To be sold by retail on the prescription of an Oncologist only.

Azacitidine Tablets 200 mg /300 mg

Xpreza®
एक्सप्रिजा

1. Generic Name
Azacitidine tablets 200 mg / 300 mg

2. Qualitative and quantitative composition
Azacitidine tablets 200 mg
Each film coated tablet contains
Azacitidine I.P.....…… 200 mg
Excipients…….....…… q.s.
Colour: Titanium Dioxide I.P. and Ferric Oxide (Red) USP/NF
Azacitidine tablets 300 mg
Each film coated tablet contains
Azacitidine I.P.....…… 300 mg
Excipients…….....…… q.s.
Colour: Titanium Dioxide I.P. and Ferric Oxide (Red) USP/NF

3. Dosage form and strength
Dosage form: Solid dosage form, Oral tablets
Strength: 200 mg / 300 mg

4. Clinical particulars
4.1 Therapeutic indication
Azacitidine tablets is indicated For continued treatment of patients with acute myeloid leukemia (AML) who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.

4.2 Posology and method of administration
Azacitidine tablets treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic medicinal products.
Patients are to be treated with an anti-emetic 30 minutes prior to each dose of Azacitidine tablets for the first 2 treatment cycles. Anti-emetic prophylaxis may be omitted after 2 cycles, if there has been no nausea and vomiting.

Posology
The recommended dose is 300 mg azacitidine orally once daily. Each repeated cycle consists of a treatment period of 14 days followed by a treatment free period of 14 days (28-day treatment cycle).
Azacitidine tablets treatment should be continued until no more than 15% blasts are observed in peripheral blood or bone marrow or until unacceptable toxicity (see dose schedule modification guidance for disease relapse).
Azacitidine tablets should not be used interchangeably with injectable azacitidine due to differences in the exposure, dose and schedule of treatment. Healthcare professionals are recommended to verify the name of the medicinal product, dose and administration route.
Laboratory tests
Complete blood counts should be performed prior to initiation of therapy. Complete blood count monitoring is also recommended every other week for the first 2 cycles (56 days), every other week for the next 2 cycles after dose adjustment, and monthly thereafter, prior to the start of subsequent cycles of treatment .
Dose schedule modification for AML disease relapse
In the case of disease relapse, with 5% to 15% blasts in peripheral blood or bone marrow, in conjunction with a clinical assessment, an extension of the dosing schedule from 14 to 21 days of repeated 28-day cycles should be considered. Dosing should not exceed 21 days during any 28-day period. Azacitidine tablets should be discontinued if more than 15% blasts are observed in either the peripheral blood or bone marrow or at the physician's discretion.
Dose adjustment for adverse reactions
Dose modification guidelines for haematologic and non-haematologic adverse reactions are recommended based on clinical and laboratory findings (see Table 1).

Criteria	Recommended action
Grade 4 neutropenia or Grade 3 neutropenia with fever	First occurrence • Interrupt Azacitidine tablets. Resume the treatment cycle at the same dose once neutrophils return to Grade 2 or lower. • Use supportive care such as granulocyte colony stimulating factor (GCSF), as clinically indicated . Occurrence in 2 consecutive cycles • Interrupt Azacitidine tablets. Resume the treatment cycle at a reduced dose of 200 mg after neutrophils return to Grade 2 or lower. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or re-occurs after dose and schedule reduction, discontinue Azacitidine tablets. • Use supportive care such as GCSF, as clinically indicated.
Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding	First occurrence • Interrupt Azacitidine tablets. Resume the treatment cycle at the same dose once platelets return to Grade 2 or lower. Occurrence in 2 consecutive cycles • Interrupt Azacitidine tablets. Resume the treatment cycle at a reduced dose of 200 mg after platelets return to Grade 2 or lower. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or re-occurs after dose and schedule reduction, discontinue Azacitidine tablets
Grade 3 or higher nausea, vomiting or diarrhoea	Interrupt Azacitidine tablets. Resume the treatment cycle at the same dose once toxicity has resolved to Grade 1 or lower. • Use supportive care such as anti-emetic therapy and treat diarrhoea at the onset of symptoms. • If event re-occurs, interrupt dose until resolved to Grade 1 or lower and reduce the dose to 200 mg. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or re-occurs after dose and schedule reduction, discontinue Azacitidine tablets
Other Grade 3 or higher non-haematological events	• Interrupt Azacitidine tablets and provide medical support according to local recommendations. Resume the treatment cycle at the same dose once toxicity has resolved to Grade 1 or lower. • If the toxicity re-occurs, interrupt Azacitidine tablets until resolved to Grade 1 or lower and reduce dose to 200 mg. • If a patient continues to experience the toxicity after dose reduction, reduce the treatment duration by 7 days. • If the toxicity continues or re-occurs after dose and schedule reduction, discontinue Azacitidine tablets

* Grade 1 is mild, Grade 2 is moderate, Grade 3 is severe, Grade 4 is life-threatening. Toxicity grades are in accordance with National Cancer Institute Common Terminology Criteria for Adverse Events Version 4.3 (NCI-CTCAE v4.3).
Missed or delayed doses
If a dose of Azacitidine tablets is missed, or not taken at the usual time, the dose should be taken as soon as possible on the same day. Then, the next scheduled dose should be taken at the normal time the following day. Two doses should not be taken on the same day. If a dose is vomited, another dose must not be taken on the same day. Instead return to the normal time of dose administration the following day.
Special populations
Elderly patients No dose adjustments are recommended for patients over 65 years of age.
Renal impairment
Azacitidine tablets can be administered to patients with mild, moderate or severe renal impairment without initial dose adjustment.
Hepatic impairment
No dose adjustment is recommended for patients with mild hepatic impairment (total bilirubin (BIL) ≤ upper limit of normal (ULN) and aspartate aminotransferase (AST) > ULN, or BIL 1 to 1.5 × ULN and any AST) .
Patients with moderate (BIL > 1.5 to 3 × ULN) and severe hepatic impairment (BIL > 3 × ULN) should be monitored more frequently for adverse reactions and appropriate dose adjustment should be made (see Table 1).
Paediatric population
The safety and efficacy of Azacitidine tablets in children and adolescents below 18 years have not been established. No data are available.
Method of administration
Azacitidine tablets is for oral use.
Azacitidine tablets can be taken with or without food. The tablets should be swallowed whole with a glass of water at about the same time each day. They should not be split, crushed, dissolved or chewed .

4.3 Contraindications
Hypersensitivity to the active substance or to any of the excipients listed in section 8.
Breast-feeding

4.4 Special warnings and precaution for use
Haematological toxicity
Treatment with Azacitidine tablets can be associated with neutropenia, thrombocytopenia and febrile neutropenia. Interruption, reduction or discontinuation of Azacitidine tablets may be necessary to manage haematological toxicities. Patients should be advised to promptly report febrile episodes. Patients with low platelet counts should be advised to report early signs or symptoms of bleeding. Supportive care such as antibiotics and/or antipyretics for management of infection/fever and GCSF for neutropenia should be provided based on individual patient characteristics, treatment response and according to the current clinical guidelines. *Gastrointestinal toxicity*
Gastrointestinal toxicities were the most frequent adverse reactions in patients treated with Azacitidine tablets. Patients should be administered prophylactic anti-emetic therapy for the first 2 cycles of Azacitidine tablets treatment. Diarrhoea should be treated promptly at the onset of symptoms. Interruption, reduction or discontinuation of Azacitidine tablets may be necessary to manage gastrointestinal toxicities.
Women of childbearing potential/Contraception in males and females
Women of childbearing potential have to use effective contraception during and up to 6 months after treatment. Men have to use effective contraception during and up to 3 months after treatment .
Lactose intolerance
Azacitidine tablets tablets contain lactose. Patients with rare hereditary problems of galactose intolerance, total lactase deficiency or glucose-galactose malabsorption should not take this medicinal product.
Sodium content
This medicinal product contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

4.5 Drugs interactions
No formal clinical drug-drug interaction studies with azacitidine have been conducted.
In case of concomitant administration with other antineoplastic agents, caution and monitoring is recommended as an antagonistic, additive, or synergistic pharmacodynamic effect cannot be excluded. These effects may be dependent on the dose, sequence and schedule of administration.
Azacitidine tablets exposure was minimally affected when co-administered with a proton pump inhibitor (omeprazole). Therefore, dose modification is not required when Azacitidine tablets is co-administered with proton pump inhibitors or other pH modifiers.
An in vitro study of azacitidine with human liver fractions indicated that azacitidine was not metabolised by cytochrome P450 isoforms (CYPs). Therefore, interactions with CYP inducers or inhibitors are considered unlikely .
Clinically relevant inhibitory or inductive effects of azacitidine on the metabolism of cytochrome P450 substrates are unlikely. No clinically relevant drug-drug interactions are expected when Azacitidine tablets is co-administered with substrates of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporters (OAT) OAT1 and OAT3, organic anion 6 transporting polypeptides (OATP) OATP1B1 and OATP1B3, or organic cation transporter (OCT) OCT2.
Azacitidine is not a substrate of P-gp, therefore it is not expected to interact with P-gp inducers or inhibitors..

4.6 Use in special populations
Women of childbearing potential/Contraception in males and females
Women of childbearing potential have to use effective contraception during and up to 6 months after treatment. Men should be advised not to father a child while receiving treatment and have to use effective contraception during and up to 3 months after treatment .
Pregnancy
There are no adequate data from the use of Azacitidine tablets in pregnant women. Studies in mice and rats have shown reproductive and developmental toxicity. The potential risk for humans is unknown. Based on results from animal studies and its mechanism of action, Azacitidine tablets is not recommended during pregnancy (especially during the first trimester, unless clearly necessary) and in women of childbearing potential not using contraception. The advantages of treatment should be weighed against the possible risk for the foetus in every individual case. If a patient or partner becomes pregnant while taking Azacitidine tablets, the patient should be informed of the potential risk to the foetus. Breast-feeding
It is unknown whether azacitidine or its metabolites are excreted in human milk. Due to the potential serious adverse reactions in the breastfed child, breast-feeding is contraindicated during Azacitidine tablets therapy .
Fertility
There are no human data on the effect of azacitidine on fertility. In animals, adverse effects of azacitidine on male fertility have been documented . Patients who wish to conceive a child should be advised to seek reproductive counselling and cryo-conservation of either the ovum or sperm prior to starting Azacitidine tablets treatment.

4.7 Effects on ability to drive and use machines
Azacitidine tablets has minor influence on the ability to drive and use machines. Fatigue has been reported with the use of Azacitidine tablets. Therefore, caution is recommended when driving or operating machines.

4.8 Undesirable effects
Summary of the safety profile
The most common adverse reactions are nausea (64.8%), vomiting (59.7%), diarrhoea (50.4%), neutropenia (44.5%), fatigue/asthenia (44.1%)[5] , constipation (38.6%), thrombocytopenia (33.5%), abdominal pain (21.6%)[4] , respiratory tract infection (17%)[2] , arthralgia (13.6%), decreased appetite (12.7%), febrile neutropenia (11.9%), back pain (11.9%), leucopenia (10.6%), pain in extremity (10.6%) and pneumonia (10.2%)[1].
Serious adverse reactions occurred in 16.1% of patients receiving Azacitidine tablets. The most common serious adverse reactions are febrile neutropenia (6.8%) and pneumonia (5.1%)[1].
Permanent discontinuation of Azacitidine tablets due to an adverse reaction occurred in 6.8% of patients. The most common adverse reactions requiring permanent discontinuation are nausea (2.1%), diarrhoea (1.7%), and vomiting (1.3%).
Dose interruptions due to an adverse reaction occurred in 36.4% of patients who received Azacitidine tablets. Adverse reactions requiring dose interruption include neutropenia (19.9%), thrombocytopenia (8.5%), nausea (5.5%), diarrhoea (4.2%), vomiting (3.8%), pneumonia (3.4%)[1] , leucopenia (2.5%), febrile neutropenia (2.1%), and abdominal pain (2.1%)[4] .
Dose reductions due to an adverse reaction period occurred in 14% of patients who received Azacitidine tablets. Adverse reactions requiring dose reduction included neutropenia (5.5%), diarrhoea (3.4%), thrombocytopenia (1.7%), and nausea (1.7%).
Tabulated list of adverse reactions
Table 2 presents the frequency category of ADRs reported in the pivotal Phase 3 study with Azacitidine tablets. A total of 236 patients received Azacitidine tablets. The median treatment duration was 11.6 months (range: 0.5 to 74.3 months) for Azacitidine tablets arm.
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); very rare (< 1/10,000); not known (cannot be estimated from the available data). Within each frequency grouping, undesirable effects are presented in order of decreasing seriousness. Adverse reactions are presented in the table below according to the highest frequency observed

System organ class	All gradesa frequency
Infections and infestations	Very common Pneumonia [1, 6], respiratory tract infection [2] Common Influenza, urinary tract infection [3] , bronchitis, rhinitis
Blood and lymphatic system disorders	Very common Neutropenia, thrombocytopenia[6] , febrile neutropenia[6], leucopenia
Metabolism and nutrition disorders	Very common Decreased appetite
Psychiatric disorders	Common Anxiety
Gastrointestinal disorders	Very common Nausea, vomiting, diarrhoea, constipation, abdominal pain[4]
Musculoskeletal and connective tissue disorders	Very common Arthralgia, back pain, pain in extremity
General disorders and administration site conditions	Very common Fatigue / asthenia[5]
Investigations	Common Weight decreased

a All AEs with at least 5.0% of patients in the Azacitidine tablets arm and at least 2.0% higher frequency than the placebo arm. 1 Grouped terms include pneumonia, bronchopulmonary aspergillosis, lung infection, Pneumocystis jirovecii pneumonia, atypical pneumonia, pneumonia bacterial, and pneumonia fungal. 2 Grouped terms include upper respiratory tract infection, respiratory tract infection, and respiratory tract infection viral. 3 Grouped terms include urinary tract infection, urinary tract infection bacterial, Escherichia urinary tract infection, and cystitis. 4 Grouped terms include abdominal pain, abdominal pain upper, abdominal discomfort, and gastrointestinal pain. 5 Grouped terms include fatigue and asthenia. 6 Adverse reactions in which at least one was considered to be life threatening (if the outcome of the reaction was death, it is included with death cases).

Description of selected adverse reactions
Haematological toxicity
New or worsening Grade 3 or higher neutropenia (41.1%), thrombocytopenia (22.5%), or febrile neutropenia (11.4%) were commonly reported adverse reactions in patients treated with Azacitidine tablets. The first occurrence of Grade 3 or 4 neutropenia, thrombocytopenia, or febrile neutropenia occurred within the first 2 cycles in 19.9%, 10.6%, and 1.7%, respectively in patients treated with Azacitidine tablets.
Gastrointestinal toxicity
Gastrointestinal toxicities were the most frequent adverse reactions in patients treated with Azacitidine tablets. Nausea (64.8%), vomiting (59.7%), and diarrhoea (50.4%) were reported in patients treated with Azacitidine tablets. Grade 3 or higher diarrhoea occurred in 5.1% of patients and Grade 3 or higher vomiting and nausea occurred in 3.0% and 2.5%, respectively in patients treated with Azacitidine tablets. The first occurrence of Grade 3 or 4 nausea, vomiting, or diarrhoea occurred within the first 2 cycles in 1.7%, 3.0%, and 1.3%, respectively, in patients treated with Azacitidine tablets.

4.9 Overdose
In the event of overdose, the patient should be monitored with appropriate blood counts and supportive treatment should be provided, as necessary, according to local recommendations. There is no known specific antidote for an overdose with Azacitidine tablets.

5. Pharmacological properties
5.1 Mechanism of Action
Pharmacotherapeutic group: Antineoplastic agents, antimetabolites, pyrimidine analogues, ATC code: L01BC07
Azacitidine is a DNA methyltransferase inhibitor and epigenetic modifier. Azacitidine is incorporated into DNA and RNA following cellular uptake and enzymatic biotransformation to nucleotide triphosphates. Incorporation of azacitidine into the DNA of AML cells, modified epigenetic pathways through the inhibition of DNA methyltransferases, and reduction of DNA methylation. This led to alteration of gene expression, including re-expression of genes regulating tumour suppression, immune pathways, cell cycle, and cell differentiation. Incorporation of azacitidine into the RNA of AML cells, inhibited RNA methyltransferase, reduced RNA methylation, decreased RNA stability, and decreased protein synthesis.

5.2 Pharmacodynamic Properties
Greater reduction in global DNA methylation was observed with higher azacitidine plasma exposure in patients with AML administered azacitidine tablets for 14 days of a 28-day cycle.

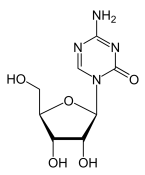
5.3 Pharmacokinetic Properties
Absorption
Exposure was generally linear with dose-proportional increases in systemic exposure; high intersubject variability was observed. The geometric mean (coefficient of variation [%CV]) C_{max} and AUC values after oral administration of a 300 mg single dose were 145.1 ng/mL (63.7)

and 241.6 ng h/mL (64.5), respectively. Multiple dosing at the recommended dose regimen did not result in drug accumulation.
Absorption of azacitidine was rapid, with a median T_{max} of 1 hour post dose. Mean oral bioavailability relative to subcutaneous (SC) administration was approximately 11%.
Effect of food
The impact of food on the exposure of Azacitidine tablets was minimal. Therefore, Azacitidine tablets can be administered with or without food.
Distribution After oral administration, the geometric mean apparent volume of distribution was 12.6 L/kg for a 70 kg person. The plasma protein binding of azacitidine was 6 to 12%.
Biotransformation
Based on in vitro data, azacitidine metabolism does not appear to be mediated by cytochrome P450 isoenzymes (CYPs). Azacitidine undergoes spontaneous hydrolysis and deamination mediated by cytidine deaminase.
Elimination
The geometric mean apparent clearance was 1242 L/hour and the geometric mean half-life was approximately 0.5 hours. Following intravenous administration of 14C azacitidine to 5 cancer patients, the cumulative urinary excretion was 85% of the radioactive dose. Faecal excretion accounted for < 2% following either subcutaneous (SC) or oral administration. Faecal excretion has not been measured following oral administration.
Pharmacodynamic effects
The epigenetic regulatory effect of azacitidine on DNA global methylation reduction in the blood was sustained with prolonged exposure of 300 mg daily administered for 14 or 21 days of a 28-day cycle in myeloid cancers including AML patients from a Phase 1/2 study. A positive correlation was observed between azacitidine plasma exposure and the pharmacodynamic effect of reduction in global DNA methylation in blood.
Special populations
Elderly
In a population pharmacokinetics (PK) analysis from 286 AML patients, age (46 to 93 years) did not have clinically meaningful effects on the PK of Azacitidine tablets. Therefore, dose modification for Azacitidine tablets is not required, regardless of patient age.
Hepatic impairment No formal studies have been conducted in patients with hepatic impairment. Hepatic impairment is unlikely to affect the PK to a clinically relevant extent since azacitidine undergoes spontaneous hydrolysis and deamination mediated by cytidine deaminase. A population PK analysis determined that AST (8 to 155 U/L), ALT (5 to 185 U/L) and mild hepatic impairment (BIL ≤ ULN and AST > ULN, or BIL 1 to 1.5 × ULN and any AST) did not have clinically meaningful effects on the PK of azacitidine. The effects of moderate to severe hepatic impairment (BIL > 1.5 × ULN and any AST) on the PK of azacitidine is unknown.
Renal impairment In patients with cancer, the PK of azacitidine in 6 patients with normal renal function (CLcr >80 mL/min) and 6 patients with severe renal impairment (CLcr <30 mL/min) were compared
following daily subcutaneous dosing (Days 1 through 5) at 75 mg/m2/day. Severe renal impairment
increased azacitidine exposure by approximately 70% after single and 41% after multiple
subcutaneous administrations. This increase in exposure was not correlated with an increase in adverse
events.
A population PK analysis following a 300 mg dose of Azacitidine tablets determined that patients with mild (CLcr: ≥ 60 to < 90 mL/min), moderate (CLcr: ≥30 to <60 mL/min), and severe (CLcr: <30 mL/min) renal impairment had 19%, 25%, and 38% increases in azacitidine plasma AUC, respectively. The effect of severe renal impairment on Azacitidine tablets was similar to the above referenced clinical renal
impairment study with injectable azacitidine (~40% increase in AUC). The exposure of Azacitidine (AUC) is approximately 75% lower after oral administration relative to the exposure achieved following SC administration; therefore, an increase in exposure of approximately 40% following oral administration is still considered safe and tolerable. Thus, no dose adjustment of Azacitidine tablets is recommended in patients with mild, moderate, or severe renal impairment.
Race/ethnicity
The effects of race/ethnicity on the PK of Azacitidine tablets is unknown

5.4 Preclinical safety data
In a 14-day oral toxicity study in dogs, mortality occurred at doses of 8 and 16 mg/m^2/day. The maximum tolerated dose (MTD) was 4 mg/m^2/day. At 1 or all doses, pancytopenia correlated with bone marrow hypoplasia, lymphoid depletion, gland/lumen dilation and single cell necrosis in mucosal crypts of small and large intestines and/or centrilobular hepatocellular vacuolation were observed. At the MTD, these findings were partially or completely resolved after 3 weeks. Following parenteral azacitidine administrations at comparable dose ranges, mortality and similar target organ toxicities were observed in rodents, dogs and monkeys. Non-clinical data from repeat-dose toxicity studies with azacitidine revealed no special hazard for humans.
Azacitidine induces both gene mutations and chromosomal aberrations in bacterial and mammalian cell systems *in vitro*. The potential carcinogenicity of azacitidine was evaluated in mice and rats. Azacitidine induced tumours of the haematopoietic system in female mice, when administered intraperitoneally 3 times per week for 52 weeks. An increased incidence of tumours in the lymphoreticular system, lung, mammary gland, and skin was seen in mice treated with Azacitidine administered intraperitoneally for 50 weeks. A tumorigenicity study in rats revealed an increased incidence of testicular tumours.
Early embryotoxicity studies in mice revealed a 44% frequency of intrauterine embryonal death (increased resorption) after a single intraperitoneal injection of azacitidine during organogenesis. Developmental abnormalities in the brain have been detected in mice given azacitidine on or before closure of the hard palate. In rats, azacitidine caused no adverse reactions when given pre-implantation, but it was clearly embryotoxic when given during organogenesis. Foetal abnormalities during organogenesis in rats included: Central nervous system (CNS) anomalies (exencephaly/encephalocele), limb anomalies (micromelia, club foot, syndactyly, oligodactyly) and others (microphthalmia, micrognathia, gastroschisis, oedema, and rib abnormalities).
Administration of azacitidine to male mice prior to mating with untreated female mice resulted in decreased fertility and loss of offspring during subsequent embryonic and postnatal development. Treatment of male rats resulted in decreased weight of the testes and epididymides, decreased sperm counts, decreased pregnancy rates, an increase in abnormal embryos and increased loss of embryos in mated females.

6. Non Clinical Properties
Carcinogenesis, Mutagenesis, Impairment of Fertility
The potential carcinogenicity of azacitidine was evaluated in mice and rats. Azacitidine induced tumors of the hematopoietic system in female mice at 2.2 mg/kg (6.6 mg/m , approximately 4% of the recommended human daily dose of oral azacitidine on a mg/m basis) administered intraperitoneal 3 times per week for 52 weeks. An increased incidence of tumors in the lymphoreticular system, lung, mammary gland, and skin was seen in mice treated with intraperitoneal azacitidine at 2 mg/kg (6 mg/m , approximately 3% of the recommended human daily dose of oral azacitidine on a mg/m basis) once a week for 50 weeks. A tumorigenicity study in rats dosed twice weekly at 15 or 60 mg/m (approximately 8% to 32% of the recommended human daily dose of oral azacitidine on a mg/m basis) revealed an increased incidence of testicular tumors compared with controls.
The mutagenic and clastogenic potential of azacitidine was tested in in vitro bacterial systems Salmonella typhimurium strains TA100 and several strains of trpE8, Escherichia coli strains WP14 Pro, WP3103P, WP3104P, and CC103; in an in vitro forward gene mutation assay in mouse lymphoma cells and human lymphoblast cells; and in an in vitro micronucleus assay in mouse L5178Y lymphoma cells and Syrian hamster embryo cells. Azacitidine was mutagenic in bacterial and mammalian cell systems. The clastogenic effect of azacitidine was shown by the induction of micronuclei in L5178Y mouse cells and Syrian hamster embryo cells.
Administration of azacitidine by intraperitoneal injection to male mice at 9.9 mg/m (at doses less than the recommended human daily dose on a mg/m basis) daily for 3 days prior to mating with untreated female mice resulted in decreased fertility and loss of offspring during subsequent embryonic and postnatal development. Treatment of male rats 3 times per week for 11 or 16 weeks at doses of 15 to 30 mg/m (at doses less than the recommended human daily dose on a mg/m basis) resulted in decreased weight of the testes and epididymides, decreased sperm counts accompanied by decreased pregnancy rates, and increased loss of embryos in mated females. In a related study, male rats treated for 16 weeks at 24 mg/m resulted in an increase in abnormal embryos in mated females when examined on Day 2 of gestation.

7. Description
Azacitidine is a nucleoside metabolic inhibitor with a molecular formula of $C_8H_{12}N_4O_5$ and a molecular weight of 244.20 g/mol.
The chemical name is: 4-amino-1-β-D-ribofuranosyl-s-triazin-2 (1H)-one and the chemical structural is:



Azacitidine is a white to off-white powder. Azacitidine was found to be soluble in dimethylsulphoxide.
Azacitidine tablets is supplied as oval shape, film-coated tablets containing 200 mg or 300 mg of azacitidine as active for oral use..

8. Pharmaceutical particulars
List of Excipients
Core Tablets contains
microcrystalline cellulose, mannitol, Croscarmellose sodium, magnesium stearate
Film Coating material for 200mg and 300 mg: Hypromellose, Polyethylene Glycol, Titanium Dioxide, Ferric Oxide Red.
8.1 Incompatibilities
No data available.
8.2 Shelf-life
Please see manufacturing date and expiry date printed on pack. Do not use the product after the expiry date which is stated on the packaging. The expiry date refers to the last day of that month.
8.3 Packaging information
HDPE bottle contains 14 tablets with literature housed in a carton.
8.4 Storage and handling instructions
Store at temperature not exceeding 30°C. Protect from light and moisture.
Keep out of reach of children.

9. Patient Counselling Information
Myelosuppression: Advise patients of the risk of myelosuppression with azacitidine tablets and of the need to monitor complete blood counts before and during treatment.
Gastrointestinal Toxicity: Advise patients of the risk of gastrointestinal toxicity with azacitidine tablets and of the potential need to use anti-emetic or anti-diarrheal medications during treatment.
Embryo-Fetal Toxicity: Advise pregnant women of the potential risk to a fetus. Advice females of reproductive potential to inform their healthcare provider of a known or suspected pregnancy. Advise females of reproductive potential to use effective contraception during treatment with azacitidine tablets and for at least 6 months after the last dose. Advise males with female partners of reproductive potential to use effective contraception during treatment with azacitidine tablets and for at least 3 months after the last dose.
Lactation: Advise women not to breastfeed during treatment with azacitidine tablets and for 1 week after the last dose.
Administration: Advise patients to take azacitidine tablets with or without food at about the same time each day and how to make up a missed or vomited dose. Advise patients to swallow tablets whole. Advice patients not to cut, split, crush, or chew the tablets.
Storage Instructions: Advise patients to keep azacitidine tablets in the original container. Advice patients to keep the container tightly closed and keep out of reach and sight of children.
What is Azacitidine Tablets?
Azacitidine Tablets is a prescription medicine used for continued treatment of patients with acute myeloid leukemia (AML) who achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following intensive induction chemotherapy and are not able to complete intensive curative therapy.
It is not known if Azacitidine Tablets is safe and effective in children under 18 years of age.
Do not take Azacitidine Tablets if you: are allergic to azacitidine or any of the ingredients in Azacitidine Tablets. See the end of this leaflet for a complete list of ingredients in Azacitidine Tablets.
Before taking Azacitidine Tablets, tell your healthcare provider about all of your medical conditions, including if you: have kidney or liver problems. are pregnant or plan to become pregnant. Azacitidine Tablets can harm your unborn baby.
Females who are able to become pregnant:
Your healthcare provider should perform a pregnancy test before you start treatment with Azacitidine Tablets.
You should use effective birth control (contraception) during treatment and for at least 6 months after your last dose of Azacitidine Tablets.
Tell your healthcare provider right away if you become pregnant during treatment with Azacitidine Tablets.
Males with a female sexual partner who can become pregnant:
You should use effective birth control (contraception) during treatment and for at least 3 months after your last dose of Azacitidine Tablets.
are breastfeeding or plan to breastfeed. It is not known if Azacitidine Tablets passes into your breast milk. Do not breastfeed during treatment and for 1 week after your last dose of Azacitidine Tablets.
Tell your healthcare provider about all the medicines you take, including prescription and over-the-counter medicines, vitamins, and herbal supplements.
How should I take Azacitidine Tablets?
Take Azacitidine Tablets exactly as your healthcare provider tells you to take it. Your healthcare provider will prescribe an anti-nausea medicine for you to take to help prevent nausea and vomiting during your treatment with Azacitidine Tablets.
Take the anti-nausea medicine 30 minutes before each dose of Azacitidine Tablets.

Your healthcare provider may decide to stop the anti-nausea medicine after your second cycle of Azacitidine Tablets, if you do not have any nausea or vomiting.
Take Azacitidine Tablets by mouth 1 time each day beginning on Day 1 through Day 14 of each 28-day cycle.
Take Azacitidine Tablets with or without food at about the same time each day.
Swallow Azacitidine Tablets tablets whole. Do not cut, crush, or chew the tablets.
If the powder from Azacitidine Tablets tablets comes in contact with your skin, wash the area well right away with soap and water.
If the powder from Azacitidine Tablets tablets comes in contact with your eyes or mouth (mucous membranes), flush the area right away with water.
If you miss a dose of Azacitidine Tablets, or if you do not take your dose at the usual time, take the dose as soon as possible that day. Take your next dose at the regular time the next day. Do not take 2 doses on the same day to make up for a missed dose.
If you vomit after taking a dose of Azacitidine Tablets, do not take another dose on the same day. Take your next dose at the regular time the next day.
What are the possible side effects of Azacitidine Tablets?
Azacitidine Tablets can cause serious side effects, including:
New or worsening low white blood cell counts (neutropenia). New or worsening low white blood cell counts are common but can also be severe worsening low white blood cell counts are common but can also be severe during treatment with Azacitidine Tablets. If your white blood cell counts become very low, you are at increased risk for infections. Your healthcare provider will check your white blood cell counts before and during treatment with Azacitidine Tablets. Your healthcare provider may prescribe a medicine to help increase your white blood cell count if needed.
Tell your healthcare provider right away if you get any of the following symptoms:
fever or chills
body aches
feeling very tired or weak
unusual headaches
New or worsening low platelet counts (thrombocytopenia). Low platelet counts are common but can also be severe during treatment with Azacitidine Tablets. Your healthcare provider will check your platelet counts before and during treatment with Azacitidine Tablets. Tell your healthcare provider right away if you have any unusual bruising or bleeding. Your healthcare provider may change your dose or tell you to stop taking Azacitidine Tablets if you have low blood cell counts. Azacitidine Tablets may cause fertility problems in males and females, which may affect your ability to have children. Talk with your healthcare provider if you have concerns about fertility.
The most common side effects of Azacitidine Tablets include:
nausea and vomiting. See **"How should I take Azacitidine Tablets**?"
diarrhea. You may need to be treated with antidiarrheal medicines.
tiredness or weakness
constipation
stomach area (abdominal) pain
pneumonia
joint pain
decreased appetite
pain in arms or legs
dizziness
These are not all of the possible side effects of Azacitidine Tablets. Call your doctor for medical advice about side effects.
How should I store Azacitidine Tablets?
Store at temperature not exceeding 30°C.
Keep Azacitidine Tablets and all medicines out of the reach of children
General information about the safe and effective use of Azacitidine Tablets.
Medicines are sometimes prescribed for purposes other than those listed in a Patient
Information leaflet. Do not use Azacitidine Tablets for a condition for which it was not prescribed. Do not give Azacitidine Tablets to other people, even if they have the same symptoms you have. It may harm them. You can ask your pharmacist or healthcare provider for information about Azacitidine Tablets that is written for health professionals.
Active ingredient: azacitidine
Inactive ingredients:
Each core tablet contains: microcrystalline cellulose, mannitol, Croscarmellose sodium, magnesium stearate
The 200 mg and 300 mg tablet coating contains: Hypromellose, Polyethylene Glycol, Titanium Dioxide, Ferric Oxide Red.

10. Details of manufacturer
Manufactured by:
BDR Pharmaceuticals International Private Limited, India.
R. S. No. 578, Near Effluent Channel Road, Vill. Luna,
Tal. Padra, Dist. Vadodara-391 440. Gujarat.

Marketed by:
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11. Details of permission or licence number with date
G/25/2071 issued on 18th Oct. 2021.

12. Date of first submission/revision
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