ANNEX I

SUMMARY OF PRODUCT CHARACTERISTICS

1. NAME OF THE MEDICINAL PRODUCT

Azacitidine Accord 25 mg/mL powder for suspension for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

100 mg/vial:
Each vial contains 100 mg azacitidine. After reconstitution, each mL of suspension contains 25 mg azacitidine.

150 mg/vial:
Each vial contains 150 mg azacitidine. After reconstitution, each mL of suspension contains 25 mg azacitidine.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for suspension for injection.

White lyophilised powder or cake.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Azacitidine Accord is indicated for the treatment of adult patients who are not eligible for haematopoietic stem cell transplantation (HSCT) with:
- Intermediate-2 and high-risk myelodysplastic syndromes (MDS) according to the International Prognostic Scoring System (IPSS),
- chronic myelomonocytic leukaemia (CMML) with 10-29 % marrow blasts without myeloproliferative disorder,
- acute myeloid leukaemia (AML) with 20-30 % blasts and multi-lineage dysplasia, according to World Health Organisation (WHO) classification,
- AML with >30% marrow blasts according to the WHO classification.

4.2 Posology and method of administration

Azacitidine Accord treatment should be initiated and monitored under the supervision of a physician experienced in the use of chemotherapeutic agents. Patients should be premedicated with anti-emetics for nausea and vomiting.

Posology
The recommended starting dose for the first treatment cycle, for all patients regardless of baseline haematology laboratory values, is 75 mg/m^2 of body surface area, injected subcutaneously, daily for 7 days, followed by a rest period of 21 days (28-day treatment cycle).

It is recommended that patients be treated for a minimum of 6 cycles. Treatment should be continued for as long as the patient continues to benefit or until disease progression.

Patients should be monitored for haematologic response/toxicity and renal toxicities (see section 4.4); a delay in starting the next cycle or a dose reduction as described below may be necessary.

Azacitidine Accord should not be used interchangeably with oral azacitidine. Due to differences in the exposure, the dose and schedule recommendations for oral azacitidine are different from those for injectable azacitidine. Healthcare professionals are recommended to verify the name of the medicinal product, dose and administration route.

Laboratory tests
Liver function tests, serum creatinine and serum bicarbonate should be determined prior to initiation of therapy and prior to each treatment cycle. Complete blood counts should be performed prior to initiation of therapy and as needed to monitor response and toxicity, but at a minimum, prior to each treatment cycle.

Dose adjustment due to haematological toxicity
Haematological toxicity is defined as the lowest count reached (nadir) in a given cycle if platelets $\leqslant$ 50.0 x 10^9/l and/or absolute neutrophil count (ANC) $\leqslant$ 1 x 10^9/L.

Recovery is defined as an increase of cell line(s) where haematological toxicity was observed of at least half of the absolute difference of nadir and the baseline count plus the nadir count (i.e. blood count at recovery $\geqslant$ nadir count + (0.5 x [baseline count – nadir count]).

Patients without reduced baseline blood counts (i.e. White Blood Cells (WBC) $\geqslant$3.0 x 10^9/l and ANC $\geqslant$ 1.5 x 10^9/l, and platelets $\geqslant$ 75.0 x 10^9/l) prior to the first treatment
If haematological toxicity is observed following Azacitidine Accord treatment, the next cycle of the therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, the dose should be reduced according to the following table. Following dose modifications, the cycle duration should return to 28 days.

Cycle Nadir		Dose in the next cycle, if recovery* is not achieved within 14 days (%)
ANC (x 10^9/l)	Platelets (x 10^9/l)	
$\leqslant$ 1.0	$\leqslant$ 50.0	50 %
> 1.0	> 50.0	100 %

*Recovery = counts ≥ nadir count + (0.5 x [baseline count – nadir count])

Patients with reduced baseline blood counts (i.e. WBC < 3.0 x 10^9/L or ANC < 1.5 x 10^9/L or platelets < 75.0 x 10^9/L) prior to the first treatment
Following Azacitidine Accord treatment, if the decrease in WBC or ANC or platelets from that prior to treatment is $\leqslant$ 50 %, or greater than 50 % but with an improvement in any cell line differentiation, the next cycle should not be delayed and no dose adjustment made.

If the decrease in WBC or ANC or platelets is greater than 50 % from that prior to treatment, with no improvement in cell line differentiation, the next cycle of Azacitidine Accord therapy should be delayed until the platelet count and the ANC have recovered. If recovery is achieved within 14 days, no dose adjustment is necessary. However, if recovery has not been achieved within 14 days, bone marrow cellularity should be determined. If the bone marrow cellularity is > 50 %, no dose adjustments should be made. If bone marrow cellularity is $\leqslant$ 50 %, treatment should be delayed and the dose reduced according to the following table:

Bone marrow cellularity	Dose in the next cycle if recovery is not achieved within 14 days (%)	
	Recovery* $\leqslant$ 21 days	Recovery* > 21 days
15-50 %	100 %	50 %
< 15 %	100 %	33 %

*Recovery = counts ⩾ nadir count + (0.5 x [baseline count – nadir count])

Following dose modifications, the next cycle duration should return to 28 days.

Special populations
Elderly patients
No specific dose adjustments are recommended for the elderly. Because elderly patients are more likely to have decreased renal function, it may be useful to monitor renal function.

Patients with renal impairment
Azacitidine can be administered to patients with renal impairment without initial dose adjustment (see section 5.2). If unexplained reductions in serum bicarbonate levels to less than 20 mmol/l occur, the dose should be reduced by 50 % on the next cycle. If unexplained elevations in serum creatinine or blood urea nitrogen (BUN) to ≥ 2-fold above baseline values and above upper limit of normal (ULN) occur, the next cycle should be delayed until values return to normal or baseline and the dose should be reduced by 50 % on the next treatment cycle (see section 4.4).

Patients with hepatic impairment
No formal studies have been conducted in patients with hepatic impairment (see section 4.4). Patients with severe hepatic organ impairment should be carefully monitored for adverse events. No specific modification to the starting dose is recommended for patients with hepatic impairment prior to starting treatment; subsequent dose modifications should be based on haematology laboratory values. Azacitidine Accord is contraindicated in patients with advanced malignant hepatic tumours (see sections 4.3 and 4.4).

Paediatric population
The safety and efficacy of azacitidine in children aged 0-17 years have not yet been established. Currently available data are described in sections 4.8, 5.1 and 5.2 but no recommendation on a posology can be made.

Method of administration
Reconstituted Azacitidine Accord should be injected subcutaneously into the upper arm, thigh or abdomen. Injection sites should be rotated. New injections should be given at least 2.5 cm from the previous site and never into areas where the site is tender, bruised, red, or hardened.

After reconstitution, the suspension should not be filtered. For instructions on reconstitution of the medicinal product before administration, see section 6.6.

4.3 Contraindications

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

Advanced malignant hepatic tumours (see section 4.4).

Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Haematological toxicity
Treatment with azacitidine is associated with anaemia, neutropenia and thrombocytopenia, particularly during the first 2 cycles (see section 4.8). Complete blood counts should be performed as needed to monitor response and toxicity, but at least prior to each treatment cycle. After administration of the recommended dose for the first cycle, the dose for subsequent cycles should be reduced or its administration delayed based on nadir counts and haematological response (see section 4.2). Patients should be advised to promptly report febrile episodes. Patients and physicians are also advised to be observant for signs and symptoms of bleeding.

Hepatic impairment
No formal studies have been conducted in patients with hepatic impairment. Patients with extensive tumour burden due to metastatic disease have been reported to experience progressive hepatic coma and death during azacitidine treatment, especially in such patients with baseline serum albumin < 30 g/L. Azacitidine is contraindicated in patients with advanced malignant hepatic tumours (see section 4.3).

Renal impairment
Renal abnormalities ranging from elevated serum creatinine to renal failure and death were reported in patients treated with intravenous azacitidine in combination with other chemotherapeutic agents. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to < 20 mmol/L in association with an alkaline urine and hypokalaemia (serum potassium < 3 mmol/L) developed in 5 subjects with chronic myelogenous leukaemia (CML) treated with azacitidine and etoposide. If unexplained reductions in serum bicarbonate (< 20 mmol/L) or elevations of serum creatinine or BUN occur, the dose should be reduced or administration delayed (see section 4.2).

Patients should be advised to report oliguria and anuria to the health care provider immediately.

Although no clinically relevant differences in the frequency of adverse reactions were noted between subjects with normal renal function compared to those with renal impairment, patients with renal impairment should be closely monitored for toxicity since azacitidine and/or its metabolites are primarily excreted by the kidney (see section 4.2).

Laboratory tests
Liver function tests, serum creatinine and serum bicarbonate should be determined prior to initiation of therapy and prior to each treatment cycle. Complete blood counts should be performed prior to initiation of therapy and as needed to monitor response and toxicity, but at a minimum, prior to each treatment cycle, see also section 4.8.

Cardiac and pulmonary disease
Patients with a history of severe congestive heart failure, clinically unstable cardiac disease or pulmonary disease were excluded from the pivotal registration studies (AZA PH GL 2003 CL 001 and AZA-AML-001) and therefore the safety and efficacy of azacitidine in these patients has not been established. Recent data from a clinical study in patients with a known history of cardiovascular or pulmonary disease showed a significantly increased incidence of cardiac events with azacitidine (see section 4.8). It is therefore advised to exercise caution when prescribing azacitidine to these patients. Cardiopulmonary assessment before and during the treatment should be considered.

Necrotising fasciitis
Necrotising fasciitis, including fatal cases, have been reported in patients treated with azacitidine. Azacitidine therapy should be discontinued in patients who develop necrotising fasciitis and appropriate treatment should be promptly initiated.

Tumour lysis syndrome
The patients at risk of tumour lysis syndrome are those with high tumour burden prior to treatment. These patients should be monitored closely and appropriate precautions taken.

Differentiation syndrome
Cases of differentiation syndrome (also known as retinoic acid syndrome) have been reported in patients receiving injectable azacitidine. Differentiation syndrome may be fatal and symptoms and clinical findings include respiratory distress, pulmonary infiltrates, fever, rash, pulmonary oedema, peripheral oedema, rapid weight gain, pleural effusions, pericardial effusions, hypotension and renal dysfunction (see section 4.8). Treatment with high-dose IV corticosteroids and haemodynamic monitoring should be considered at first onset of symptoms or signs suggestive of differentiation syndrome. Temporary discontinuation of injectable azacitidine should be considered until resolution of symptoms and if resumed, caution is advised.

4.5 Interaction with other medicinal products and other forms of interaction

Based on *in vitro* data, azacitidine metabolism does not appear to be mediated by cytochrome P450 isoenzymes (CYPs), UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), and glutathione transferases (GSTs); interactions related to these metabolizing enzymes *in vivo* are therefore considered unlikely.

Clinically significant inhibitory or inductive effects of azacitidine on cytochrome P450 enzymes are unlikely (see section 5.2).

No formal clinical drug interaction studies with azacitidine have been conducted.

4.6 Fertility, pregnancy and lactation

Women of childbearing potential / Contraception in males and females
Women of childbearing potential have to use effective contraception during and for at least 6 months after treatment. Men should be advised not to father a child while receiving treatment and must use effective contraception during and for at least 3 months after treatment.

Pregnancy
There are no adequate data from the use of azacitidine in pregnant women. Studies in mice have shown reproductive toxicity (see section 5.3). The potential risk for humans is unknown. Based on results from animal studies and its mechanism of action, azacitidine should not be used during pregnancy, especially during the first trimester, unless clearly necessary. The advantages of treatment should be weighed against the possible risk for the foetus in every individual case.

Breast-feeding
It is unknown whether azacitidine/metabolites are excreted in human milk. Due to the potential serious adverse reactions in the nursing child, breast-feeding is contraindicated during azacitidine therapy.

Fertility
There are no human data on the effect of azacitidine on fertility. In animals, adverse reactions with azacitidine use on male fertility have been documented (see section 5.3). Before starting treatment, male patients should be advised to seek counselling on sperm storage.

4.7 Effects on ability to drive and use machines

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

4.8 Undesirable effects

Summary of the safety profile
Adult population with MDS, CMML and AML (20-30% marrow blasts)
Adverse reactions considered to be possibly or probably related to the administration of azacitidine have occurred in 97 % of patients.

The most common serious adverse reactions noted from the pivotal study (AZA PH GL 2003 CL 001) included febrile neutropenia (8.0 %) and anaemia (2.3 %), which were also reported in the supporting studies (CALGB 9221 and CALGB 8921). Other serious adverse reactions from these 3 studies included infections such as neutropenic sepsis (0.8%) and pneumonia (2.5%) (some with fatal outcome), thrombocytopenia (3.5%), hypersensitivity reactions (0.25%) and haemorrhagic events (e.g. cerebral haemorrhage [0.5%], gastrointestinal haemorrhage [0.8%] and intracranial haemorrhage [0.5%])).

The most commonly reported adverse reactions with azacitidine treatment were haematological reactions (71.4 %) including thrombocytopenia, neutropenia and leukopenia (usually Grade 3-4), gastrointestinal events (60.6 %) including nausea, vomiting (usually Grade 1-2) or injection site reactions (77.1 %; usually Grade 1-2).

Adult population aged 65 years or older with AML with > 30% marrow blasts
The most common serious adverse reactions (⩾10%) noted from AZA-AML-001 within the azacitidine treatment arm included febrile neutropenia (25.0%), pneumonia (20.3%), and pyrexia (10.6%). Other less frequently reported serious adverse reactions in the azacitidine treatment arm included sepsis (5.1%), anaemia (4.2%), neutropenic sepsis (3.0%), urinary tract infection (3.0%), thrombocytopenia (2.5%), neutropenia (2.1%), cellulitis (2.1%), dizziness (2.1%) and dyspnoea (2.1%).

The most commonly reported (⩾ 30%) adverse reactions with azacitidine treatment were gastrointestinal events, including constipation (41.9%), nausea (39.8%), and diarrhoea (36.9%; usually Grade 1-2), general disorders and administration site conditions including pyrexia (37.7%; usually Grade 1-2) and haematological events, including febrile neutropenia (32.2%) and neutropenia (30.1%; usually Grade 3-4).

Tabulated list of adverse reactions
Table 1 below contains adverse reactions associated with azacitidine treatment obtained from the main clinical studies in MDS and AML and post marketing surveillance.

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 in any of the main clinical studies.

Table 1: Adverse reactions reported in patients with MDS or AML treated with azacitidine (clinical studies and post- marketing)

System Organ Class	Very common	Common	Uncommon	Rare	Not Known
Infections and infestations	pneumonia* (including bacterial, viral and fungal), nasopharyngitis	sepsis* (including bacterial, viral and fungal), neutropenic sepsis*, respiratory tract infection (includes upper and bronchitis), urinary tract infection, cellulitis, diverticulitis, oral fungal infection, sinusitis, pharyngitis, rhinitis, herpes simplex, skin infection			necrotising fasciitis *

System Organ Class	Very common	Common	Uncommon	Rare	Not Known
Neoplasms benign, malignant and unspecified (including cysts and polyps)					differentiation syndrome*,a
Blood and lymphatic system disorders	febrile neutropenia*, neutropenia, leukopenia, thrombocytopenia, anaemia	pancytopenia*, bone marrow failure			
Immune system disorders			hypersensitivity reactions		
Metabolism and nutrition disorders	anorexia, decreased appetite, hypokalemia	dehydration		tumour lysis syndrome	
Psychiatric disorders	insomnia	confusional state, anxiety			
Nervous system disorders	dizziness, headache	intracranial haemorrhage*, syncope, somnolence, lethargy			
Eye disorders		eye haemorrhage, conjunctival haemorrhage			
Cardiac disorders		pericardial effusion	pericarditis		
Vascular disorders		hypotension*, hypertension, orthostatic hypotension, haematoma			
Respiratory, thoracic and mediastinal disorders	dyspnoea, epistaxis	pleural effusion, dyspnoea exertional, pharyngolaryngeal pain		interstitial lung disease	
Gastrointestinal disorders	diarrhoea, vomiting, constipation, nausea, abdominal pain (includes upper	gastrointestinal haemorrhage* (includes mouth haemorrhage), haemorrhoidal haemorrhage,			

System Organ Class	Very common	Common	Uncommon	Rare	Not Known
	and abdominal discomfort)	stomatitis, gingival bleeding, dyspepsia			
Hepatobiliary disorders			hepatic failure*, progressive hepatic coma		
Skin and subcutaneous tissue disorders	petechiae, pruritus (includes generalized), rash, ecchymosis	purpura, alopecia, urticaria, erythema, rash macular	acute febrile neutrophilic dermatosis, pyoderma gangrenosum		Cutaneous vasculitis
Musculoskeletal and connective tissue disorders	arthralgia, musculoskeletal pain (includes back, bone and pain in extremity)	muscle spasms, myalgia			
Renal and urinary disorders		renal failure*, haematuria, elevated serum creatinine	renal tubular acidosis		
General disorders and administration site conditions	pyrexia*, fatigue, asthenia, chest pain, injection site erythema, injection site pain, injection site reaction (unspecified)	bruising, haematoma, induration, rash, pruritus, inflammation, discoloration, nodule and haemorrhage (at injection site), malaise, chills, catheter site hemorrhage		injection site necrosis (at injection site)	
Investigations	weight decreased				

* = rarely fatal cases have been reported
a = see section 4.4

Description of selected adverse reactions

Haematologic adverse reactions

The most commonly reported (≥ 10%) haematological adverse reactions associated with azacitidine treatment include anaemia, thrombocytopenia, neutropenia, febrile neutropenia and leukopenia, and were usually Grade 3 or 4. There is a greater risk of these events occurring during the first 2 cycles, after which they occur with less frequency in patients with restoration of haematological function. Most haematological adverse reactions were managed by routine monitoring of complete blood counts and delaying azacitidine administration in the next cycle, prophylactic antibiotics and/or growth factor support (e.g. G-CSF) for neutropenia and transfusions for anaemia or thrombocytopenia as required.

Infections
Myelosuppression may lead to neutropenia and an increased risk of infection. Serious adverse reactions such as sepsis, including neutropenic sepsis, and pneumonia were reported in patients receiving azacitidine, some with a fatal outcome. Infections may be managed with the use of anti-infectives plus growth factor support (e.g. G-CSF) for neutropenia.

Bleeding
Bleeding may occur with patients receiving azacitidine. Serious adverse reactions such as gastrointestinal haemorrhage and intracranial haemorrhage have been reported. Patients should be monitored for signs and symptoms of bleeding, particularly those with pre-existing or treatment-related thrombocytopenia.

Hypersensitivity
Serious hypersensitivity reactions have been reported in patients receiving azacitidine. In case of an anaphylactic-like reaction, treatment with azacitidine should be immediately discontinued and appropriate symptomatic treatment initiated.

Skin and subcutaneous tissue adverse reactions
The majority of skin and subcutaneous adverse reactions were associated with the injection site. None of these adverse reactions led to discontinuation of azacitidine, or reduction of azacitidine dose in the pivotal studies. The majority of adverse reactions occurred during the first 2 cycles of treatment and tended to decrease with subsequent cycles. Subcutaneous adverse reactions such as injection site rash/inflammation/pruritus, rash, erythema and skin lesion may require management with concomitant medicinal products, such as antihistamines, corticosteroids and non-steroidal anti-inflammatory medicinal products (NSAIDs). These cutaneous reactions have to be distinguished from soft tissue infections, sometimes occurring at injection site. Soft tissue infections, including cellulitis and necrotising fasciitis in rare cases leading to death, have been reported with azacitidine in the post marketing setting. For clinical management of infectious adverse reactions, see section-4.8 Infections.

Gastrointestinal adverse reactions
The most commonly reported gastrointestinal adverse reactions associated with azacitidine treatment included constipation, diarrhoea, nausea and vomiting. These adverse reactions were managed symptomatically with anti-emetics for nausea and vomiting; anti-diarrhoeals for diarrhoea, and laxatives and/or stool softeners for constipation.

Renal adverse reactions
Renal abnormalities, ranging from elevated serum creatinine and haematuria to renal tubular acidosis, renal failure and death were reported in patients treated with azacitidine (see section-4.4).

Hepatic adverse reactions
Patients with extensive tumour burden due to metastatic disease have been reported to experience hepatic failure, progressive hepatic coma and death during azacitidine treatment (see section-4.4).

Cardiac events
Data from a clinical study allowing enrolment of patients with known history of cardiovascular or pulmonary disease showed an increase in cardiac events in patients with newly diagnosed AML treated with azacitidine (see section 4.4).

Elderly population
There is limited safety information available with azacitidine in patients ⩾85 years (with 14 [5.9%] patients ⩾85 years treated in Study AZA-AML-001).

Paediatric population
In Study AZA-JMML-001, 28 paediatric patients (1 month to less than 18 years of age) were treated with azacitidine for MDS (n = 10) or juvenile myelomonocytic leukaemia (JMML) (n = 18) (see section 5.1).

All 28 patients experienced at least 1 adverse event and 17 (60.7%) experienced at least 1 treatment-related event. The most commonly reported adverse events in the overall paediatric population were pyrexia, haematologic events including anaemia, thrombocytopenia and febrile neutropenia, and gastrointestinal events including constipation and vomiting.

Three (3) subjects experienced a treatment emergent event leading to drug discontinuation (pyrexia, disease progression and abdominal pain).

In Study AZA-AML-004, 7 paediatric patients (aged 2 to 12 years) were treated with azacitidine for AML in molecular relapse after first complete remission [CR1] (see section 5.1).

All 7 patients experienced at least 1 treatment-related adverse event. The most commonly reported adverse events were neutropenia, nausea, leukopenia, thrombocytopenia, diarrhoea and increased alanine aminotransferase (ALT). Two patients experienced a treatment-related event leading to dose interruption (febrile neutropenia, neutropenia).

No new safety signals were identified in the limited number of paediatric patients treated with azacitidine during the course of the clinical study. The overall safety profile was consistent with that of the adult population.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

4.9 Overdose

One case of overdose with azacitidine was reported during clinical studies. A patient experienced diarrhoea, nausea, and vomiting after receiving a single intravenous dose of approximately 290 mg/m^2, almost 4 times the recommended starting dose.

In the event of overdose, the patient should be monitored with appropriate blood counts and should receive supportive treatment, as necessary. There is no known specific antidote for azacitidine overdose.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

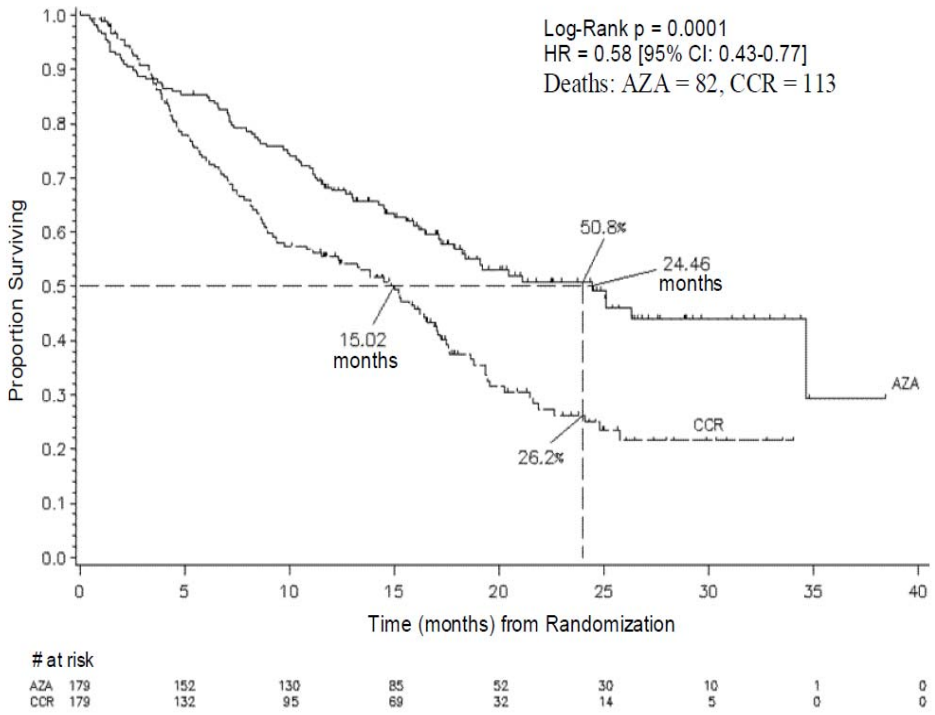
Pharmacotherapeutic group: Antineoplastic agents, pyrimidine analogues; ATC code: L01BC07

Mechanism of action
Azacitidine is believed to exert its antineoplastic effects by multiple mechanisms including cytotoxicity on abnormal haematopoietic cells in the bone marrow and hypomethylation of DNA. The cytotoxic effects of azacitidine may result from multiple mechanisms, including inhibition of DNA, RNA and protein synthesis, incorporation into RNA and DNA, and activation of DNA damage pathways. Non-proliferating cells are relatively insensitive to azacitidine. Incorporation of azacitidine into DNA results in the inactivation of DNA methyltransferases, leading to hypomethylation of DNA. DNA hypomethylation of aberrantly methylated genes involved in normal cell cycle regulation, differentiation and death pathways may result in gene re-expression and restoration of cancer-suppressing functions to cancer cells. The relative importance of DNA hypomethylation versus cytotoxicity or other activities of azacitidine to clinical outcomes has not been established.

Clinical efficacy and safety

Adult population (MDS, CMML and AML [20-30% marrow blasts])
The efficacy and safety of azacitidine were studied in an international, multicenter, controlled, open-label, randomised, parallel-group, Phase 3 comparative study (AZA PH GL 2003 CL 001) in adult patients with: intermediate-2 and high-risk MDS according to the International Prognostic Scoring System (IPSS), refractory anaemia with excess blasts (RAEB), refractory anaemia with excess blasts in transformation (RAEB-T) and modified chronic myelomonocytic leukaemia (mCMML) according to the French American British (FAB) classification system. RAEB-T patients (21-30 % blasts) are now considered to be AML patients under the current WHO classification system. Azacitidine plus best supportive care (BSC) (n = 179) was compared to conventional care regimens (CCR). CCR consisted of BSC alone (n = 105), low-dose cytarabine plus BSC (n = 49) or standard induction chemotherapy plus BSC (n = 25). Patients were pre-selected by their physician to 1 of the 3 CCR prior to randomisation. Patients received this pre-selected regimen if not randomised to azacitidine. As part of the inclusion criteria, patients were required to have an Eastern Cooperative Oncology Group (ECOG) performance status of 0-2. Patients with secondary MDS were excluded from the study. The primary endpoint of the study was overall survival. Azacitidine was administered at a subcutaneous dose of 75 mg/m^2 daily for 7 days, followed by a rest period of 21 days (28-day treatment cycle) for a median of 9 cycles (range = 1-39) and a mean of 10.2 cycles. Within the Intent to Treat population (ITT), the median age was 69 years (range 38 to 88 years).

In the ITT analysis of 358 patients (179 azacitidine and 179 CCR), azacitidine treatment was associated with a median survival of 24.46 months versus 15.02 months for those receiving CCR treatment, a difference of 9.4 months, with a stratified log-rank p-value of 0.0001. The hazard ratio (HR) for the treatment effect was 0.58 (95 % CI: 0.43, 0.77). The two-year survival rates were 50.8 % in patients receiving azacitidine versus 26.2 % in patients receiving CCR (p < 0.0001).



KEY: AZA = azacitidine; CCR = conventional care regimens; CI = confidence interval; HR = hazard ratio

The survival benefits of azacitidine were consistent regardless of the CCR treatment option (BSC alone, low-dose cytarabine plus BSC or standard induction chemotherapy plus BSC) utilised in the control arm.

When IPSS cytogenetic subgroups were analysed, similar findings in terms of median overall survival were observed in all groups (good, intermediate, poor cytogenetics, including monosomy 7).

On analyses of age subgroups, an increase in median overall survival was observed for all groups (< 65 years, ⩾ 65 years and ⩾ 75 years).

Azacitidine treatment was associated with a median time to death or transformation to AML of 13.0 months versus 7.6 months for those receiving CCR treatment, an improvement of 5.4 months with a stratified log-rank p-value of 0.0025.

Azacitidine treatment was also associated with a reduction in cytopenias, and their related symptoms. Azacitidine treatment led to a reduced need for red blood cell (RBC) and platelet transfusions. Of the patients in the azacitidine group who were RBC transfusion dependent at baseline, 45.0 % of these patients became RBC transfusion independent during the treatment period, compared with 11.4 % of the patients in the combined CCR groups (a statistically significant ($p < 0.0001$) difference of 33.6 % (95 % CI: 22.4, 44.6). In patients who were RBC transfusion dependent at baseline and became independent, the median duration of RBC transfusion independence was 13 months in the azacitidine group.

Response was assessed by the investigator or by the Independent Review Committee (IRC). Overall response (complete remission [CR] + partial remission [PR]) as determined by the investigator was 29 % in the azacitidine group and 12% in the combined CCR group ($p = 0.0001$). Overall response (CR + PR) as determined by the IRC in AZA PH GL 2003 CL 001 was 7 % (12/179) in the azacitidine group compared with 1 % (2/179) in the combined CCR group ($p = 0.0113$). The differences between the IRC and investigator assessments of response were a consequence of the International Working Group (IWG) criteria requiring improvement in peripheral blood counts and maintenance of these improvements for a minimum of 56 days. A survival benefit was also demonstrated in patients that had not achieved a complete/partial response following azacitidine treatment. Haematological improvement (major or minor) as determined by the IRC was achieved in 49 % of patients receiving azacitidine compared with 29 % of patients treated with combined CCR ($p < 0.0001$).

In patients with one or more cytogenetic abnormalities at baseline, the percentage of patients with a major cytogenetic response was similar in the azacitidine and combined CCR groups. Minor cytogenetic response was statistically significantly ($p = 0.0015$) higher in the azacitidine group (34 %) compared with the combined CCR group (10 %).

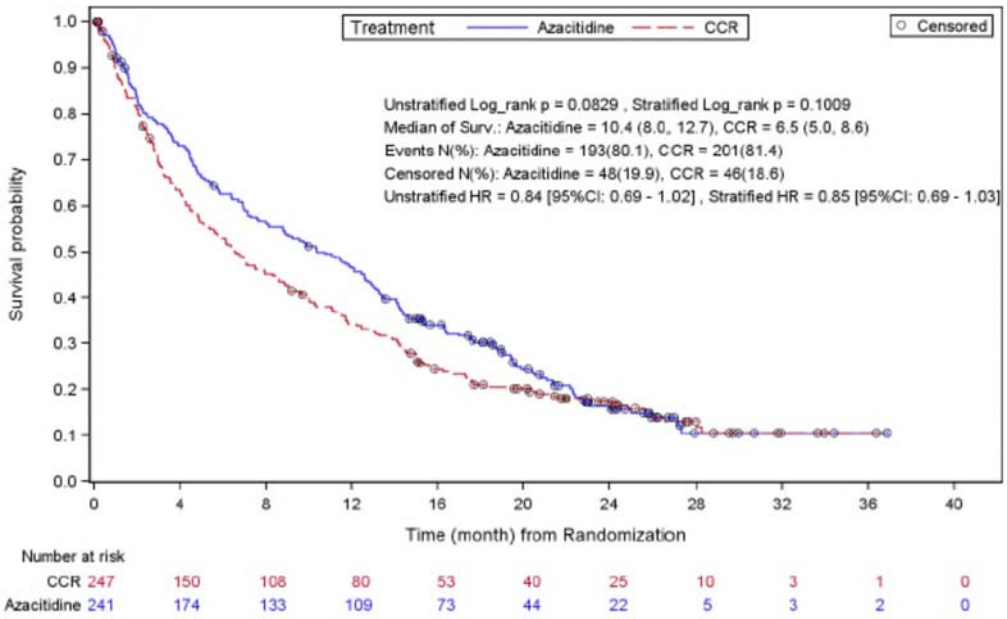
Adult population aged 65 years or older with AML with > 30% marrow blasts
The results presented below represent the intent-to-treat population studied in AZA-AML-001 (see section 4.1 for the approved indication).

The efficacy and safety of azacitidine was studied in an international, multicentre, controlled, open-label, parallel group Phase 3 study in patients 65 years and older with newly diagnosed de novo or secondary AML with >30% bone marrow blasts according to the WHO classification, who were not eligible for HSCT. Azacitidine plus BSC (n=241) was compared to CCR. CCR consisted of BSC alone (n=45), low-dose cytarabine plus BSC (n=158), or standard intensive chemotherapy with cytarabine and anthracycline plus BSC (n=44). Patients were pre-selected by their physician to 1 of the 3 CCRs prior to randomization. Patients received the pre-selected regimen if not randomised to azacitidine. As part of the inclusion criteria, patients were required to have an ECOG performance status of 0-2 and intermediate- or poor-risk cytogenetic abnormalities. The primary endpoint of the study was overall survival.

Azacitidine was administered at a SC dose of 75mg/m^2/day for 7 days, followed by a rest period of 21 days (28 day treatment cycle), for a median of 6 cycles (range: 1 to 28), BSC- only patients for a median of 3 cycles (range: 1 to 20), low-dose cytarabine patients for a median of 4 cycles (range 1 to 25) and standard intensive chemotherapy patients for a median of 2 cycles (range: 1 to 3, induction cycle plus 1 or 2 consolidation cycles).

The individual baseline parameters were comparable between the azacitidine and CCR groups. The median age of the subjects was 75.0 years (range: 64 to 91 years), 75.2% were Caucasian and 59.0% were male. At baseline 60.7% were classified as AML not otherwise specified, 32.4% AML with myelodysplasia-related changes, 4.1% therapy-related myeloid neoplasms and 2.9% AML with recurrent genetic abnormalities according to the WHO classification.

In the ITT analysis of 488 patients (241 azacitidine and 247 CCR), azacitidine treatment was associated with a median survival of 10.4 months versus 6.5 months for those receiving CCR treatment, a difference of 3.8 months, with a stratified log-rank p-value of 0.1009 (two- sided). The hazard ratio for the treatment effect was 0.85 (95% CI= 0.69, 1.03). The one-year survival rates were 46.5% in patients receiving azacitidine versus 34.3% in patients receiving CCR.



The Cox PH model adjusted for pre-specified baseline prognostic factors defined a HR for azacitidine versus CCR of 0.80 (95% CI= 0.66, 0.99; p = 0.0355).

In addition, although the study was not powered to demonstrate a statistically significant difference when comparing azacitidine to the preselection CCR treatment groups, the survival of azacitidine treated patients was longer when compared to CCR treatment options BSC alone, low-dose cytarabine plus BSC and were similar when compared to standard intensive chemotherapy plus BSC.

In all pre- specified subgroups age [(< 75 years & ≥ 75 years), gender, race, ECOG performance status (0 or 1 & 2), baseline cytogenetic risk (intermediate & poor) , geographic region, WHO classification of AML (including AML with myelodysplasia-related changes), baseline WBC count (≤ 5 x109/L & >5 x 109/L), baseline bone marrow blasts (≤ 50% & > 50%) and prior history of MDS] there was a trend in OS benefit in favour of azacitidine. In a few pre-specified subgroups, the OS HR reached statistical significance including patients with poor cytogenetic risk, patients with AML with myelodysplasia-related changes, patients < 75 years, female patients and white patients.

Haematologic and cytogenetic responses were assessed by the investigator and by the IRC with similar results. Overall response rate (complete remission [CR] + complete remission with incomplete blood count recovery [CRi]) as determined by the IRC was 27.8% in the azacitidine group and 25.1% in the combined CCR group (p = 0.5384). In patients who achieved CR or CRi, the median duration of remission was 10.4 months (95% CI = 7.2, 15.2) for the azacitidine subjects and 12.3 months (95% CI = 9.0, 17.0) for the CCR subjects. A survival benefit was also demonstrated in patients that had not achieved a complete response for azacitidine compared to CCR.

Azacitidine treatment improved peripheral blood counts and led to a reduced need for RBC and platelet transfusions. A patient was considered RBC or platelet transfusion dependent at baseline if the subject had one or more RBC or platelet transfusions during the 56 days (8 weeks) on or prior to randomization, respectively. A patient was considered RBC or platelet transfusion independent during the treatment period if the subject had no RBC or platelet transfusions during any consecutive 56 days during the reporting period, respectively.

Of the patients in the azacitidine group who were RBC transfusion dependent at baseline, 38.5% (95% CI = 31.1, 46.2) of these patients became RBC transfusion independent during the treatment period, compared with 27.6% of (95% CI = 20.9, 35.1) patients in the combined CCR groups. In patients who were RBC transfusion dependent at baseline and achieved transfusion independence on treatment, the median duration of RBC transfusion independence was 13.9 months in the azacitidine group and was not reached in the CCR group.
Of the patients in the azacitidine group who were platelet transfusion dependent at baseline, 40.6% (95% CI = 30.9, 50.8) of these patients became platelet transfusion independent during the treatment period, compared with 29.3% of (95% CI = 19.7, 40.4) patients in the combined CCR groups. In patients who were platelet transfusion dependent at baseline and achieved transfusion independence on treatment, the median duration of platelet transfusion independence was 10.8 months in the azacitidine group and 19.2 months in the CCR group.

Health- Related Quality of Life (HRQoL) was assessed using the European Organization for Research and Treatment of Cancer Core Quality of Life Questionnaire (EORTC QLQ-C30). HRQoL data could be analysed for a subset of the full trial population. While there are limitations in the analysis, the available data suggest that patients do not experience meaningful deterioration in quality of life during treatment with azacitidine.

Paediatric population
Study AZA-JMML-001 was a Phase 2, international, multicentre, open-label study to evaluate the pharmacokinetics, pharmacodynamics, safety and activity of azacitidine prior to HSCT in paediatric patients with newly diagnosed advanced MDS or JMML. The primary objective of the clinical study was to evaluate the effect of azacitidine on response rate at Cycle 3, Day 28.

Patients (MDS, n = 10; JMML, n = 18, 3 months to 15 years; 71% male) were treated with intravenous azacitidine 75 mg/m², daily on Days 1 to 7 of a 28-day cycle for a minimum of 3 cycles and a maximum of 6 cycles.

Enrolment in the MDS study arm was stopped after 10 MDS patients due to a lack of efficacy: no confirmed responses were recorded in these 10 patients.

In the JMML study arm, 18 patients (13 PTPN11, 3 NRAS, 1 KRAS somatic mutations and 1 clinical diagnosis of neurofibromatosis type 1 [NF-1]) were enrolled. Sixteen patients completed 3 cycles of therapy and 5 of them completed 6 cycles. A total of 11 JMML patients had a clinical response at Cycle 3, Day 28, of these 11 subjects, 9 (50%) subjects had a confirmed clinical response (3 subjects with cCR and 6 subjects with cPR). Among the cohort of JMML patients treated with azacitidine, 7 (43.8%) patients had a sustained platelet response (counts ≥ 100 × 109/L) and 7 (43.8%) patients required transfusions at HSCT. 17 of 18 patients proceeded to HSCT.

Because of the study design (small patient numbers and various confounding factors), it cannot be concluded from this clinical study whether azacitidine prior to HSCT improves survival outcome in JMML patients.

Study AZA-AML-004 was a Phase 2, multicentre, open-label study to evaluate the safety, pharmacodynamics and efficacy of azacitidine compared to no anti-cancer treatment in children and young adults with AML in molecular relapse after CR1.

Seven patients (median age 6.7 years [range 2 to 12 years]; 71.4% male) were treated with intravenous azacitidine 100 mg/m^2, daily on Days 1 to 7 of each 28-day cycle for a maximum of 3 cycles.

Five patients had minimal residual disease (MRD) assessment at Day 84 with 4 patients achieving either molecular stabilization (n = 3) or molecular improvement (n = 1) and 1 patient had clinical relapse. Six of 7 patients (90% [95% CI = 0.4, 1.0]) treated with azacitidine underwent HSCT.

Due to the small sample size, the efficacy of azacitidine in paediatric AML cannot be established. See section 4.8 for safety information.

5.2 Pharmacokinetic properties

Absorption
Following subcutaneous administration of a single 75 mg/m^2 dose, azacitidine was rapidly absorbed with peak plasma concentrations of 750 ± 403 ng/mL occurring at 0.5 h after dosing (the first sampling point). The absolute bioavailability of azacitidine after subcutaneous relative to intravenous administration (single 75 mg/m^2 doses) was approximately 89% based on the area under the curve (AUC).

Area under the curve and maximum plasma concentration (C_{max}) of subcutaneous admiminstration of azacitidine were approximately proportional within the 25 to 100 mg/m^2 dose range.

Distribution
Following intravenous administration, the mean volume of distribution was 76 ± 26 L, and systemic clearance was 147 ± 47 L/h.

Biotransformation
Based on *in vitro* data, azacitidine metabolism does not appear to be mediated by cytochrome P450 isoenzymes (CYPs), UDP-glucuronosyltransferases (UGTs), sulfotransferases (SULTs), and glutathione transferases (GSTs).

Azacitidine undergoes spontaneous hydrolysis and deamination mediated by cytidine deaminase. In human liver S9 fractions, formation of metabolites was independent of NADPH implying that azacitidine metabolism was not mediated by cytochrome P450 isoenzymes. An *in vitro* study of azacitidine with cultured human hepatocytes indicates that at concentrations of 1.0 μM to 100 μM (i.e. up to approximately 30-fold higher than clinically achievable concentrations), azacitidine does not induce CYP 1A2, 2C19, or 3A4 or 3A5. In studies to assess inhibition of a series of P450 isoenzymes (CYP 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1 and 3A4) azacitidine up to 100 μM did not produce inhibition. Therefore, CYP enzyme induction or inhibition by azacitidine at clinically achievable plasma concentrations is unlikely.

Elimination
Azacitidine is cleared rapidly from plasma with a mean elimination half-life ($t_{½}$) after subcutaneous administration of 41 ± 8 minutes. No accumulation occurs after subcutaneous administration of 75 mg/m^2 azacitidine once daily for 7 days. Urinary excretion is the primary route of elimination of azacitidine and/or its metabolites. Following intravenous and subcutaneous administration of ^{14}C-azacitidine, 85 and 50 % of the administered radioactivity was recovered in urine respectively, while < 1 % was recovered in faeces.

Special populations
The effects of hepatic impairment (see section 4.2), gender, age, or race on the pharmacokinetics of azacitidine have not been formally studied.

Paediatric population
In Study AZA-JMML-001, pharmacokinetic analysis was determined from 10 MDS and 18 JMML paediatric patients on Day 7 of Cycle 1 (see section 5.1). The median age (range) of the MDS patients was 13.3 (1.9-15) years and 2.1 (0.2-6.9) years for JMML patients.

Following intravenous administration of a 75 mg/m^2 dose, azacitidine rapidly reached Cmax within

0.083 hours in both MDS and JMML populations. The geometric mean Cmax were 1797.5 and 1066.3 ng/mL, and the geometric mean AUC0-∞ were 606.9 and 240.2 ng·h/mL, for MDS and JMML patients, respectively. The geometric mean volume of distribution in MDS and JMML subjects were 103.9 and 61.1 L, respectively. It appeared that the total plasma exposure of azacitidine was higher in MDS subjects; however, moderate to high between-patient variability was noted for both AUC and Cmax.

The geometric mean t½ were 0.4 and 0.3 hours, and the geometric mean clearances were 166.4 and 148.3 L/h for MDS and JMML, respectively.

Pharmacokinetic data from Study AZA-JMML-001 were pooled together and compared to pharmacokinetic data from 6 adult subjects with MDS administered 75 mg/m^2 azacitidine intravenously in Study AZA-2002-BA-002. Mean Cmax and AUC0-t of azacitidine were similar between adult patients and paediatric patients after intravenous administration (2750 ng/mL versus 2841 ng/mL and 1025 ng·h/mL versus 882.1 ng·h/mL, respectively).

In Study AZA-AML-004, pharmacokinetic analysis was determined from 6 of the 7 paediatric patients, which had at least one measurable postdose pharmacokinetic concentration (see section 5.1). The median age (range) of the AML patients was 6.7 (2-12) years.

Following multiple doses of 100 mg/m^2, the geometric means for Cmax and AUC0-tau on Cycle 1 Day 7 were 1557 ng/mL and 899.6 ng·h/mL, respectively, with high inter-subject variability (CV% of 201.6% and 87.8%, respectively) observed. Azacitidine rapidly reached Cmax, with a median time of 0.090 hours post-intravenous administration and declined with a geometric mean t1/2 of 0.380 hours. The geometric means for clearance and volume of distribution were 127.2 L/h and 70.2 L, respectively.

Pharmacokinetic (azacitidine) exposure observed in children with AML at molecular relapse after CR1 was comparable to exposure from pooled data of 10 children with MDS and 18 children with JMML and also comparable to azacitidine exposure in adults with MDS.

Renal impairment
Renal impairment has no major effect on the pharmacokinetic exposure of azacitidine after single and multiple subcutaneous administrations. Following subcutaneous administration of a single 75 mg/m^2 dose, mean exposure values (AUC and C_{max}) from subjects with mild, moderate and severe renal impairment were increased by 11-21%, 15-27%, and 41-66%, respectively, compared to normal renal function subjects. However, exposure was within the same general range of exposures observed for subjects with normal renal function. Azacitidine can be administered to patients with renal impairment without initial dose adjustment provided these patients are monitored for toxicity since azacitidine and/or its metabolites are primarily excreted by the kidney.

Pharmacogenomics
The effect of known cytidine deaminase polymorphisms on azacitidine metabolism has not been formally investigated.

5.3 Preclinical safety data

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: 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 (see section 4.4).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol (E421)

6.2 Incompatibilities

This medicinal product must not be mixed with other medicinal products except those mentioned in section 6.6.

6.3 Shelf life

Unopened powder vial
3 years

After reconstitution
When Azacitidine Accord is reconstituted using water for injections that has not been refrigerated, chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated at 25 °C for 60 minutes and at 2 °C to 8 °C for 8 hours.

The shelf life of the reconstituted medicinal product can be extended by reconstituting with refrigerated (2 °C to 8 °C) water for injections. When Azacitidine Accord is reconstituted using refrigerated (2 °C to 8 °C) water for injections, the chemical and physical in-use stability of the reconstituted medicinal product has been demonstrated at 2 °C to 8 °C for 22 hours.

From a microbiological point of view, the reconstituted product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user and must not be longer than 8 hours at 2 °C to 8 °C when reconstituted using water for injections that has not been refrigerated or not longer than 22 hours when reconstituted using refrigerated (2 °C to 8 °C) water for injections.

6.4 Special precautions for storage

Unopened vials
This medicinal product does not require any special storage conditions.

Reconstituted suspension
For storage conditions after reconstitution of the medicinal product, see section 6.3.

6.5 Nature and contents of container

Colourless type I glass vial sealed with butyl rubber stopper and aluminium seal with plastic button, containing 100 mg or 150 mg of azacitidine.

Pack sizes:
1 vial containing 100 mg Azacitidine.
1 vial containing 150 mg Azacitidine.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Recommendations for safe handling
Azacitidine Accord is a cytotoxic medicinal product and, as with other potentially toxic compounds, caution should be exercised when handling and preparing azacitidine suspensions. Procedures for proper handling and disposal of anticancer medicinal products should be applied.

If reconstituted azacitidine comes into contact with the skin, immediately and thoroughly wash with soap and water. If it comes into contact with mucous membranes, flush thoroughly with water.

Reconstitution procedure
Azacitidine Accord should be reconstituted with water for injections. The shelf life of the reconstituted medicinal product can be extended by reconstituting with refrigerated (2 °C to 8 °C) water for injections. Details on storage of the reconstituted product are provided below.

1. The following supplies should be assembled:
   Vial (s) of azacitidine; vial(s) of water for injections; non-sterile surgical gloves; alcohol wipes; 5 mL injection syringe(s) with needle(s).
2. The appropriate volume of water for injections (see table below) should be drawn into the syringe, making sure to purge any air trapped within the syringe.

Vial containing	Volume of water for injections	Final concentration
100 mg	4 mL	25 mg/mL
150 mg	6 mL	25 mg/mL

3. The needle of the syringe containing the water for injections should be inserted through the rubber top of the azacitidine vial followed by injection of the water for injections into the vial.
4. Following removal of the syringe and needle, the vial should be vigorously shaken until a uniform cloudy suspension is achieved. After reconstitution each mL of suspension will contain 25 mg of azacitidine (100 mg/4 mL or 150 mg/6 mL). The reconstituted product is a homogeneous, cloudy suspension, free of agglomerates. The product should be discarded if it contains large particles or agglomerates. Do not filter the suspension after reconstitution since this could remove the active substance. It must be taken into account that filters are present in some adaptors, spikes and closed systems; therefore such systems should not be used for administration of the medicinal product after reconstitution.
5. The rubber top should be cleaned and a new syringe with needle inserted into the vial. The vial should then be turned upside down, making sure the needle tip is below the level of the liquid. The plunger should then be pulled back to withdraw the amount of medicinal product required for the proper dose, making sure to purge any air trapped within the syringe. The syringe with needle should then be removed from the vial and the needle disposed of.
6. A fresh subcutaneous needle (recommended 25-gauge) should then be firmly attached to the syringe. The needle should not be purged prior to injection, in order to reduce the incidence of local injection site reactions.
7. When more than 1 vial is needed all the above steps for preparation of the suspension should be repeated. For doses requiring more than 1 vial, the dose should be equally divided e.g., dose 150 mg = 6 mL, 2 syringes with 3 mL in each syringe. Due to retention in the vial and needle, it may not be feasible to withdraw all of the suspension from the vial.

8. The contents of the dosing syringe must be re-suspended immediately prior to administration. The syringe filled with reconstituted suspension should be allowed up to 30 minutes prior to administration to reach a temperature of approximately 20 °C-25 °C. If the elapsed time is longer than 30 minutes, the suspension should be discarded appropriately and a new dose prepared. To re-suspend, vigorously roll the syringe between the palms until a uniform, cloudy suspension is achieved. The product should be discarded if it contains large particles or agglomerates.

Storage of the reconstituted product
For storage conditions after reconstitution of the medicinal product, see section 6.3.

Calculation of an individual dose
The total dose, according to the body surface area (BSA) can be calculated as follows:

Total dose (mg) = Dose (mg/m^2) x BSA (m^2)

The following table is provided only as an example of how to calculate individual azacitidine doses based on an average BSA value of 1.8 m^2.

Dose mg/m^2 *(% of recommended starting dose)*	Total dose based on BSA value of 1.8 m^2	Number of vials required		Total volume of reconstituted suspension required
		100 mg vial	150 mg vial	
75 mg/m^2 (100 %)	135 mg	2 vials	1 vial	5.4 mL
37.5 mg/m^2 (50 %)	67.5 mg	1 vial	1 vial	2.7 mL
25 mg/m^2 (33 %)	45 mg	1 vial	1 vial	1.8 mL

Method of administration
Reconstituted Azacitidine Accord should be injected subcutaneously (insert the needle at a 45-90°angle) using a 25-gauge needle into the upper arm, thigh or abdomen.

Doses greater than 4 mL should be injected into two separate sites.

Injection sites should be rotated. New injections should be given at least 2.5 cm from the previous site and never into areas where the site is tender, bruised, red, or hardened.

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

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center,
Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona, Spain

8. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1413/001
EU/1/19/1413/002

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 13th February 2020
Date of latest renewal: 19th December 2024

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

1. NAME OF THE MEDICINAL PRODUCT

Azacitidine Accord 200 mg film-coated tablets
Azacitidine Accord 300 mg film-coated tablets

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Azacitidine Accord 200 mg film-coated tablets
Each tablet contains 200 mg of azacitidine.

Excipient with known effect
Each tablet contains 4.5 mg of lactose (as lactose monohydrate).

Azacitidine Accord 300 mg film-coated tablets
Each tablet contains 300 mg of azacitidine.

Excipient with known effect
Each tablet contains 6.7 mg of lactose (as lactose monohydrate).

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Film-coated tablet (tablet).

Azacitidine Accord 200 mg film-coated tablets
Pink color, approximate 17 × 7.6 mm oval shaped film coated tablet debossed with “MA1” on one side and plain on the other side.

Azacitidine Accord 300 mg film-coated tablets
Brown, approximate 19 × 9 mm oval shaped film coated tablet debossed with “MA2” on one side and plain on the other side.

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Azacitidine Accord is indicated as maintenance therapy in adult patients with acute myeloid leukaemia (AML) who achieved complete remission (CR) or complete remission with incomplete blood count recovery (CRi) following induction therapy with or without consolidation treatment and who are not candidates for, including those who choose not to proceed to, hematopoietic stem cell transplantation (HSCT).

4.2 Posology and method of administration

Azacitidine Accord 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 Accord for the first 2 treatment cycles. Anti-emetic prophylaxis may be omitted after 2 cycles, if there has been no nausea and vomiting (see section 4.4).

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 Accord 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 Accord 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 (see section 4.4).

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 Accord 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).

Table 1: Dose adjustments for haematologic and non-haematologic adverse reactions

Criteria*	**Recommended action**
Grade 4 neutropenia or Grade 3 neutropenia with fever	First occurrence • Interrupt Azacitidine Accord. 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 (see section 4.4). Occurrence in 2 consecutive cycles • Interrupt Azacitidine Accord. 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 Accord. • Use supportive care such as GCSF, as clinically indicated (see section 4.4).
Grade 4 thrombocytopenia or Grade 3 thrombocytopenia with bleeding	First occurrence • Interrupt Azacitidine Accord. Resume the treatment cycle at the same dose once platelets return to Grade 2 or lower. Occurrence in 2 consecutive cycles • Interrupt Azacitidine Accord. 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 Accord.

Criteria*	Recommended action
Grade 3 or higher nausea, vomiting or diarrhoea	• Interrupt Azacitidine Accord. 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 (see section 4.4). • 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 Accord.
Other Grade 3 or higher non-haematological events	• Interrupt Azacitidine Accord 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 Accord 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 Accord.

*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 Accord 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 (see section 5.2).

Renal impairment
Azacitidine Accord can be administered to patients with mild, moderate or severe renal impairment without initial dose adjustment (see section 5.2).

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) (see section 5.2).

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 Accord in children and adolescents below 18 years have not been established. No data are available.

Method of administration

Azacitidine Accord is for oral use.
Azacitidine Accord 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 (see section 6.6).

4.3 Contraindications

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

Breast-feeding (see section 4.6).

4.4 Special warnings and precautions for use

Haematological toxicity
Treatment with Azacitidine Accord can be associated with neutropenia, thrombocytopenia and febrile neutropenia (see section 4.8 for frequencies). Interruption, reduction or discontinuation of Azacitidine Accord 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 (see section 4.2 table 1).

Gastrointestinal toxicity
Gastrointestinal toxicities were the most frequent adverse reactions in patients treated with Azacitidine Accord (see section 4.8). Patients should be administered prophylactic anti-emetic therapy for the first 2 cycles of Azacitidine Accord treatment (see section 4.2). Diarrhoea should be treated promptly at the onset of symptoms.
Interruption, reduction or discontinuation of Azacitidine Accord may be necessary to manage gastrointestinal toxicities (see section 4.2).

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 (see section 4.6).

Lactose intolerance
Azacitidine Accord 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 Interaction with other medicinal products and other forms of interaction

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 Accord exposure was minimally affected when co-administered with a proton pump inhibitor (omeprazole). Therefore, dose modification is not required when Azacitidine Accord 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 (see section 5.2).

Clinically relevant inhibitory or inductive effects of azacitidine on the metabolism of cytochrome P450 substrates are unlikely (see section 5.2). No clinically relevant drug-drug interactions are expected when Azacitidine Accord is co-administered with substrates of P-glycoprotein (P-gp), breast cancer resistance protein (BCRP), organic anion transporters (OAT) OAT1 and OAT3, organic anion 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 Fertility, pregnancy and lactation

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 (see sections 4.4 and 5.3).

Pregnancy
There are no adequate data from the use of Azacitidine Accord in pregnant women. Studies in mice and rats have shown reproductive and developmental toxicity (see section 5.3). The potential risk for humans is unknown. Based on results from animal studies and its mechanism of action, Azacitidine Accord 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 Accord, 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 Accord therapy (see section 4.3).

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 (see section 5.3). 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 Accord treatment.

4.7 Effects on ability to drive and use machines

Azacitidine Accord has minor influence on the ability to drive and use machines. Fatigue has been reported with the use of Azacitidine Accord. 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 Accord. The most common serious adverse reactions are febrile neutropenia (6.8%) and pneumonia (5.1%)[1].
Permanent discontinuation of Azacitidine Accord 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 Accord. 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 Accord.
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 Accord. A total of 236 patients received Azacitidine Accord. The median treatment duration was 11.6 months (range: 0.5 to 74.3 months) for Azacitidine Accord 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.

Table 2: Adverse drug reactions (ADRs) in AML patients receiving Azacitidine Accord maintenance therapy

System organ class	All grades[a] 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

System organ class	All grades[a] frequency
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 Accord 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 Accord. 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 Accord. See section 4.2 for monitoring and management guidance.

Gastrointestinal toxicity
Gastrointestinal toxicities were the most frequent adverse reactions in patients treated with Azacitidine Accord. Nausea (64.8%), vomiting (59.7%), and diarrhoea (50.4%) were reported in patients treated with Azacitidine Accord. 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 Accord. 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 Accord. See section 4.2 for monitoring and management guidance.

Reporting of suspected adverse reactions
Reporting suspected adverse reactions after authorisation 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 via the national reporting system listed in Appendix V.

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 Accord.

5. PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents, antimetabolites, pyrimidine analogues,
ATC code: L01BC07

Mechanism of action
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.

Clinical efficacy and safety

The efficacy and safety of Azacitidine Accord was studied in a multi-centre, placebo-controlled, Phase 3 study QUAZAR AML-001 (CC-486-AML-001) with a double-blind, randomised, parallel-group design which evaluated Azacitidine Accord versus placebo as maintenance therapy in AML patients. Patients were enrolled with *de novo* AML, AML secondary to prior diagnosis of myelodysplastic syndromes (MDS), or chronic myelomonocytic leukaemia (CMML); the patients were aged ≥ 55 years, and had achieved first complete remission (CR) or complete remission with incomplete blood count recovery (CRi) within 4 months (+/- 7 days) after intensive induction chemotherapy with or without consolidation therapy. Patients were not eligible for HSCT at the time of randomisation, which included patients who did not have a transplant donor, or who chose not to proceed to HSCT.

Patients in both treatment arms received best supportive care as deemed necessary by the investigator. Best supportive care included, but was not limited to, treatment with red blood cell (RBC) transfusions, platelet transfusions, use of erythropoiesis stimulating agent, antibiotic, antiviral and/or antifungal therapy, GCSF, anti-emetic therapy, and nutritional support.

Patients who achieved a CR/CRi after completion of intensive induction therapy with or without consolidation were administered Azacitidine Accord 300 mg (N=236) or placebo (N=233) once daily on Days 1 through 14 of each 28-day cycle. In the event of disease relapse (5% to 15% blasts in peripheral blood or bone marrow), the dose schedule was extended to 21 days of repeated 28-day treatment cycles per medical discretion. Treatment continued until disease progression (more than 15% blasts were observed in peripheral blood or bone marrow) or until unacceptable toxicity.

A total of 472 patients were randomised 1:1 between Azacitidine Accord and placebo treatment arms. Baseline demographic and disease characteristics for the AML patient population were balanced between treatment arms as shown in table 3. The median treatment duration was 11.6 months (range: 0.5 to 74.3 months) for the Azacitidine Accord arm *versus* 5.7 months (range: 0.7 to 68.5 months) for the placebo arm. A total of 51 patients (21%) receiving Azacitidine Accord and 40 patients (17%) receiving placebo extended their dose schedule to 300 mg daily for 21 days due to AML disease relapse.

Of the 469 patients in the Phase 3 study who received treatment, 61% (285/469) were 65 years of age or older and 11% (51/469) were 75 years of age or older. No overall differences in safety or efficacy of Azacitidine Accord were observed between these patients and younger patients.

Table 3: Baseline demographics and disease-related characteristics in study CC-486-AML-001

Parameter	**Azacitidine Accord (N = 238)**	**Placebo (N = 234)**
Age (years)		
Median (min, max)	68.0 (55, 86)	68.0 (55, 82)
Age category, n (%)		
<65 years	66 (27.7)	68 (29.1)
≥65 years to <75 years	144 (60.5)	142 (60.7)
≥75 years	28 (11.8)	24 (10.3)
Sex, n (%)		
Male	118 (49.6)	127 (54.3)
Female	120 (50.4)	107 (45.7)

Parameter	Azacitidine Accord (N = 238)	Placebo (N = 234)
Race, n (%)		
White	216 (90.8)	197 (84.2)
Black or African American	2 (0.8)	6 (2.6)
Asian	6 (2.5)	20 (8.5)
Other	12 (5.0)	11 (4.7)
Not collected or reported	2 (0.8)	0 (0)
ECOG performance status, n (%)		
0	116 (48.7)	111 (47.4)
1	101 (42.4)	106 (45.3)
2	21 (8.8)	15 (6.4)
3	0 (0)	2 (0.9)
Cytogenetic risk status at diagnosis, n (%)		
Intermediate risk[1]	203 (85.3)	203 (86.6)
Poor risk[2]	35 (14.7)	31 (13.2)
Initial AML classification, n (%)		
AML with recurrent genetic abnormalities	39 (16.4)	46 (19.7)
AML with myelodysplasia-related changes	49 (20.6)	42 (17.9)
Therapy related myeloid neoplasms	2 (0.8)	0 (0)
AML not otherwise specified	148 (62.2)	145 (62.0)
Missing	0 (0)	1 (0.4)
Type of AML, n (%)		
Primary (de novo)	213 (89.5)	216 (92.3)
Secondary	25 (10.5)	18 (7.7)
MRD status at randomisation[3], n (%)		
Negative	133 (55.9)	111 (47.4)
Positive	103 (43.3)	116 (49.6)
Missing	2 (0.8)	7 (3.0)

AML=Acute myelogenous leukemia; MDS=Myelodysplastic syndrome; CMML=Chronic myelomonocytic Leukemia; ECOG=Eastern cooperative oncology group; CR=Morphologic complete remission; CRi=Morphologic CR with incomplete blood count recovery.

[1]Intermediate risk was defined as normal cytogenetics +8, t(9;11), or other undefined.

[2]Poor risk was defined as complex (≥ 3 abnormalities): -5; 5q-; -7; 7q-; 11q23 - non t(9;11); inv(3); t(3;3); t(6;9); or t(9;22). Source for Intermediate and Poor Risk: National comprehensive cancer network clinical practice guidelines in oncology for AML.

[3]MRD status in bone marrow was measured during screening period by flow cytometric assay at a sensitivity level of 0.1%.

Most patients received consolidation therapy after induction therapy in both the Azacitidine Accord (78%) and placebo (82%) treatment arms; more than 90% of these patients in each treatment arm received 1 or 2 cycles of consolidation therapy after induction therapy (table 4).

Table 4: Consolidation therapy in study CC-486-AML-001

Parameter	Azacitidine Accord (N = 238)	Placebo (N = 234)
Received consolidation therapy following induction		
Yes, n (%)	186 (78.2)	192 (82.1)
1 Cycle, n (%)	110 (46.2)	102 (43.6)
2 Cycles, n (%)	70 (29.4)	77 (32.9)
3 Cycles, n (%)	6 (2.5)	13 (5.6)
No, n (%)	52 (21.8)	42 (17.9)

Parameter	Azacitidine Accord (N = 238)	Placebo (N = 234)
CR / CRi status at randomisation		
CR, n (%)	183 (76.9)	177 (75.6)
CRi, n (%)	50 (21.0)	44 (18.8)
Not in CR/CRi [a], n (%)	5 (2.1)	11 (4.7)
Missing, n (%)	0 (0)	2 (0.9)

CR=Complete remission; CRi=Morphologic CR with incomplete blood count recovery.

[a] These patients had baseline bone marrow of less than 5% blasts and both ANC <1 x 10^9 and platelets <100 x 10^9.

The efficacy of Azacitidine Accord in adult patients with AML was established based on overall survival (OS) and relapse-free survival (RFS).

The efficacy results are summarised in the table 5.

Table 5: CC-486-AML-001 efficacy results (ITT Population)

Endpoints	Azacitidine Accord (N=238)	Placebo (N=234)
Overall survival		
OS events, n (%)	158 (66.4)	171 (73.1)
Median OS, months (95% CI)	24.7 (18.7, 30.5)	14.8 (11.7, 17.6)
Hazard ratio (95% CI) p-value	0.69 (0.55, 0.86) 0.0009	
Relapse-free survival		
Events, n (%)	164 (68.9)	181 (77.4)
Median RFS, months (95% CI)	10.2 (7.9, 12.9)	4.8 (4.6, 6.4)
Hazard ratio (95% CI) p-value	0.65 (0.52, 0.81) 0.0001	
Time to relapse		
Relapsed, n (%)	154 (64.7)	179 (76.5)
Median time to relapse, months (95% CI)	10.2 (8.3, 13.4)	4.9 (4.6, 6.4)
Time to discontinuation from treatment		
Treatment discontinued, n (%)	193 (81.1)	208 (88.9)
Median time to treatment discontinuation, months (95% CI)	11.4 (9.8, 13.6)	6.1 (5.1, 7.4)
Treatment discontinued - disease relapse, n (%)	143 (60.1)	180 (76.9)

CI=Confidence interval.

Prespecified subgroup analyses of OS and RFS showed a consistent treatment effect for Azacitidine Accord across demographic and disease-related subgroups including baseline cytogenetic risk, the number of prior consolidation cycles received, and CR/CRi status.

The Kaplan-Meier curves display the OS (see figure 1) and RFS (see figure 2) results.

Figure 1: Kaplan-Meier curve for overall survival: Azacitidine Accord *versus* placebo (ITT Population)

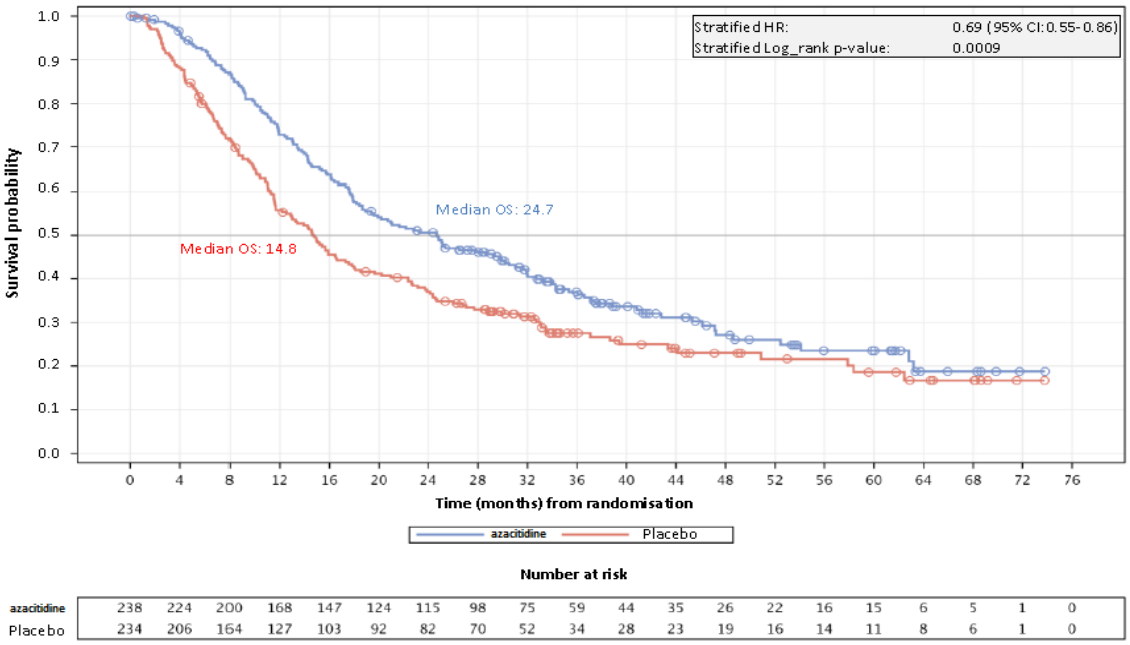
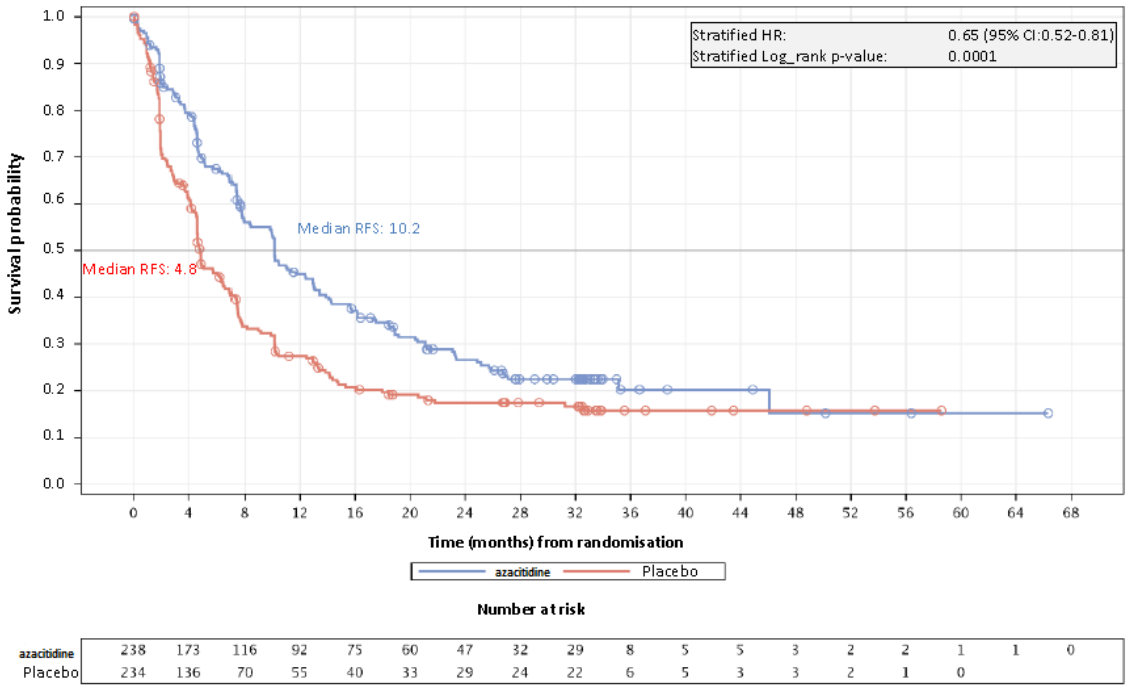


Figure 2: Kaplan-Meier curve for relapse free survival: Azacitidine Accord *versus* placebo (ITT Population)



In patients who had their dose schedule extended to 300 mg for 21 days due to disease relapse, the median OS (22.8 months for Azacitidine Accord and 14.6 months for placebo) and median RFS (7.4 months for Azacitidine Accord and 4.6 months for placebo) were comparable to the overall study results.

Azacitidine Accord demonstrated a favorable treatment effect for OS compared with placebo in both minimal residual disease (MRD)-positive and MRD-negative patients. The treatment effect for OS was more pronounced in MRD-positive patients (HR=0.69; 95% CI: 0.51, 0.93) than in MRD-negative patients (HR=0.81; 95% CI: 0.59, 1.12).

Health related quality of life (HRQoL)
HRQoL was assessed using the Functional assessment of chronic illness therapy-fatigue scale (FACIT - fatigue scale) and the Five dimensions three levels (EQ-5D-3L) health utility index and visual analogue scale (VAS). At baseline, patients had a low level of fatigue and good level of HRQoL that were generally comparable to those of the general population of similar age. This level of HRQoL was maintained over time with Azacitidine Accord, as compared to baseline, as well as to placebo. Both the time to definitive deterioration and the proportion of patients experiencing clinically meaningful deterioration was found to be similar between those receiving Azacitidine Accord and placebo. Overall, the findings demonstrate that HRQoL was similar between Azacitidine Accord treatment and placebo arms, with no clinically meaningful deterioration over time.

5.2 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 Accord was minimal. Therefore, Azacitidine Accord 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 1 242 L/hour and the geometric mean half-life was approximately 0.5 hours. Following intravenous administration of ^{14}C azacitidine to 5 cancer patients, the cumulative urinary excretion was 85% of the radioactive dose. Faecal excretion accounted for < 1% of administered radioactivity over 3 days. Mean excretion of radioactivity in urine following subcutaneous administration of ^{14}C-azacitidine was 50%. The amount of unchanged azacitidine recovered in urine relative to dose was < 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 Accord. Therefore, dose modification for Azacitidine Accord 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/m^2/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 Accord 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 Accord 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 Accord is recommended in patients with mild, moderate, or severe renal impairment.

Race/ethnicity
The effects of race/ethnicity on the PK of Azacitidine Accord is unknown.

5.3 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 (see section 4.6).

6. PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Tablet core
Mannitol,
Silicified microcrystalline cellulose,
Croscarmellose sodium
Magnesium stearate

Film-coating
For 200 mg:
Hypromellose (E464)
Lactose monohydrate
Polyethylene glycol (E1521)
Triacetin (E1518)
Titanium dioxide (E171)
Iron oxide red (E172)

For 300 mg:
Hypromellose (E464)
Lactose monohydrate
Polyethylene glycol (E1521)
Triacetin (E1518)
Titanium dioxide (E171)
Iron oxide red (E172)
Iron oxide yellow (E172)
Iron oxide black (E172)

6.2 Incompatibilities

Not applicable.

6.3 Shelf life

3 years

6.4 Special precautions for storage

This medicinal product does not require any special storage conditions.

6.5 Nature and contents of container

Azacitidine Accord 200 mg, 300 mg film-coated tablets

The film-coated tablets are available in carton containing 7 and 14 film-coated tablets in alu-alu blisters or alu/PVC/PCTFE blister with push through aluminium foil, and in carton containing 7 × 1 and 14 × 1 film-coated tablets in cross-perforated unit-dose blisters.

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Azacitidine Accord is a cytotoxic medicinal product. If powder from the film-coated tablets makes contact with the skin, the skin should be washed immediately and thoroughly with soap and water. If the powder comes in contact with mucous membranes, the area should be thoroughly flushed with water.

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

7. MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n
Edifici Est, 6ª Planta
08039 Barcelona
Spain

8. MARKETING AUTHORISATION NUMBER(S)

Azacitidine Accord 200 mg film-coated tablets

alu-alu blisters

EU/1/19/1413/003 7 tablets
EU/1/19/1413/004 14 tablets
EU/1/19/1413/005 7 x 1 tablets (unit dose)
EU/1/19/1413/006 14 x 1 tablets (unit dose)

alu/PVC/PCTFE blister

EU/1/19/1413/007 7 tablets
EU/1/19/1413/008 14 tablets
EU/1/19/1413/009 7 x 1 tablets (unit dose)
EU/1/19/1413/010 14 x 1 tablets (unit dose)

Azacitidine Accord 300 mg film-coated tablets

alu-alu blisters

EU/1/19/1413/011 7 tablets
EU/1/19/1413/012 14 tablets
EU/1/19/1413/013 7 x 1 tablets (unit dose)
EU/1/19/1413/014 14 x 1 tablets (unit dose)

alu/PVC/PCTFE blister

EU/1/19/1413/015 7 tablets
EU/1/19/1413/016 14 tablets
EU/1/19/1413/017 7 x 1 tablets (unit dose)
EU/1/19/1413/018 14 x 1 tablets (unit dose)

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 17 September 2025

10. DATE OF REVISION OF THE TEXT

Detailed information on this medicinal product is available on the website of the European Medicines Agency https://www.ema.europa.eu.

ANNEX II

A. MANUFACTURER(S) RESPONSIBLE FOR BATCH RELEASE

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

A. MANUFACTURERS RESPONSIBLE FOR BATCH RELEASE

Name and address of the manufacturer(s) responsible for batch release

Accord Healthcare Polska Sp.z.o.o.
ul. Lutomierska 50,
95-200, Pabianice,
Poland

Laboratori Fundació Dau (For Azacitidine Accord 25 mg/mL powder for suspension for injection Only)
C/ C, 12-14 Pol. Ind.
Zona Franca, Barcelona, 08040,
Spain

Accord Healthcare B.V., (For Azacitidine Accord 200 mg, 300 mg film-coated tablets Only)
Winthontlaan 200,
3526 KV Utrecht,
The Netherlands

Accord Healthcare Single Member S.A.
64th Km National Road Athens,
Lamia, Schimatari, 32009,
Greece

The printed package leaflet of the medicinal product must state the name and address of the manufacturer responsible for the release of the concerned batch.

B. CONDITIONS OR RESTRICTIONS REGARDING SUPPLY AND USE

Medicinal product subject to restricted medical prescription (See Annex I: Summary of Product Characteristics, section 4.2)

C. OTHER CONDITIONS AND REQUIREMENTS OF THE MARKETING AUTHORISATION

- **Periodic safety update reports (PSURs)**

The requirements for submission of periodic safety update reports for this medicinal product are set out in the list of Union reference dates (EURD list) provided for under Article 107c(7) of Directive 2001/83/EC and any subsequent updates published on the European medicines web-portal.

D. CONDITIONS OR RESTRICTIONS WITH REGARD TO THE SAFE AND EFFECTIVE USE OF THE MEDICINAL PRODUCT

- **Risk Management plan (RMP)**

The MAH shall perform the required pharmacovigilance activities and interventions detailed in the agreed RMP presented in Module 1.8.2 of the marketing authorisation and any agreed subsequent updates of the RMP.

An updated RMP should be submitted:

- At the request of the European Medicines Agency,
- Whenever the risk management system is modified, especially as the result of new information being received that may lead to a significant change to the benefit/risk profile or as the result of an important (pharmacovigilance or risk minimisation) milestone being reached.

ANNEX III

LABELLING AND PACKAGE LEAFLET

A. LABELLING

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

OUTER CARTON

1. NAME OF THE MEDICINAL PRODUCT

Azacitidine Accord 25 mg/mL powder for suspension for injection
azacitidine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each vial contains 100 mg azacitidine. After reconstitution, each mL suspension contains 25 mg azacitidine.

Each vial contains 150 mg azacitidine. After reconstitution, each mL suspension contains 25 mg azacitidine.

3. LIST OF EXCIPIENTS

Also contains mannitol.

4. PHARMACEUTICAL FORM AND CONTENTS

Powder for suspension for injection.

100 mg
150 mg

1 vial

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
For single use only. Shake the suspension vigorously before administration.
Subcutaneous use.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

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

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center,
Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona, Spain

12. MARKETING AUTHORISATION NUMBER(S)

EU/1/19/1413/001
EU/1/19/1413/002

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

Medicinal product subject to medical prescription

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Justification for not including Braille accepted.

17. UNIQUE IDENTIFIER – 2D BARCODE

2 D bar code carrying the unique identifier

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON SMALL IMMEDIATE PACKAGING UNITS

VIAL LABEL

1. NAME OF THE MEDICINAL PRODUCT AND ROUTE(S) OF ADMINISTRATION

Azacitidine Accord 25 mg/mL powder for suspension for injection
azacitidine
Subcutaneous use (SC)

2. METHOD OF ADMINISTRATION

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. CONTENTS BY WEIGHT, BY VOLUME OR BY UNIT

100 mg
150 mg

6. OTHER

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Azacitidine Accord 200 mg film-coated tablets
azacitidine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 200 mg of azacitidine.

3. LIST OF EXCIPIENTS

Contains lactose.
See the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
7 tablets
14 tablets
7 × 1 tablet
14 × 1 tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

Do not split, crush, dissolve or chew the tablets.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n
Edifici Est, 6ª Planta
08039 Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

alu-alu blisters

EU/1/19/1413/003
EU/1/19/1413/004
EU/1/19/1413/005
EU/1/19/1413/006

alu/PVC/PCTFE blister

EU/1/19/1413/007
EU/1/19/1413/008
EU/1/19/1413/009
EU/1/19/1413/010

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Azacitidine Accord 200 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS or PERFORATED UNIT DOSE BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

Azacitidine Accord 200 mg tablets
azacitidine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Oral use.

PARTICULARS TO APPEAR ON THE OUTER PACKAGING

CARTON

1. NAME OF THE MEDICINAL PRODUCT

Azacitidine Accord 300 mg film-coated tablets
azacitidine

2. STATEMENT OF ACTIVE SUBSTANCE(S)

Each tablet contains 300 mg of azacitidine.

3. LIST OF EXCIPIENTS

Contains lactose.
See the leaflet for further information.

4. PHARMACEUTICAL FORM AND CONTENTS

Film-coated tablet
7 tablets
14 tablets
7 × 1 tablet
14 × 1 tablet

5. METHOD AND ROUTE(S) OF ADMINISTRATION

Read the package leaflet before use.
Oral use.

Do not split, crush, dissolve or chew the tablets.

6. SPECIAL WARNING THAT THE MEDICINAL PRODUCT MUST BE STORED OUT OF THE SIGHT AND REACH OF CHILDREN

Keep out of the sight and reach of children.

7. OTHER SPECIAL WARNING(S), IF NECESSARY

Cytotoxic.

8. EXPIRY DATE

EXP

9. SPECIAL STORAGE CONDITIONS

10. SPECIAL PRECAUTIONS FOR DISPOSAL OF UNUSED MEDICINAL PRODUCTS OR WASTE MATERIALS DERIVED FROM SUCH MEDICINAL PRODUCTS, IF APPROPRIATE

Dispose of in accordance with local requirements.

11. NAME AND ADDRESS OF THE MARKETING AUTHORISATION HOLDER

Accord Healthcare S.L.U.
World Trade Center, Moll de Barcelona s/n
Edifici Est, 6ª Planta
08039 Barcelona
Spain

12. MARKETING AUTHORISATION NUMBER(S)

alu-alu blisters

EU/1/19/1413/011
EU/1/19/1413/012
EU/1/19/1413/013
EU/1/19/1413/014

alu/PVC/PCTFE blister

EU/1/19/1413/015
EU/1/19/1413/016
EU/1/19/1413/017
EU/1/19/1413/018

13. BATCH NUMBER

Lot

14. GENERAL CLASSIFICATION FOR SUPPLY

15. INSTRUCTIONS ON USE

16. INFORMATION IN BRAILLE

Azacitidine Accord 300 mg

17. UNIQUE IDENTIFIER – 2D BARCODE

2D barcode carrying the unique identifier included.

18. UNIQUE IDENTIFIER - HUMAN READABLE DATA

PC
SN
NN

MINIMUM PARTICULARS TO APPEAR ON BLISTERS OR STRIPS

BLISTERS or PERFORATED UNIT DOSE BLISTER PACK

1. NAME OF THE MEDICINAL PRODUCT

Azacitidine Accord 300 mg tablets
azacitidine

2. NAME OF THE MARKETING AUTHORISATION HOLDER

Accord

3. EXPIRY DATE

EXP

4. BATCH NUMBER

Lot

5. OTHER

Oral use.

B. PACKAGE LEAFLET

Package leaflet: Information for the user

Azacitidine Accord 25 mg/mL powder for suspension for injection
azacitidine

Read all of this leaflet carefully before you start using this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- If you get any side effects talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Azacitidine Accord is and what it is used for
2. What you need to know before you use Azacitidine Accord
3. How to use Azacitidine Accord
4. Possible side effects
5. How to store Azacitidine Accord
6. Contents of the pack and other information

1. What Azacitidine Accord is and what it is used for

What Azacitidine Accord is
Azacitidine Accord is an anti-cancer agent which belongs to a group of medicines called 'anti-metabolites'. Azacitidine Accord contains the active substance 'azacitidine'.

What Azacitidine Accord is used for
Azacitidine Accord is used in adults who are not able to have a stem cell transplantation to treat:
- higher-risk myelodysplastic syndromes (MDS).
- chronic myelomonocytic leukaemia (CMML).
- acute myeloid leukaemia (AML).

These are diseases which affect the bone marrow and can cause problems with normal blood cell production.

How Azacitidine Accord works
Azacitidine Accord works by preventing cancer cells from growing. Azacitidine becomes incorporated into the genetic material of cells (ribonucleic acid (RNA) and deoxyribonucleic acid (DNA)). It is thought to work by altering the way the cell turns genes on and off and also by interfering with the production of new RNA and DNA. These actions are thought to correct problems with the maturation and growth of young blood cells in the bone marrow that cause myelodysplastic disorders, and to kill cancerous cells in leukaemia.

Talk to your doctor or nurse if you have any questions about how Azacitidine Accord works or why this medicine has been prescribed for you.

2. What you need to know before you use Azacitidine Accord

Do not use Azacitidine Accord
- if you are allergic to azacitidine or any of the other ingredients of this medicine (listed in section 6).
- if you have advanced liver cancer.
- if you are breast-feeding.

Warnings and precautions
Talk to your doctor, pharmacist or nurse before using Azacitidine Accord:
- if you have decreased counts of platelets, red or white blood cells.
- if you have kidney disease.
- if you have liver disease.
- if you have ever had a heart condition or heart attack or any history of lung disease.

Azacitidine Accord can cause a serious immune reaction called 'differentiation syndrome' (see section 4).

Blood test
You will have blood tests before you begin treatment with Azacitidine Accord and at the start of each period of treatment (called a 'cycle'). This is to check that you have enough blood cells and that your liver and kidneys are working properly.

Children and adolescents
Azacitidine Accord is not recommended for use in children and adolescents below the age of 18.

Other medicines and Azacitidine Accord
Tell your doctor or pharmacist if you are using, have recently used or might use any other medicines. This is because Azacitidine Accord may affect the way some other medicines work. Also, some other medicines may affect the way Azacitidine Accord works.

Pregnancy, breast-feeding and fertility

Pregnancy
You should not use Azacitidine Accord during pregnancy as it may be harmful to the baby.
If you are a woman who can become pregnant you should use an effective method of contraception while taking Azacitidine Accord and for 6 months after stopping treatment with Azacitidine Accord. Tell your doctor straight away if you become pregnant during treatment.

If you are pregnant or breast-feeding, think you may be pregnant or are planning to have a baby, ask your doctor or pharmacist for advice before taking this medicine.

Breast-feeding
You should not breast-feed when using Azacitidine Accord. It is not known if this medicine passes into human milk.

Fertility
Men should not father a child while receiving treatment with Azacitidine Accord. Men should use an effective method of contraception while taking Azacitidine Accord and for 3 months after stopping treatment with Azacitidine Accord.

Talk to your doctor if you wish to conserve your sperm before starting this treatment.

Driving and using machines
Do not drive or use any tools or machines if you experience side effects, such as tiredness.

3. How to use Azacitidine Accord

Before giving you Azacitidine Accord, your doctor will give you another medicine to prevent nausea and vomiting at the start of each treatment cycle.

- The recommended dose is 75 mg per m^2 body surface area. Your doctor will decide your dose of this medicine, depending on your general condition, height and weight. Your doctor will check your progress and may change your dose if necessary.

- Azacitidine Accord is given every day for one week, followed by a rest period of 3 weeks. This "treatment cycle" will be repeated every 4 weeks. You will usually receive at least 6 treatment cycles.

This medicine will be given to you as an injection under the skin (subcutaneously) by a doctor or nurse. It may be given under the skin on your thigh, tummy or upper arm.

If you have any further questions on the use of this medicine, ask your doctor, pharmacist or nurse.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Tell your doctor straight away if you notice any of the following side effects:
- Drowsiness, shaking, jaundice, abdominal bloating and easy bruising. These may be symptoms of liver failure and can be life-threatening.
- **Swelling of the legs and feet, back pain, reduced passing of water, increased thirst, rapid pulse, dizziness and nausea, vomiting or reduced appetite and feelings of confusion, restlessness or fatigue.** These may be symptoms of kidney failure and can be life-threatening.
- **A fever**. This could be due to an infection as a result of having low levels of white blood cells, which can be life-threatening.
- **Chest pain or shortness of breath which may be accompanied with a fever.** This may be due to an infection of the lung called "pneumonia", and can be life-threatening.
- **Bleeding.** Such as blood in the stools due to bleeding in the stomach or gut, or such as bleeding inside your head. These may be symptoms of having low levels of platelets in your blood.
- **Difficulty breathing, swelling of the lips, itching or rash.** This may be due to an allergic (hypersensitivity) reaction.

Other side effects include:

Very common side effects (may affect more than 1 in 10 people)
- Reduced red blood count (anaemia). You may feel tired and pale.
- Reduced white blood cell count. This may be accompanied by a fever. You are also more likely to get infections.
- A low blood platelet count (thrombocytopenia). You are more prone to bleeding and bruising.
- Constipation, diarrhoea, nausea, vomiting.
- Pneumonia.
- Chest pain, being short of breath.
- Tiredness (fatigue).
- Injection site reaction including redness, pain or a skin reaction.
- Loss of appetite.
- Joint aches.
- Bruising.
- Rash.
- Red or purple spots under your skin.
- Pain in your belly (abdominal pain).
- Itching.
- Fever.
- Sore nose and throat.
- Dizziness.
- Headache.
- Having trouble sleeping (insomnia).
- Nosebleeds (epistaxis).
- Muscle aches.
- Weakness (asthenia).
- Weight loss.

- Low levels of potassium in your blood.

Common side effects (may affect up to 1 in 10 people)
- Bleeding inside your head.
- An infection of the blood caused by bacteria (sepsis). This may be due to low levels of white cells in your blood.
- Bone marrow failure. This can cause low levels of red and white blood cells and platelets.
- A type of anaemia where your red and white blood cells and platelets are reduced.
- An infection in your urine.
- A viral infection causing cold sores (herpes).
- Bleeding gums, bleeding in the stomach or gut, bleeding from around your back passage due to piles (haemorrhoidal haemorrhage), bleeding in your eye, bleeding under your skin, or into your skin (haematoma).
- Blood in your urine.
- Ulcers of your mouth or tongue.
- Changes to your skin at the injection site. These include swelling, a hard lump, bruising, bleeding into your skin (haematoma), rash, itching and changes in the skin colour.
- Redness of your skin.
- Skin infection (cellulitis).
- An infection of the nose and throat, or sore throat.
- Sore or runny nose or sinuses (sinusitis)..
- High or low blood pressure (hypertension or hypotension).
- Being short of breath when you move.
- Pain in your throat and voicebox.
- Indigestion.
- Lethargy.
- Feeling generally unwell.
- Anxiety.
- Being confused.
- Hair loss.
- Kidney failure.
- Dehydration.
- White coating covering tongue, inner cheeks, and sometimes on the roof of your mouth, gums and tonsils (oral fungal infection).
- Fainting.
- A fall in blood pressure when standing (orthostatic hypotension) leading to dizziness when moving to a standing or sitting position.
- Sleepiness, drowsiness (somnolence).
- Bleeding due to a catheter line.
- A disease affecting the gut which can result in fever, vomiting and stomach pain (diverticulitis).
- Fluid around the lungs (pleural effusion).
- Shivering (chills).
- Muscle spasms.
- Raised itchy rash on the skin (urticaria).
- Collection of fluid around the heart (pericardial effusion).

Uncommon side effects (may affect up to 1 in 100 people)
- Allergic (hypersensitivity) reaction.
- Shaking.
- Liver failure.
- Large plum-coloured, raised painful patches on the skin with fever.
- Painful skin ulceration (pyoderma gangrenosum).
- Inflammation of the lining around the heart (pericarditis).

Rare side effects (may affect up to 1 in 1,000 people)
- Dry cough.
- Painless swelling in the finger tips (clubbing).

- Tumour lysis syndrome - Metabolic complications that can occur during treatment of cancer and sometimes even without treatment. These complications are caused by the product of dying cancer cells and may include the following: changes to blood chemistry; high potassium, phosphorus, uric acid, and low calcium consequently leading to changes in kidney function, heartbeat, seizures, and sometimes death.

Not known (frequency cannot be estimated from the available data)
- Infection of the deeper layers of skin, which spreads quickly, damaging the skin and tissue, which can be life-threatening (necrotizing fasciitis).
- Serious immune reaction (differentiation syndrome) that may cause fever, cough, difficulty breathing, rash, decreased urine, low blood pressure (hypotension), swelling of the arms or legs and rapid weight gain.
- Inflammation of blood vessels in the skin which may result in rash (cutaneous vasculitis)

Reporting of side effects
If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. You can also report side effects directly the national reporting system listed in Appendix V. By reporting side effects you can help provide more information on the safety of this medicine.

5. How to store Azacitidine Accord

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the vial label and the carton. The expiry date refers to the last day of that month.

Your doctor, pharmacist or nurse are responsible for storing Azacitidine Accord. They are also responsible for preparing and disposing of any unused Azacitidine Accord correctly.

For unopened vials of this medicine – there are no special storage conditions.

When using immediately
Once the suspension has been prepared it should be administered within 60 minutes.

When using later on
If the Azacitidine Accord suspension is prepared using water for injections that has not been refrigerated, the suspension must be placed in the refrigerator (2 °C – 8 °C) immediately after it is prepared and kept refrigerated for up to a maximum of 8 hours.

If the Azacitidine Accord suspension is prepared using water for injections that has been stored in the refrigerator (2 °C – 8 °C), the suspension must be placed in the refrigerator (2 °C – 8 °C) immediately after it is prepared and kept refrigerated for up to a maximum of 22 hours.

The suspension should be allowed up to 30 minutes prior to administration to reach room temperature (20 °C – 25 °C).

If large particles are present in the suspension it should be discarded.

6. Contents of the pack and other information

What Azacitidine Accord contains
- The active substance is azacitidine. One vial contains 100 mg or 150 mg azacitidine. After reconstitution with 4 mL or 6 mL of water for injections, the reconstituted suspension contains 25 mg/mL azacitidine.

- The other ingredient is mannitol (E421).

What Azacitidine Accord looks like and contents of the pack
Azacitidine Accord is a white powder for suspension for injection and is supplied in a glass vial containing 100 mg or 150 mg of azacitidine.
Pack sizes
1 vial containing 100 mg Azacitidine.
1 vial containing 150 mg Azacitidine.

Marketing Authorisation Holder
Accord Healthcare S.L.U.
World Trade Center,
Moll de Barcelona, s/n,
Edifici Est 6ª planta,
08039 Barcelona, Spain

Manufacturer

Accord Healthcare Polska Sp.z o.o.
ul. Lutomierska 50,
95-200 Pabianice
Poland

Or
Laboratori Fundació Dau
C/ C, 12-14 Pol. Ind.
Zona Franca, Barcelona, 08040,
Spain

Or
Accord Healthcare Single Member S.A.
64th Km National Road Athens,
Lamia, Schimatari, 32009,
Greece

For any information about this medicine, please contact the local representative of the Marketing Authorisation Holder:

AT / BE / BG / CY / CZ / DE / DK / EE / FI / FR / HR / HU / IE / IS / IT / LT / LV / LU / MT / NL / NO / PT / PL / RO / SE / SI / SK / ES
Accord Healthcare S.L.U.
Tel: +34 93 301 00 64

EL
Win Medica Pharmaceutical S.A.
Tel: +30 210 7488 821

This leaflet was last revised in {MM/YYYY}.

Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu. There are also links to other websites about rare diseases and treatments.

The following information is intended for healthcare professionals only:

Recommendations for safe handling
Azacitidine Accord is a cytotoxic medicinal product and, as with other potentially toxic compounds, caution should be exercised when handling and preparing azacitidine suspensions. Procedures for proper handling and disposal of anticancer medicinal products should be applied.

If reconstituted azacitidine comes into contact with the skin, immediately and thoroughly wash with soap and water. If it comes into contact with mucous membranes, flush thoroughly with water.

Incompatibilities
This medicinal product must not be mixed with other medicinal products except those mentioned below (see "Reconstitution Procedure").

Reconstitution procedure
Azacitidine Accord should be reconstituted with water for injections. The shelf life of the reconstituted medicinal product can be extended by reconstituting with refrigerated (2 °C to 8 °C) water for injections. Details on storage of the reconstituted product are provided below.

1. The following supplies should be assembled:
   Vial(s) of azacitidine; vial(s) of water for injections; non-sterile surgical gloves; alcohol wipes; 5 mL injection syringe(s) with needle(s).
2. The appropriate volume of water for injections should be drawn into the syringe, making sure to purge any air trapped within the syringe.

Vial containing	Volume of water for injections	Final concentration
100 mg	4 ml	25 mg/ml
150 mg	6 ml	25 mg/ml

3. The needle of the syringe containing the water for injections should be inserted through the rubber top of the azacitidine vial followed by injection of the water for injections into the vial.
4. Following removal of the syringe and needle, the vial should be vigorously shaken until a uniform cloudy suspension is achieved. After reconstitution each mL of suspension will contain 25 mg of azacitidine (100 mg/4 mL or 150 mg/6 mL). The reconstituted product is a homogeneous, cloudy suspension, free of agglomerates. The product should be discarded if it contains large particles or agglomerates. Do not filter the suspension after reconstitution since this could remove the active substance. It must be taken into account that filters are present in some adaptors, spikes and closed systems; therefore such systems should not be used for administration of the medicinal product after reconstitution.
5. The rubber top should be cleaned and a new syringe with needle inserted into the vial. The vial should then be turned upside down, making sure the needle tip is below the level of the liquid. The plunger should then be pulled back to withdraw the amount of medicinal product required for the proper dose, making sure to purge any air trapped within the syringe. The syringe with needle should then be removed from the vial and the needle disposed of.
6. A fresh subcutaneous needle (recommended 25-gauge) should then be firmly attached to the syringe. The needle should not be purged prior to injection, in order to reduce the incidence of local injection site reactions.
7. When more than 1 vial is needed all the above steps for preparation of the suspension should be repeated. For doses requiring more than 1 vial, the dose should be equally divided e.g., dose 150 mg = 6 mL, 2 syringes with 3 mL in each syringe. Due to retention in the vial and needle, it may not be feasible to withdraw all of the suspension from the vial.
8. The contents of the dosing syringe must be re-suspended immediately prior to administration. The temperature of the suspension at the time of injection should be approximately 20 ºC-25 ºC. To re-suspend, vigorously roll the syringe between the palms until a uniform, cloudy suspension is achieved. The product should be discarded if it contains large particles or agglomerates.

Storage of the reconstituted product

For immediate use
The Azacitidine Accord suspension may be prepared immediately before use and the reconstituted suspension should be administered within 60 minutes. If elapsed time is greater than 60 minutes, the reconstituted suspension should be discarded appropriately and a new dose prepared.

For later use
When reconstituting using water for injections that has not been refrigerated, the reconstituted suspension must be placed in a refrigerator (2 °C to 8 °C) immediately after reconstitution, and kept in the refrigerator for a maximum of 8 hours. If the elapsed time in the refrigerator is greater than 8 hours, the suspension should be discarded appropriately and a new dose prepared.

When reconstituting using refrigerated (2 °C to 8 °C) water for injections, the reconstituted suspension must be placed in a refrigerator (2 °C to 8 °C) immediately after reconstitution, and kept in a refrigerator for a maximum of 22 hours. If the elapsed time in the refrigerator is greater than 22 hours, the suspension should be discarded appropriately and a new dose prepared.

The syringe filled with reconstituted suspension should be allowed up to 30 minutes prior to administration to reach a temperature of approximately 20 ºC-25 ºC. If the elapsed time is longer than 30 minutes, the suspension should be discarded appropriately and a new dose prepared.

Calculation of an individual dose
The total dose, according to the body surface area (BSA) can be calculated as follows:

Total dose (mg) = Dose (mg/m^2) x BSA (m^2)

The following table is provided only as an example of how to calculate individual azacitidine doses based on an average BSA value of 1.8 m^2.

Dose mg/m^2 *(% of recommended starting dose)*	Total dose based on BSA value of 1.8 m^2	Number of vials required		Total volume of reconstituted suspension required
		100 mg vial	150 mg vial	
75 mg/m^2 (100 %)	135 mg	2 vials	1 vial	5.4 mL
37.5 mg/m^2 (50 %)	67.5 mg	1 vial	1 vial	2.7 mL
25 mg/m^2 (33 %)	45 mg	1 vial	1 vial	1.8 mL

Method of administration
Do not filter the suspension after reconstitution.

Reconstituted Azacitidine Accord should be injected subcutaneously (insert the needle at a 45-90ºangle) using a 25-gauge needle into the upper arm, thigh or abdomen.

Doses greater than 4 mL should be injected into two separate sites.

Injection sites should be rotated. New injections should be given at least 2.5 cm from the previous site and never into areas where the site is tender, bruised, red, or hardened.

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

Package leaflet: Information for the user

Azacitidine Accord 200 mg film-coated tablets
Azacitidine Accord 300 mg film-coated tablets
azacitidine

Read all of this leaflet carefully before you start taking this medicine because it contains important information for you.
- Keep this leaflet. You may need to read it again.
- If you have any further questions, ask your doctor, pharmacist or nurse.
- This medicine has been prescribed for you only. Do not pass it on to others. It may harm them, even if their signs of illness are the same as yours.
- If you get any side effects, talk to your doctor, pharmacist or nurse. This includes any possible side effects not listed in this leaflet. See section 4.

What is in this leaflet

1. What Azacitidine Accord is and what it is used for
2. What you need to know before you take Azacitidine Accord
3. How to take Azacitidine Accord
4. Possible side effects
5. How to store Azacitidine Accord
6. Contents of the pack and other information

1. What Azacitidine Accord is and what it is used for

What Azacitidine Accord is
Azacitidine Accord is an anti-cancer medicine that belongs to a group of medicines called anti-metabolites.
Azacitidine Accord contains the active substance azacitidine.

What Azacitidine Accord is used for
Azacitidine Accord is used to treat adults with acute myeloid leukaemia (AML). This is a form of cancer which affects your bone marrow and can cause problems with producing normal blood cells.

Azacitidine Accord is used to keep the disease in control (remission, when the disease is less severe or not active).

How Azacitidine Accord works
Azacitidine Accord works by preventing cancer cells from growing. Azacitidine, the active substance in Azacitidine Accord, works by altering the way the cell turns genes on and off. It also reduces the production of new genetic material (RNA and DNA). These effects are thought to block growth of cancer cells in leukaemia.

Talk to your doctor or nurse if you have any questions about how Azacitidine Accord works or why this medicine has been prescribed for you.

2. What you need to know before you take Azacitidine Accord

Do not take Azacitidine Accord
- if you are allergic to azacitidine or any of the other ingredients of this medicine (listed in section 6).
- if you are breast-feeding.

Warnings and precautions

Blood tests
You will have blood tests before you begin treatment with Azacitidine Accord and during treatment with Azacitidine Accord to check that you have enough blood cells and that your liver and kidneys are working properly. Your doctor will decide how often you have blood tests.

Tell your doctor, pharmacist or nurse straight away if you get any of these symptoms during treatment with Azacitidine Accord:
- bruising or bleeding - this could be due to a low count of blood cells called platelets;
- fever - this could be due to an infection as a result of having low levels of white blood cells, which can be life-threatening;
- diarrhoea, vomiting or nausea (feeling sick).

Your doctor may need to change the dose, interrupt treatment or stop treatment with Azacitidine Accord completely. The doctor may prescribe other medicines to help manage these symptoms.

Children and adolescents
Azacitidine Accord is not recommended for use in children and adolescents below the age of 18.

Other medicines and Azacitidine Accord
Tell your doctor if you are taking, have recently taken or might take any other medicines. This is because Azacitidine Accord may affect the way some other medicines work. Also, some other medicines may affect the way Azacitidine Accord works.

Pregnancy, contraception and breast-feeding
If you are pregnant or breast-feeding, you think you may be pregnant or are planning to have a baby, ask your doctor for advice before taking this medicine. Men should not father a child while receiving treatment with Azacitidine Accord.

Pregnancy
Do not take Azacitidine Accord during pregnancy as it may be harmful to your baby. Tell your doctor straight away if you become pregnant during treatment.

Contraception
If you are a woman who can become pregnant you should use an effective method of contraception while taking Azacitidine Accord and for 6 months after stopping treatment with Azacitidine Accord. Men should use an effective method of contraception while taking Azacitidine Accord and for 3 months after stopping treatment with Azacitidine Accord.

Your doctor will discuss with you the most suitable method of contraception for you to use.

Breast-feeding
Do not breast-feed while taking Azacitidine Accord as it may be harmful to your child.

Fertility
Azacitidine Accord may affect your ability to have a baby. Talk to your doctor for advice before using it.

Driving and using machines or tools
You may feel tired, weak or have trouble concentrating. If this happens to you or if you have other side effects, do not drive or use any machines or tools.

Azacitidine Accord contains lactose
Azacitidine Accord contains lactose. If you have been told by your doctor that you have intolerance to some sugars, contact your doctor before taking this medicine.

Azacitidine Accord contains sodium
This medicine contains less than 1 mmol sodium (23 mg) per tablet, that is to say essentially 'sodium-free'.

3. How to take Azacitidine Accord

Always take this medicine exactly as your doctor has told you. Check with your doctor if you are not sure.

How much to take
- The recommended dose is 300 mg taken by mouth once daily.
- Your doctor may reduce your dose to 200 mg once daily.

Azacitidine Accord is given in treatment cycles of 28 days.
- You take Azacitidine Accord every day for the first 14 days of each 28 day cycle.
- This is followed by a treatment-free period of 14 days for the rest of the cycle.

Your doctor will tell you what dose of Azacitidine Accord to take. The doctor may decide to:
- extend your treatment beyond 14 days in each treatment cycle
- lower your dose or temporarily stop treatment
- reduce your treatment to 7 days.

Always take Azacitidine Accord as prescribed by your doctor.

Your doctor will give you a medicine that helps to reduce nausea (feeling sick) and vomiting. You take it 30 minutes before each Azacitidine Accord tablet, during your first and second treatment cycles. Your doctor will tell you to take it for a longer period, if you need it.

Taking this medicine
- Take Azacitidine Accord once a day - at the same time each day.
- Swallow the tablets whole with a full glass of water.
- To make sure you get the right dose, do not break, crush, dissolve or chew the tablets.
- You can take the medicine with food or between meals.

If you vomit after taking a tablet, do not take another dose on the same day. Instead, wait till the next day and take your next scheduled dose then. Do not take two doses on the same day.

If powder from a broken tablet touches your skin, wash the skin straight away and thoroughly with soap and water. If the powder gets into your eyes, nose or mouth, flush the area thoroughly with water.

If you take more Azacitidine Accord than you should
If you take more tablets than you should, contact your doctor or go to a hospital straightaway. If possible, take the medicine pack and this leaflet with you.

If you forget to take Azacitidine Accord
If you forget to take Azacitidine Accord at the usual time, take your usual dose as soon as you remember on the same day and take your next dose at the usual time the next day. Do not take a double dose to make up for a forgotten or vomited tablet.

If you stop taking Azacitidine Accord
Do not stop taking Azacitidine Accord unless your doctor tells you to.

If you have any further questions on the use of this medicine, ask your doctor.

4. Possible side effects

Like all medicines, this medicine can cause side effects, although not everybody gets them.

Serious side effects
Tell your doctor, pharmacist or nurse straight away if you get any of these symptoms during treatment with Azacitidine Accord:
- bruising or bleeding - this could be due to a low count of blood cells called platelets;
- fever - this could be due to an infection as a result of having low levels of white blood cells, which can be life-threatening;
- diarrhoea, vomiting or nausea (feeling sick).

Other side effects include:

Very common side effects (may affect more than 1 in 10 people):
- constipation
- pain in your belly
- infections of the nose, sinuses and throat
- infection of the lungs
- feeling tired or weak
- loss of appetite
- pain that affect different parts of the body - this can range from a sharp pain to a dull ache
- stiff joints
- back pain.

Common side effects (may affect up to 1 in 10 people):
- flu
- infection of the urinary tract
- hay fever
- anxiety
- loss of weight.

Reporting of side effects
If you get any side effects, talk to your doctor. This includes any possible side effects not listed in this leaflet. You can also report side effects directly via the national reporting system listed in Appendix V. By reporting side affects you can help provide more information on the safety of this medicine.

5. How to store Azacitidine Accord

Keep this medicine out of the sight and reach of children.

Do not use this medicine after the expiry date which is stated on the blister and the carton after EXP. The expiry date refers to the last day of that month.

This medicine does not require any special storage conditions.

Do not throw away any medicines via wastewater or household waste. Ask your pharmacist how to throw away medicines you no longer use. These measures will help protect the environment.

6. Contents of the pack and other information

What Azacitidine Accord contains
- The active substance is azacitidine. Each film-coated tablet contains either 200 mg or 300 mg azacitidine.
- The other ingredients are mannitol, silicified microcrystalline cellulose, croscarmellose sodium and magnesium stearate.

- The 200 mg tablet coating: hypromellose (E464), lactose monohydrate, polyethylene glycol (E1521), triacetin (E1518), titanium dioxide (E171), iron oxide red (E172). See section 2 “Azacitidine Accord contains sodium”.

- The 300 mg tablet coating: hypromellose (E464), lactose monohydrate, polyethylene glycol (E1521), triacetin (E1518), titanium dioxide (E171), iron oxide red (E172), iron oxide yellow (E172), iron oxide black (E172). See section 2 “Azacitidine Accord contains sodium”.

What Azacitidine Accord looks like and contents of the pack
Azacitidine Accord 200 mg film-coated tablets are pink color, approximate 17 × 7.6 mm oval shaped film coated tablet debossed with “MA1” on one side and plain on other side.

Azacitidine Accord 300 mg film-coated tablets are brown color, approximate 19 × 9 mm oval shaped film coated tablet debossed with “MA2” on one side and plain on other side.

Azacitidine Accord 200 mg and 300 mg film-coated tablets are available in carton containing 7 and 14 film-coated tablets in alu-alu blisters or alu/PVC/PCTFE blister with push through aluminium foil, and in carton containing 7 × 1 and 14 × 1 film-coated tablets in cross-perforated unit-dose blisters.

Not all pack sizes may be marketed.

Marketing Authorisation Holder

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Other sources of information
Detailed information on this medicine is available on the European Medicines Agency web site: https://www.ema.europa.eu.