (see section Pharmacodynamics).

Pancreatitis

Cases of pancreatitis were observed. Evaluate and monitor patients closely who develop signs and symptoms suggestive of pancreatitis.

Embryo-foetal toxicity

Xospata can harm the embryo or foetus if it is administered to pregnant women. Pregnant women must be informed of the potential risk for the foetus. Women of childbearing potential must use an effective method of contraception during the treatment with Xospata and for at least 6 months after the last dose. Men with partners of childbearing potential must use an effective method of contraception during the treatment with Xospata and for at least 4 months after the last dose (see sections Pregnancy, Lactation and Preclinical data).

Fertility

There is no available data regarding the effect of Xospata on fertility in humans.

Animal studies indicated toxicity in male dogs (see section Preclinical data).

Interactions

Pharmacokinetic interactions

Gilteritinib exposure (AUC_{inf}) decreased approximately 70% when Xospata was coadministered with a strong CYP3A/P-gp inducer (rifampin). Gilteritinib C_{max} decreased by 30%.

Gilteritinib exposure increased approximately to 2.2-fold when Xospata was coadminstered with a strong CYP3A inhibitor (itraconazole) in healthy adult subjects and approximately to 1.5-fold in patients with relapsed or refractory AML.

Pharmacodynamic interactions

In vitro studies

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

Enzyme inducers

Concomitant use of gilteritinib with drugs that are strong inducers of CYP3A/P-gp (e.g., rifampin, phenytoin, St. John's Wort) should be avoided as they can decrease the plasma exposure of gilteritinib.

Enzyme inhibitors

Concomitant use of gilteritinib with drugs that are strong inhibitors of CYP3A (e.g., voriconazole, itraconazole, posaconazole, clarithromycin, erythromycin) should be avoided as they can increase the plasma exposure of gilteritinib. Alternatives should be considered. However, the patient should be monitored more closely for adverse reactions if a combination with strong CYP3A4 inhibitors cannot be avoided.
Drugs that are strong inhibitors of P-gp (e.g., captopril, azithromycin, carvedilol, ritonavir) may increase the plasma exposure of gilteritinib. Avoid concomitant use of these drugs with gilteritinib unless use is considered essential for the care of the patient.

Effect of XOSPATA on other medicinal products

Gilteritinib is not an inhibitor or inducer of CYP3A4 or and inhibitor of MATE1 *in vivo*. The pharmacokinetics of midazolam (a sensitive CYP3A4 substrate) were not significantly (C_{max} 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 (C_{max} 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.

Pregnancy, lactation

Pregnancy

Gilteritinib can cause foetal harm when administered to pregnant women. There is no data from the use of gilteritinib in pregnant women. Gilteritinib can cause foetal harm based upon findings from animal studies (see section Preclinical data).
Xospata must not be used during pregnancy unless the benefit to the mother is considered to be higher than the risk to the foetus. Pregnant women must be informed of the potential risk to the foetus.

Lactation

It is unknown whether gilteritinib passes into human milk, or what the effects on the breastfed infant, or the effects on milk production are. In animal studies gilteritinib and/or its metabolite(s) were distributed to the tissues in infant rats via the milk. A risk to breast-fed children cannot be excluded. Breastfeeding should be discontinued during gilteritinib treatment and for at least two months after the last dose (see section Preclinical data).

Contraception in men and women

Xospata can harm the embryo or foetus if it is administered to pregnant women (see section Preclinical data). Women of childbearing potential must use an effective method of contraception during the treatment with Xospata and for at least 6 months after the last dose. Fertile men should be instructed to use an effective method of contraception during the treatment with Xospata and for at least 4 months after the last dose.

Women of childbearing potential

Pregnancy testing is recommended for females of reproductive potential within seven days prior to initiating gilteritinib treatment.

Effects on ability to drive and use machines

Dizziness has been reported in patients taking gilteritinib and should be considered when assessing a patient's ability to drive or use machines.
No corresponding studies have been performed.

Undesirable effects

The safety evaluation of gilteritinib is based on 319 patients with relapse or refractory AML who have received at least one dose of 120 mg gilteritinib daily.
The most common undesirable effects (≥10%) were alanine aminotransferase (ALT) increased, aspartate aminotransferase (AST) increased, diarrhoea, fatigue, nausea, constipation, cough, peripheral oedema, dyspnoea, blood alkaline phosphatase increased, dizziness, hypotension, pain in extremity, asthenia, blood creatine phosphokinase increased, arthralgia and myalgia.
The most frequent serious undesirable effects (≥2%) reported in patients were acute kidney injury, diarrhoea, ALT increased, AST increased, hypotension, dyspnoea and differentiation syndrome.
Undesirable effects 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); isolated cases (frequency cannot be estimated from the available data). Within each grouping, undesirable effects are presented in order of decreasing frequency.

Cardiac disorders
Common: electrocardiogram QT prolonged, pericardial effusion, pericarditis, cardiac failure

Gastrointestinal disorders
Very common: diarrhoea (35.1%), nausea (29.8%), constipation (28.2%), stomatitis (13.5%), abdominal pain (13.2%)

Hepatobiliary disorders
Very common: alanine aminotransferase increased (82.1%)*, aspartate aminotransferase increased (80.6%)*

General disorders and administration site conditions
Very common: pyrexia (41.1%), fatigue (30.4%), peripheral oedema (24.1%), asthenia (13.8%)
Common: malaise

Immune system disorders
Common: anaphylactic reaction

Metabolism and nutrition disorders
Very common: hyperglycaemia (88.1%)*, hypocalcaemia (64.9%)*, hypoalbuminaemia (59.9%)*, hypophosphataemia (51.1%)*, hypokalaemia (33.9%)*, hyponatraemia (32.0%)*, hypomagnesaemia (18.8%)*, reduced appetite (17.2%)

Psychiatric disorders
Very common: insomnia/sleeplessness (15%)

Musculoskeletal and connective tissue disorders
Very common: blood alkaline phosphatase increased (68.7%)*, blood creatine phosphokinase increased (53.9%)*, pain in extremity (14.7%), arthralgia (12.5%), myalgia (12.5%)
Common: musculoskeletal pain

Nervous system disorders
Very common: dizziness (20.4%), headache (23.5%), dysgeusia (11%)
Uncommon: posterior reversible encephalopathy syndrome

Respiratory, thoracic and mediastinal disorders
Very common: cough (28.2%), dyspnoea (24.1%)

Common: differentiation syndrome

Vascular disorders
Very common: hypotension (17.2%)

Renal and urinary disorders
Common: acute kidney injury

* Investigations (frequency is based on central laboratory values)

Description of selected adverse reactions
Differentiation syndrome
Of 319 patients treated with Xospata in the clinical studies, 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 and clinical findings 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 Dosage/Administration and Warnings and precautions.

PRES
Of the 319 patients treated with Xospata in the clinical studies, 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 Dosage/Administration and Warnings and precautions).

QT prolongation
Of the 317 patients treated with gilteritinib at 120 mg with a post-baseline QTC value in clinical studies, 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 Dosage/Administration, Warnings and precautions and Properties/Effects). A concentration-related increase in change from baseline of QTcF (ΔQTcF) 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.

Reporting suspected adverse reactions after authorisation of the medicinal product is very important. It allows continued monitoring of the benefit/risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions online via the EIViS portal (Electronic Vigilance System). You can obtain information about this at www.swissmedic.ch.

Overdose

No cases of overdose have been reported.

Treatment

In the case of an overdose, stop treatment with gilteritinib and initiate general supportive measures taking into consideration the long half-life estimated at 113 hours.

Properties/Effects

ATC code

L01XE54

Mechanism of action

Gilteritinib is a FLT3 and AXL inhibitor. Gilteritinib inhibits FLT3 receptor signalling and proliferation in cells exogenously expressing FLT3 including FLT3-ITD, FLT3-D835Y, and FLT3-ITD-D835Y, and it induced apoptosis in leukemic cells expressing FLT3-ITD.

Pharmacodynamics

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

Clinical efficacy

ADMIRAL Study (2215-CL-0301)

The ADMIRAL study is a Phase 3, open-label, multicentre, randomized clinical study of adult patients with relapsed or refractory AML and a FLT3 mutation (FLT3-ITD, FLT3-TKD/D835 or FLT3-TKD/I836). FLT3 mutations were identified by a diagnostic test.

Patients included were relapsed or refractory after first line AML therapy and were stratified by response to prior AML treatment and preselected chemotherapy (i.e. high or low intensity). While the

study included patients with various AML-related cytogenetic abnormalities, patients with acute promyelocytic leukaemia (APL) or therapy-induced AML were excluded.
In this study, 371 patients were randomised 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 (day 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 µg/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).

Sixteen patients were randomised but not treated in the study (1 patient in the gilteritinib arm and 15 patients in the chemotherapy arm). 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 events, and dose increases were allowed for those patients who did not respond at the starting dose of 120 mg. Of the patients who were pre-selected to receive salvage chemotherapy, 60.5% were randomised to high intensity and 39.5% to low intensity. 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.
Patients receiving gilteritinib who had a haematopoietic stem cell transplantation (HSCT) were able to continue in the study. Patients administered the conditioning regimen for HSCT within one week of interruption of gilteritinib, resumed gilteritinib 30 to 90 days after HSCT if engraftment was successful, the patient did not have grade ≥2 acute graft versus host disease and was in composite complete remission (CRc).
Demographic information for the study population (N=371) is as follows: median age was 62 (19, 85), <65 years (58.2%) and ≥65 years (41.8%), 45.8% were male and 54.2% were female; ethics: 59.3% Caucasian, 27.5% Asian, 5.7% Black or African American, 0.3% native Hawaiian or other Pacific Islander, 7.3% other or unknown/missing.
Disease characteristics of study population: Baseline ECOG PS (Eastern Cooperative Oncology Group performance status) 0-1 (83.8%), ≥2 (16.2); relapsed AML (60.6%), refractory AML (39.4%); ITD alone (88.4%), TKD alone (8.4%), ITD and TKD (1.9%). Twelve percent of patients received previous treatment with another FLT3 inhibitor. A majority of patients had AML with intermediate risk

cytogenetics (73%), 10% had unfavourable, 1.3% had favourable and 15.6% had unclassified cytogenetics.
Response to prior therapy of study population: relapse within 6 months after allogeneic hematopoietic stem cell transplantation (HSCT): 12.9%, relapse after 6 months after allogeneic HSCT (6.7%), primary refractory without HSCT (39.4%), relapse within 6 months after composite complete remission (CRc) and no HSCT (27.2%) and relapse after 6 months after CRc and no HSCT (13.7%).

The primary efficacy endpoint for the final analysis was OS in the intent-to-treat (ITT) population, measured from the date of randomization until death by any cause (number of events analysed was 261). Patients randomized to the gilteritinib arm had significantly longer survival compared to the chemotherapy arm (hazard ratio (HR) 0.637; 95% confidence interval (CI) 0.490 – 0.830; 1 sided p-value: 0.0004). The median OS was 284 days (CI 234, 326) for patients receiving gilteritinib and 170 days (CI 142, 223) for those receiving chemotherapy. The 1 year survival rate was 37.1% (CI 30.7, 43.6) for patients receiving gilteritinib and 16.7% (9.9, 25) for patients receiving chemotherapy.
Efficacy was supported by the rate of complete remission (CR), complete remission with partial hematologic recovery (CRh), the duration of CR/CRh (DOR), and the rate of conversion from transfusion dependence to transfusion independence. CR for patients receiving gilteritinib was 21.1% (CI 16.1, 26.7) and for chemotherapy 10.5% (CI 5.7, 17.3), CRh for patients receiving gilteritinib was 13% (CI 9, 17.8) and for chemotherapy 4.8% (CI 1.8, 10.2), CR/CRh (DOR) for patients receiving gilteritinib was 336 days (CI 141, NR) and for chemotherapy 54 days (CI not estimable).
For patients who achieved a CR/CRh, the median time to first response was 112.5 days (range: 27 to 324 days) in the gilteritinib arm and 36 days (range: 29 to 78 days) in the salvage chemotherapy arm. The median time to best response of CR/CRh was 114.5 days (range: 27 to 486 days) in the gilteritinib arm and 36 days (range: 29 to 78 days) in the salvage chemotherapy arm.
Among the 178 patients with evaluable transfusion status post-baseline who were dependent on red blood cell (RBC) and/or platelet transfusions at baseline 68 (38.2%) became independent of RBC and platelet transfusions during 56-day post-baseline period. Of the 41 patients with evaluable transfusion status post-baseline who were independent of both RBC and platelet transfusions at baseline, 29 (70.7%) remained transfusion independent during any 56-day post-baseline period.

Pharmacokinetics

Absorption

Following oral administration of tablet formulations, peak gilteritinib concentrations are observed at a median T_{max} approximately between 4 and 6 hours in healthy volunteers and patients with relapsed or refractory AML. Median steady-state maximum concentration (C_{max}) is 282.0 ng·ml^{-1} (CV% = 50.8), and (area under the plasma concentration curve during 24-hours dosing interval) AUC_{0-24} is 6180 ng·ml^{-1}·h (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 coadministered 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 liters and 1100 liters, respectively. These data indicate gilteritinib distributes extensively outside of plasma, which may indicate extensive tissue distribution. *In vivo* plasma protein binding in human is approximately 90% and gilteritinib is primarily bound to albumin.

Metabolism

Based on *in vitro* data, gilteritinib is primarily metabolized 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.

Elimination

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. Approximately 16.4% of the total dose was excreted 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 $l \cdot h^{-1}$.

Linearity/non-linearity

Gilteritinib exhibits linear, dose-proportional pharmacokinetics in patients with relapsed or refractory AML at doses ranging from 20 mg to 450 mg administered once-daily.
Kinetics in specific patient groups

A population pharmacokinetic analysis was performed to evaluate the impact of intrinsic and extrinsic covariates on the predicted exposure of gilteritinib in patients with relapsed or refractory AML. Covariate analysis indicated that age (20 to 90 years), and body weight (36 to 157 kg) were statistically significant; however predicted change in gilteritinib exposure was less than 2 fold.

Hepatic impairment

The effect of hepatic impairment on gilteritinib pharmacokinetics has been 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. Gilteritinib has not been studied in patients with severe hepatic impairment (Child-Pugh Class C).
The effect of mild hepatic impairment 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 clinical assessment of the effect of renal functions on gilteritinib exposure was not conducted based on nonclinical and clinical data that indicate renal excretion is a minor elimination route. Although the population PK model included serum creatinine, a marker of renal function, as statistically significant covariate, the impact on gilteritinib exposure was less than 2-fold . Therefore, mild or moderate renal impairment is not expected to significantly affect gilteritinib exposure indicating dose adjustment is not warranted in patients with renal impairment. The effect of severe renal impairment on gilteritinib exposure has not been investigated.

Preclinical data

Safety pharmacology

In rats treated with gilteritinib, decreased urination at 30 mg/kg and higher and decreased defecation at 100 mg/kg were observed. In dogs, positive faecal occult blood at 10 mg/kg and higher, a decrease in the blood calcium concentration at 30 mg/kg, and salivation and an increase followed by a decrease in the blood calcium concentration at 100 mg/kg were observed. These changes were observed at plasma exposure levels similar to or less than clinical exposure levels.

Long-term toxicity (or repeat dose toxicity)

In the 1-week oral repeated dose toxicity study in rats, interstitial pneumonia in the lung and vacuolar changes in the rod-cone layer of the retina were observed at 30 mg/kg/day. Deaths occurred in the 13-week oral repeated dose toxicity study in rats at 20 mg/kg/day. Target-organ toxicity was identified in the gastrointestinal tract, lymphohematopoietic system, eye, lung, kidney and liver with plasma exposures below the clinical exposure. A no-observed adverse effect level (NOAEL) was not determined.
In the 4-week oral repeated dose toxicity study in dogs, mortality was observed at 10 mg/kg/day. Target-organ toxicity was identified in the gastrointestinal tract, lymphohematopoietic system, eye, epithelial tissue, kidney and liver (including gall bladder). The NOAEL was 1 mg/kg/day (approximately 0.08 times the RHD exposition based on AUC-mean value of 6943 ng.h/mL).
In the 13-week oral repeated dose toxicity study in dogs, mortality was observed at 5 mg/kg/day. Target-organ toxicity was identified in the gastrointestinal tract, epithelial tissue, liver (including gall bladder), kidney, urinary bladder, eye, lung and lymphohematopoietic system. The NOAEL was 1

mg/kg/day (approximately 0.06 times the RHD exposition based on AUC-mean value of 6943 ng.h/mL).
Reversibility of the changes most likely connected to the investigational medicinal product could be observed by the end of the 4-week recovery period.

Mutagenicity

Gilteritinib did not induce gene mutation in the *in vitro* reversion test in bacteria, and no chromosomal aberrations in mammalian cells. In the *in vivo* study in mice, gilteritinib treatment led to the induction of micronuclei.

Carcinogenicity

No carcinogenicity studies have been conducted.

Reproductive toxicity

Gilteritinib showed suppressed foetal growth, and induced embryo-foetal deaths and teratogenicity in the embryo-foetal development studies in rats at exposure levels similar to clinical exposure levels. Placental transfer of gilteritinib was shown in the rat resulting in transfer of radioactivity to the foetus similar to that observed in maternal plasma.
Gilteritinib was excreted into the milk of lactating rats with milk concentrations being higher than in maternal plasma. Gilteritinib was distributed to other tissues except the brain via breast milk in suckling rats.
Fertility studies in animals were not conducted for gilteritinib. However, degeneration and necrosis of germ cells and formation of spermatid giant cells in the testis, as well as single cell necrosis of the epididymal duct epithelia of the epididymal head occurred 12 days after administration in the 4-week oral repeated dose toxicity study in dogs at 10 mg/kg/day.
Other data

Phototoxicity

Gilteritinib showed no potential to induce phototoxicity to cultured mammalian cells.

Juvenile animals

In the pivotal juvenile animal toxicity study in rats, the minimum lethal dose level was 2.5 mg/kg/day which was much lower than that of adult rats (20 mg/kg/day). Juvenile animals thus appear to be more sensitive than adults. The gastrointestinal tract was identified as one of the target organs similar as in adult rats. The NOAEL was 1 mg/kg/day (approximately 0.003 times the RHD exposition based on AUC-mean value of 6943 ng.h/mL).

Other information

Shelf life

Do not use this medicine after the expiry date ("EXP") stated on the pack.

Special precautions for storage

Do not store above 30°C.
Store in the original packaging. Keep out of the reach of children.

Authorisation number

67211 (Swissmedic).

Packs

84 film-coated tablets, 40 mg each [A].

Marketing authorisation holder

Astellas Pharma AG, 8304 Wallisellen

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