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 https://www.tga.gov.au/reporting-problems.

AUSTRALIAN PRODUCT INFORMATION

IDHIFA (enasidenib) film-coated tablets

WARNING: DIFFERENTIATION SYNDROME
Patients treated with IDHIFA have experienced symptoms of differentiation syndrome, which can be fatal if not treated. Symptoms may include fever, dyspnoea, acute respiratory distress, pulmonary infiltrates, pleural or pericardial effusions, rapid weight gain or peripheral oedema, lymphadenopathy, bone pain, and hepatic, renal, or multi-organ dysfunction. If differentiation syndrome is suspected, initiate corticosteroid therapy and haemodynamic monitoring until symptom resolution. Please see section 4.2.3 for dose adjustment and section 4.4.1 for treatment information relating to differentiation syndrome.

1. NAME OF THE MEDICINE

Australian approved name: enasidenib

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each 50 mg film-coated tablet contains 50 mg of enasidenib, equivalent to 60 mg enasidenib mesilate.
Each 100 mg film-coated tablet contains 100 mg of enasidenib, equivalent to 120 mg enasidenib mesilate.

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

Description
Enasidenib is available as the mesilate salt and is practically insoluble (solubility ≤ 74 µg / mL) in aqueous solutions across physiological pH range (pH 1.2 and 7.4).

3. PHARMACEUTICAL FORM

Film-coated tablet.

Idhifa 50 mg film-coated tablets
Pale yellow to yellow oval-shaped film-coated tablet, 11.8 mm, engraved with "ENA" on one side and "50" on the other side.

Idhifa 100 mg film-coated tablets
Pale yellow to yellow capsule-shaped film-coated tablet, 15.2 mm, engraved with "ENA" on one side and "100" on the other side.

4. CLINICAL PARTICULARS

4.1. THERAPEUTIC INDICATIONS

This medicine has **Provisional Approval** in Australia for the treatment of adult patients with relapsed or refractory acute myeloid leukaemia who are ineligible for haematopoietic stem cell transplant, and who have an isocitrate dehydrogenase-2 (IDH2) mutation confirmed by a validated diagnostic test.

The decision to approve this indication has been made on the basis of preliminary clinical data from a Phase 1/2 clinical trial with a primary endpoint of overall response rate. An improvement in OS or PFS has not been established. The sponsor is required to submit further clinical data to confirm the efficacy and safety of the medicine.

4.2. DOSE AND METHOD OF ADMINISTRATION

Treatment with Idhifa must be initiated and monitored under the supervision of a registered Specialist Physician experienced in the management of haematological and oncological malignancies.

4.2.1. Dosage

The recommended starting dose of Idhifa is 100 mg taken orally once daily. It is recommended to treat patients for a minimum of 6 months to allow time for clinical response and to continue treatment until disease progression or unacceptable toxicity.

4.2.2. Method of administration

Idhifa film-coated tablets should be swallowed whole with a glass of water, and should not be chewed, split or crushed.

Administer Idhifa film-coated tablets orally with or without food about the same time each day. If a dose of Idhifa is vomited, 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.

4.2.3. Dosage Adjustments

Assess blood counts, including differential distribution, and blood chemistries for leukocytosis and tumour lysis syndrome prior to the initiation of Idhifa and monitor at a minimum of every 2 weeks for at least the first 3 months during treatment. Manage any abnormalities promptly.

Interrupt dosing or reduce dose for toxicities. See Table 1 for dose modification guidelines.

Table 1: Dose Modification Instructions for Idhifa-Related Toxicities

Adverse Reaction	Recommended Action
Differentiation syndrome	• If differentiation syndrome is suspected, administer systemic corticosteroids and initiate haemodynamic monitoring (see section 4.4). • Interrupt Idhifa if severe pulmonary symptoms requiring intubation or ventilator support, and / or renal dysfunction persist for more than 48 hours after initiation of corticosteroids (see section 4.4). • Resume Idhifa at the original dose when signs and symptoms improve to Grade 2* or lower.
Non-infectious leukocytosis [white blood cell (WBC) count > 30 x 10^9 / L]	• Initiate treatment with hydroxyurea, as per standard institutional practices. • Interrupt Idhifa if leukocytosis is not improved with hydroxyurea, and then resume Idhifa at 100 mg daily when WBC is < 30 x 10^9 / L.
Isolated hyperbilirubinemia> 3 times the upper limit of normal (ULN) sustained for ≥ 2 weeks	• Reduce Idhifa dose to 50 mg daily. • Resume Idhifa at 100 mg daily if bilirubin elevation resolves to < 2 x ULN.
Other Grade 3* or higher toxicity considered related to treatment including tumour lysis syndrome	• Interrupt Idhifa until toxicity resolves to Grade 2* or lower. • Resume Idhifa at 50 mg daily; may increase to 100 mg daily if toxicities resolve to Grade 1* or lower. • If Grade 3* or higher toxicity recurs, discontinue Idhifa.

* Grade 1 is mild, Grade 2 is moderate, Grade 3 is serious, Grade 4 is life threatening.

Special populations

Elderly

No dosage adjustment is required for Idhifa based on age. In the clinical study AG221-C-001, 60.3 % of 214 patients with relapsed or refractory AML with an IDH2 mutation were 65 years of age or older, while 23.8 % were 75 years of age or older. No overall differences in efficacy or safety were observed between patients aged 75 years or older, aged 65 years or older or younger patients.

Hepatic impairment

Idhifa has not been formally studied in patients with moderately or severely impaired hepatic function and there are no specific dose recommendations.

Renal impairment

Idhifa has not been studied in patients with renal impairment. Based on a population pharmacokinetic analysis, no dose adjustments are required for patients with renal impairment [creatinine clearance (CrCl) > 30 ml / min]. There is not enough data to draw a conclusion for patients with CrCl below 30 ml / min.

Paediatric population

The safety and efficacy of Idhifa in patients under 18 years of age has not been established.

4.3. CONTRAINDICATIONS

Hypersensitivity to enasidenib or to any of the excipients listed in section 6.1

4.4. SPECIAL WARNINGS AND PRECAUTIONS FOR USE

4.4.1. Differentiation Syndrome

In the clinical trial AG221-C-001, 12.6 % of patients treated with Idhifa experienced differentiation syndrome, which may be life-threatening or fatal if not treated. Differentiation syndrome is associated with rapid proliferation and differentiation of myeloid cells. While there is no diagnostic test for differentiation syndrome, symptoms reported by more than 50 % of patients included acute respiratory distress represented by dyspnoea and / or hypoxia and need for supplemental oxygen, fever, pulmonary infiltrates, and renal impairment. Less common symptoms may include pleural effusion, lymphadenopathy, bone pain, peripheral oedema with rapid weight gain, and pericardial effusion. Alanine aminotransferase (ALT) or aspartate aminotransferase (AST) elevation has been observed.

Differentiation syndrome has been observed with and without concomitant hyperleukocytosis, and as early as 1 day and up to 5 months after Idhifa initiation.

If differentiation syndrome is suspected, promptly initiate oral or intravenous corticosteroids (e.g., dexamethasone 10 mg every 12 hours) and haemodynamic monitoring until improvement (see section 4.2.3 Dose Adjustments). Taper corticosteroids only after resolution of symptoms. Symptoms of differentiation syndrome may recur with premature discontinuation of corticosteroid treatment. If severe pulmonary symptoms requiring intubation or ventilator support, and / or renal dysfunction persist for more than 48 hours after initiation of corticosteroids, interrupt Idhifa treatment until signs and symptoms are no longer severe. Hospitalisation for close observation and monitoring of patients with pulmonary and / or renal manifestation is recommended.

4.4.2. Noninfectious Leukocytosis

IDHIFA can induce myeloid proliferation resulting in a rapid increase in white blood cell count without evidence of infection or clinical signs of differentiation syndrome. In the pooled Phase 1/2 clinical trial, 13.6% of patients were reported with a treatment emergent adverse event of noninfectious leukocytosis. The majority of cases occurred within the first 3 months of treatment.

Non-infectious leukocytosis led to treatment interruption in 1.9 % and treatment discontinuation in 0.9 % of patients. No patients required dose reduction due to non-infectious leukocytosis.

Monitor blood count levels at baseline and at a minimum of every 2 weeks for at least the first 3 months during treatment. If noninfectious leukocytosis is suspected, initiate treatment with hydroxyurea, as per standard institutional practices (see section 4.2.3 Dose Adjustments).

4.4.3. Tumor Lysis Syndrome

Tumor lysis syndrome (TLS) can co-occur with differentiation syndrome. Six percent (6%) of patients treated with Idhifa experienced tumor lysis syndrome, usually occurring within the first 3 months of treatment. Signs and symptoms of tumor lysis included hyperuricemia and electrolyte abnormalities with or without serum creatinine elevation.

TLS led to treatment discontinuation in 0.9% of patients and treatment interruption in 0.5 %. No patients required dose reduction due to TLS.

Monitor blood count levels at baseline and at a minimum of every 2 weeks for at least the first 3 months during treatment. Signs and symptoms should be managed with adequate hydration and the use of hypouricemic agents (see section 4.2.3 Dose Adjustments).

4.4.4. Hyperbilirubinemia

Through inhibition of UGT1A1 enzyme involved with bilirubin metabolism, blood bilirubin elevation was very common, observed in 37.4% of enasidenib treated patients. Enasidenib caused dose dependent bilirubin elevation observed following start of treatment beginning from the first on treatment assessment and stabilizing after about 1 month of treatment. Bilirubin elevation led to treatment interruption in 4.2 %, treatment discontinuation in 1.4%, and dose modification or reduction in 0.5 % of patients.

Monitor liver function for bilirubin changes at baseline and in regular intervals. Blood bilirubin elevation was usually managed by treatment interruption or dose reduction (see section 4.2.3 Dose Adjustments).

4.5. INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No formal clinical drug interaction studies have been performed with Idhifa. *In vitro* data indicate potential inhibition of multiple CYPs (1A2, 2C8, 2C9, 2C19 and 2D6), UGT1A1, and transporters (P-glycoprotein, BCRP, OAT1, OATP1B1 and OATP1B3), as well as induction of CYP3A4, in patients.

Upon initiation or discontinuation of Idhifa in patients being treated with other medicinal products that are substrates of CYP enzymes, UGT1A1 (uridine diphosphate

glucuronosyltransferase) or transporters and have narrow therapeutic index, monitoring of the expected effect or drug concentration (if warranted) of the other medicinal product is recommended and the individual dose may be adjusted as needed (see section 5.2).

Co administration of Idhifa may decrease the concentrations of combined hormonal contraceptives. The clinical significance of this potential drug interaction is unknown at this time.

4.6. FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

No fertility studies have been performed with enasidenib. Impairment of male and female fertility in patients is suggested by findings in general repeat-dose toxicity studies in rats, with seminiferous tubular degeneration in the testes, hypospermia, epididymal luminal debris, decreased corpora lutea, increased atretic follicles in the ovaries, and disruption of oestrus cycling observed at exposure levels (plasma AUC) comparable to that of patients at the maximum recommended human dose. It is not known whether these effects on fertility are reversible.

Use in pregnancy (Category D)

There are no adequate and well controlled studies of Idhifa in pregnant women. Enasidenib can cause embryofetal harm when administered to a pregnant woman based on adverse findings in animal studies.

Placental transfer of enasidenib and its major circulating metabolite (AGI-16903) was demonstrated in rats and rabbits. Administration of enasidenib during the period of organogenesis caused embryofetal lethality (increased post-implantation loss and decreased live litter size), reduced fetal weight and impaired fetal ossification in rats at an oral dose of 30 mg/kg twice daily, and abortions in rabbits at ≥5 mg/kg/day. These doses were maternally toxic, but associated with exposure levels in animals that were only marginally above (1.6-times higher in rats) or well below (~15-times lower) the plasma AUC in patients at the maximum recommended human dose.

Use Idhifa during pregnancy only if the potential benefit to the patient justifies the potential risk to the fetus. If a patient or partner becomes pregnant while taking Idhifa, advise the patient of the potential risk to a fetus.

Females of reproductive potential are advised to use effective contraception during treatment with Idhifa and for at least 2 monthly cycles after the last dose of Idhifa. Males with female partners of reproductive potential are advised to use effective contraception during treatment

with Idhifa and for at least 2 monthly cycles after the last dose of the medicine. Idhifa may affect the effectiveness of combined hormonal contraceptives (see section 4.5).

A pregnancy test should be conducted for females of reproductive potential prior to starting treatment with Idhifa.

Use in lactation

It is unknown whether enasidenib or its metabolites are excreted in human milk. Because of the potential for adverse reactions in breastfed infants, women should be advised not to breastfeed during treatment with Idhifa and for at least 2 monthly cycles after the last dose.

4.7. EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

No studies on the effects of enasidenib on the ability to drive and the use of machines have been performed.

4.8. ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The safety evaluation of single-agent Idhifa is based on the clinical study AG221-C-001, in which 214 patients with relapsed or refractory AML with an IDH2 mutation were assigned to receive 100 mg daily. The median duration of exposure to enasidenib was 5.4 months (range 0.4 to 34.2).

4.8.1. Tabulated Summary of Adverse Events

Among the Treatment-Emergent Adverse Events (TEAEs) that were reported for ≥ 20% of subjects were disorders commonly observed in patients with AML and other hematologic malignancies such as anemia, febrile neutropenia, and thrombocytopenia; associated infections and respiratory disorders, including pneumonia with dyspnea and cough; and general disorders, including fatigue, peripheral oedema, pyrexia; and also hypokalemia, and headache. Constipation was a common TEAE that occurred at a rate expected in this age group.

Table 2: Treatment-emergent Adverse Events (grades 1-5) Reported in ≥ 20% of Subjects with R / R AML who received a Total Daily Dose of 100 mg in Phase 1/2 of Study AG221-C-001.

System Organ Class Preferred Term	R / R AML 100 mg Daily (N = 214)				
	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Blood and Lymphatic System Disorders					
Anaemia	2 (0.9)	15 (7.0)	53 (24.8)	3 (1.4)	0

System Organ Class Preferred Term	R / R AML 100 mg Daily (N = 214)				
	Grade 1 n (%)	Grade 2 n (%)	Grade 3 n (%)	Grade 4 n (%)	Grade 5 n (%)
Febrile Neutropenia	2 (0.9)	1 (0.5)	69 (32.2)	7 (3.3)	0
Leukocytosis	7 (3.3)	21 (9.8)	16 (7.5)	5 (2.3)	1 (0.5)
Thrombocytopenia	3 (1.4)	3 (1.4)	6 (2.8)	33 (15.4)	0
Gastrointestinal Disorders					
Constipation	39 (18.2)	16 (7.5)	0	0	0
Diarrhoea	46 (21.5)	30 (14.0)	10 (4.7)	0	0
Nausea	58 (27.1)	39 (18.2)	11 (5.1)	0	0
Vomiting	48 (22.4)	22 (10.3)	3 (1.4)	1 (0.5)	0
General Disorders and Administration Site Conditions					
Fatigue	30 (14.0)	46 (21.5)	17 (7.9)	0	0
Peripheral oedema	37 (17.3)	20 (9.3)	3 (1.4)	0	0
Pyrexia	33 (15.4)	22 (10.3)	9 (4.2)	0	0
Infections and Infestations					
Pneumonia	2 (0.9)	10 (4.7)	28 (13.1)	4 (1.9)	3 (1.4)
Investigations					
Blood Bilirubin Increased	15 (7.0)	32 (15.0)	18 (8.4)	0	0
Metabolism and Nutrition Disorders					
Decreased Appetite	30 (14.0)	34 (15.9)	9 (4.2)	0	0
Hypokalaemia	23 (10.7)	15 (7.0)	21 (9.8)	0	0
Nervous System Disorders					
Headache	39 (18.2)	9 (4.2)	2 (0.9)	0	0
Respiratory, Thoracic and Mediastinal Disorders					
Cough	62 (29.0)	8 (3.7)	0	0	0
Dyspnoea	28 (13.1)	25 (11.7)	16 (7.5)	0	0

AML = acute myelogenous leukemia, R/R = relapsed or refractory

4.8.2. Tabulated summary of drug adverse reactions

The most common adverse reactions (≥ 20 %) were nausea, vomiting, diarrhoea, elevated bilirubin, and decreased appetite (see Table 3).

The most frequent serious events determined to be expected adverse reactions to Idhifa were differentiation syndrome (11.2 %), non-infectious leukocytosis (6.5 %), nausea and / or vomiting (5.6 %), tumour lysis syndrome (4.7 %), diarrhoea (4.2 %), decreased appetite (2.8 %), and increased bilirubin levels (1.4 %).

The most common adverse events determined to be expected reactions to Idhifa and leading to dose interruption were differentiation syndrome (5.6 %) and elevated bilirubin (4.2 %); dose reductions were differentiation syndrome (0.5 %) and increased serum bilirubin (0.5 %); permanent discontinuations were elevated bilirubin (1.4 %), differentiation syndrome (0.9 %), tumour lysis syndrome (0.9 %), and non-infectious leukocytosis (0.5 %).

The table below contains the adverse reactions for which a causal relationship with Idhifa treatment could reasonably be established based on the observations during the pivotal clinical study. Frequencies are defined as: 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) and very rare (< 1 / 10,000). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness.

Table 3: ADRs Reported in Patients with R / R AML with IDH2 Mutation Treated with Idhifa at 100 mg Dose

Frequency	All ADRs	Grade 3 and 4 ADRs
Blood and lymphatic system disorders		
Very common	Non-infectious leucocytosis[1]; Differentiation syndrome[a]	
Common		Non-infectious leucocytosis[1]; Differentiation syndrome[a]
Metabolism and nutrition disorders		
Very common	Decreased appetite	
Common	Tumour lysis syndrome[2]	Tumour lysis syndrome[2]; Decreased appetite
Nervous system disorders		
Very common	Dysgeusia	
Gastrointestinal disorders		
Very common	Nausea; Diarrhoea; Vomiting	
Common		Nausea; Diarrhoea; Vomiting
Hepatobiliary disorders		
Very common	Blood bilirubin increased[3]	
Common		Blood bilirubin increased[3]

[a] MedDRA preferred term of acute promyelocytic leukaemia differentiation syndrome.
[1] Refer to section 4.4.2
[2] Refer to section 4.4.3
[3] Refer to section 4.4.4

Gilbert's Syndrome

Patients with congenital UGT1A1 deficiency (Gilbert´s Syndrome) who received Idhifa experienced a more rapid increase in bilirubin values, as compared to patients without this mutation and more frequently experienced bilirubin increase > 3 ULN. Starting dose adjustment is not recommended for patients with Gilbert's syndrome. Dose can be reduced for higher bilirubin levels (see section 4.2).

Gastrointestinal Disturbance

Adverse reactions such as nausea, diarrhoea, vomiting, and other reactions such as dysgeusia and decreased appetite were usually mild to moderate in severity, did not lead to treatment discontinuation and infrequently required dose reduction or interruption. These reactions were not dose related and generally occurred (approximately 50 %) during the first month of treatment and often resolved with continued treatment.

Elderly Patients

In the clinical trial (Study AG221-C-001), 60.3% of R / R AML patients with IDH2 mutation (N=214) were 65 years of age or older, and 23.8% were 75 years of age or older. No overall differences in safety were observed between patients ≥65 years and patients younger than 65 years of age.

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 http://www.tga.gov.au/reporting-problems

4.9. OVERDOSE

In the event of overdose, monitor patients for adverse reactions and provide appropriate supportive care. It is not known if enasidenib or its metabolites are removed by dialysis.

For information on the management of overdose, contact the Poison Information Centre on 131126 (Australia).

5. PHARMACOLOGICAL PROPERTIES

5.1. PHARMACODYNAMIC PROPERTIES

Pharmacotherapeutic group: {group}, ATC code: L01XX59

Mechanism of action

Enasidenib is a small molecule inhibitor of the isocitrate dehydrogenase 2 (IDH2) enzyme. Mutant IDH2 variants R140Q, R172S and R172K are selectively targeted by enasidenib, with the drug's potency against these approximately 40 times greater than against wildtype IDH2. Such IDH2 mutations confer a gain of function, whereby the aberrant enzyme catalyses the production of the oncogenic metabolite 2-hydroxyglutarate (2-HG). 2-HG induces a block of cell differentiation by inhibiting the activity of chromatin-modifying histone and DNA demethylases. Inhibition of the IDH2 mutant variants R140Q and R172S/K by enasidenib, led to decreased 2-HG levels and induction of myeloid differentiation *in vitro* and *in vivo* in human xenograft models of IDH2-mutated AML.

In patients with IDH2 mutated AML, enasidenib decreased 2-HG levels in blood, releasing the differentiation block of leukaemic cells and resulting in increased percentages of mature myeloid cells in bone marrow. Enasidenib reduced blast counts in a subset of patients and was not myelosuppressive.

Cardiac Electrophysiology

The potential for QTc prolongation with enasidenib was evaluated in an open-label study in patients with advanced haematological malignancies with an IDH2 mutation. Based on the QTc data for a single dose of 50 mg to 650 mg and multiple doses of 100 mg daily in the fasted state, no large mean changes in the QTc interval (> 20 ms) were observed following treatment with enasidenib.

Clinical trials

Idhifa is approved under the 'Provisional Registration Pathway'. Data provided in this section are provisional and the sponsor is required to submit Phase 3 confirmatory data to further support the provisionally approved indication.

The efficacy of enasidenib was established in an open-label, single-arm, international, multicenter, clinical trial of 214 patients with relapsed or refractory acute myeloid leukemia with an IDH2 mutation who received a 100-mg daily dose. IDH2 mutations were identified by a local diagnostic test and retrospectively confirmed by the Abbott RealTi*m*e™ IDH2 assay, or prospectively identified by the Abbott RealTi*m*e™ IDH2 assay. Enasidenib was given until disease progression or unacceptable toxicity. Dose reductions were allowed to manage adverse events.

The baseline demographic and disease characteristics are shown in the following table.

Table 4: Baseline Demographic and Disease Characteristics in Patients with Relapsed or Refractory AML and IDH2 Mutation

Demographic and Disease Characteristics	**Enasidenib (100 mg daily) N=214**
Demographics	
Age (Years) Median (Min, Max)	68.0 (19.0, 100.0)
Age Categories, n (%)	
<65 years	85 (39.7)
≥65 years to <75 years	78 (36.4)
≥75 years	51 (23.8)
Sex, n (%)	
Male	109 (50.9)
Female	105 (49.1)
Race, n (%)	
White	164 (76.6)
Black	12 (5.6)
Asian	1 (0.5)
Native Hawaiian/Other Pacific Islander	1 (0.5)
Other / Not Provided	36 (16.8)
Disease Characteristics, n (%)	

Demographic and Disease Characteristics	Enasidenib (100 mg daily) N=214
ECOG PS [a], n (%)	
0	49 (22.9)
1	132 (61.7)
2	32 (15.0)
Relapsed AML, n (%)	130 (60.7)
Refractory AML, n (%)	84 (39.3)
IDH2 Mutation [b], n (%)	
R140	162 (75.7)
R172	51 (23.8)
Missing[c]	1 (0.5)
Time from Initial AML Diagnosis (months)	10.4
Median (min, max) (179 patients)	(1.2, 129.1)
Cytogenetic Risk Status, n (%)	
Intermediate	108 (50.5)
Poor	55 (25.7)
Missing /Failure	51 (23.8)
Prior Stem Cell Transplantation for AML, n (%)	29 (13.6)
Transfusion Dependent at Baseline [d], n (%)	169 (79.0)
Transfusion Dependent at Baseline [d]	
Red Blood Cells	153 (71.5)
Median number of transfusions	3.0
Median number of RBC units	5.0
Platelets	132 (61.7)
Median number of transfusions	4.5
Median number of platelet units	5.0
Number of Prior Anticancer Regimens, n (%) [e]	
1	101 (47.2)
2	65 (30.4)
≥3	48 (22.4)
Median number of prior therapies (min, max)	2.0 (1.0, 5.0)

ECOG PS: *Eastern Cooperative Oncology Group Performance Status.*

[a] 1 patient had missing baseline ECOG PS.

[b] For 3 patients with different mutations detected in bone marrow compared to blood, the result of blood is reported.

[c] The subject marked as missing had an IDH2 R140Q mutation and should have been included in the R140 group.

[d] Patients were defined as transfusion dependent at baseline if they received any red blood cell or platelet transfusions within the 8-week baseline period.

[e] Includes intensive and/or nonintensive therapies.

The primary efficacy endpoint for the AG221-C001 study was overall response rate (ORR). ORR was based on investigator assessment and was defined as the rate of responses, including complete remission (CR), CR with incomplete neutrophil recovery (CRi), CR with incomplete platelet recovery (CRp), partial remission (PR), and morphologic leukaemia-free state (MLFS).

The key secondary endpoints of the study included CR rate, CR + CRi / CRp, duration of response, OS, event-free survival, time to response, time to best response, time to complete response and transfusion requirements.

The efficacy results are shown in Table 5. The median follow-up time was 7.8 months (range 0.4 to 43.6).

Table 5: Efficacy Results in Patients with Relapsed or Refractory AML with an IDH2 mutation

Endpoint	**Idhifa (100 mg daily) N=214**
Overall Response Rate (CR + CRi + CRp + PR + MLFS), n (%) 95 % CI Median DOR (months) 95 % CI	83 (38.8) (32.2, 45.7) 5.6 (3.8, 7.4)
CR n (%) 95 % CI Median DOR in subjects with CR (months) 95 % CI	42 (19.6) (14.5, 25.6) 7.4 (6.5, 16.3)
CRi / CRp n (%) 95% CI Median DOR (months) 95% CI	17 (7.9) (4.7, 12.4) 4.6 (1.5, NA)
CR + CRi / CRp, n (%) 95 % CI KM Median DOR in subjects with CR + CRi / CRp (months) 95 % CI	62 (29.0) (23.0, 35.5) 6.7 (5.3, 9.7)
Non-CR Response PR MLFS	 9 (4.2) 12 (5.6)
Non-Responders SD PD	 98 (45.8) 19 (8.9)

Endpoint	Idhifa (100 mg daily) N=214
Median Overall Survival (months) 95 % CI	8.8 (7.7, 9.6)

CI = confidence interval; CR = complete remission; CRi = complete remission with incomplete haematological recovery; CRp = complete remission with incomplete platelet recovery; DOR = duration of response; MLFS = morphologic leukaemia-free state; ORR = overall response rate; PD = progressive disease; PR = partial remission; SD = stable disease.

Consistent with the mechanism of action, treatment with Idhifa was associated with leukaemic cell differentiation leading to an improvement in haematopoiesis and durable responses, including CR.

The median time to first response was 1.9 months while the median time to best response was 3.7 months. Of the subjects who achieved a best response of CR, 19.0 % achieved a CR by Cycle 3, 59.5 % by Cycle 5, and 83.3 % by Cycle 7. The median duration of response for subjects who achieved CR was 7.4 months (range: 6.5 to 16.3).

Transfusion independence was defined as a period of at least 56 consecutive days during which no transfusions (red blood cells or platelets) were administered. Among the 153 patients (71.5 %) who were dependent on red blood cell (RBC) transfusions at baseline, 66 patients (43.1 %) became RBC transfusion independent (TI). In addition, of the 61 patients who were RBC-TI at baseline, 40 (65.6 %) remained TI. One hundred and six patients (49.5%) remained or became RBC-TI while receiving Idhifa treatment.

Similarly, of the 132 patients (61.7 %) who were dependent on platelet transfusions at baseline, 53 (40.2 %) became TI. Eighty-two patients were platelet-TI at baseline, of which 62 (75.6 %) remained TI. One hundred and fifteen patients (53.7%) remained or became platelet-TI while receiving Idhifa treatment.

Transfusion independence was maintained / achieved in patients that did not achieve a full CR. In the case of RBC, in non-CR responders (i.e. patients with Cri / CRp / PR / MLFS), transfusion independence was achieved in 57.6 % of the patients and was maintained in 87.5 %. In the case of platelets, transfusion independence was achieved in 60.9 % of patients and maintained in 83.3 %.

5.2. PHARMACOKINETIC PROPERTIES

The pharmacokinetics of enasidenib were studied in healthy subjects and patients with advanced hematologic malignancies with an IDH2 mutation.

Absorption

The peak plasma concentration (C_{max}) was 1.4 µg / ml [% coefficient of variation (CV%) 50.2] after a single dose of 100 mg, and 13.1 µg / ml (CV% 44.8) at steady state for 100 mg daily. Steady-state plasma levels were reached within 29 days of once-daily dosing. Accumulation is approximately 10-fold when administered once daily.

In healthy volunteers, the absolute bioavailability after a 100 mg oral dose of Idhifa is approximately 57 %.

After a single oral dose, the median time to C_{max} (T_{max}) is 4 hours in patients with advanced haematological malignancies.

Co-administration of Idhifa (single 100 mg dose) was evaluated in fasted versus fed conditions in 30 healthy male subjects. There was an approximate 50% increase in AUC_{0-t} and AUC_{0-}

5.3. PRECLINICAL SAFETY DATA

Genotoxicity

Enasidenib was not mutagenic in bacterial reverse mutation assays and was not clastogenic *in vitro* in Chinese hamster ovary cells or *in vivo* in the rat bone marrow micronucleus test.

Carcinogenicity

Carcinogenicity studies have not been performed with enasidenib.

6. PHARMACEUTICAL PARTICULARS

6.1. LIST OF EXCIPIENTS

Tablet contents
Microcrystalline cellulose
Sodium starch glycollate
Hydroxypropyl cellulose
Colloidal silicon dioxide
Magnesium stearate
Hypromellose acetate succinate
Sodium lauryl sulphate (E487)

Tablet film coating

Polyvinyl alcohol
Titanium dioxide (E171)
Polyethylene glycol 3350 (Macrogol 3350 / PEG 3350)
Purified talc
Iron oxide yellow (E172)

6.2. INCOMPATIBILITIES

Not applicable.

6.3. SHELF LIFE

2 years.

6.4. SPECIAL PRECAUTIONS FOR STORAGE

Store below 25°C. Keep container tightly closed. Store in original container. Protect from moisture.

6.5. NATURE AND CONTENTS OF CONTAINER

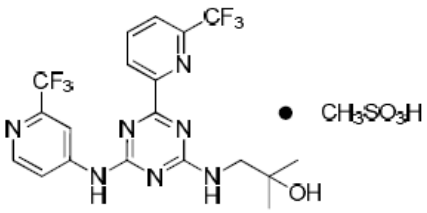
Idhifa film-coated tablets are packaged in high density polyethylene (HDPE) bottles with a desiccant, induction seal (tamper evident), and child resistant cap.

Idhifa 50 mg and 100 mg film-coated tablets are available in packs of 30 tablets each.

6.6. SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7. PHYSICOCHEMICAL PROPERTIES

Molecular formula:	$C_{20}H_{21}F_6N_7O_4S$
Molecular weight:	569.48 g/mol
Chemical name:	2-methyl-1-[(4-[6-(trifluoromethyl)pyridin-2-yl]-6-{[2-(trifluoromethyl)pyridin-4-yl]amino}-1,3,5-triazin-2-yl)amino]propan-2-ol methanesulfonate.
Chemical Abstract Service (CAS) registry number:	1650550-25-6
Chemical structure:	

7. MEDICINE SCHEDULE (POISONS STANDARD)

Schedule 4 (Prescription Only Medicine)

8. SPONSOR

Sponsored in Australia by:

Celgene Pty Limited
Level 15, 60 City Road
Southbank VIC 3006
Australia.
Telephone: 1800 CELGENE (1800 235 4363)

9. DATE OF FIRST APPROVAL

17 January 2020

10. DATE OF REVISION

N/A

Summary table of changes

Section Changed	Summary of new information
N/A	First version