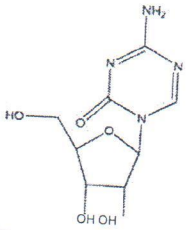
UA/19294/01/01
від 08.04.2021

Тільки для онколога/лікарні/онкологічних закладів

Азацитидин для ін'єкцій Експреза

ОПИС

ЕКСПРЕЗА (азацитидин для ін'єкцій) містить азацитидин І.Р., який є піримідиновим нуклеозидним аналогом цитидину. Азацитидин — це 4-аміно-1-р-D-рибофуранозил-s-триазин-2(1Н)-он. Структурна формула така:



Емпірична формула $C_8H_{12}N_4O_5$. Молекулярна вага 244. Азацитидин є собою сухою речовиною від білого до майже білого кольору. Встановлено, що азацитидин не розчиняється в ацетоні, етанолі та метилетилкетоні; малорозчинний в етанолі/воді (50/50), пропіленгліколі та поліетиленгліколі; важкорозчинний у воді, насиченому водою октанолі, 5% декстрози у воді, N-метил-2-піролідоні, фізіологічному розчині й 5% Твін-80 у воді; і розчинний у диметилсульфоксиді (ДМСО).

Готовий продукт поставляється в стерильній формі для відновлення у вигляді суспензії для підшкірних ін'єкцій або розчинення у вигляді розчину з подальшим розведенням для внутрішньовенної інфузії. Кожен ліофілізований флакон Експреза містить 100 мг азацитидину І.Р. і 100 мг маніту у вигляді стерильного ліофілізованого порошку.

КЛІНІЧНА ФАРМАКОЛОГІЯ

Механізм дії

Азацитидин є аналогом піримідинового нуклеозиду цитидину. Вважається, що азацитидин проявляє свою протипухлинну дію, зумовлюючи гіпометилювання ДНК і пряму цитотоксичність на аномальні гемопоетичні клітини в кістковому мозку. Концентрація азацитидину, необхідна для максимального пригнічення метилювання ДНК in vitro, не викликає значного пригнічення синтезу ДНК. Гіпометилювання може відновити нормальну функцію генів, які є критичними для диференціації та проліферації. Цитотоксичні ефекти азацитидину викликають загибель клітин, які швидко діляться, включаючи ракові клітини, які більше не реагують на нормальні механізми контролю росту. Непроліферуючі клітини відносно нечутливі до азацитидину.

Фармакокінетика

Фармакокінетику азацитидину вивчали у 6 пацієнтів з МДС після одноразової підшкірної (ПШ) дози 75 мг/м2 та одноразової внутрішньовенної (в/в) дози 75 мг/м2. Азацитидин швидко всмоктується після підшкірного введення; максимальна концентрація азацитидину в плазмі 750 ± 403 нг/мл відбулася через 0,5 години. Біодоступність азацитидину підшкірно по відношенню до азацитидину внутрішньовенно становить приблизно 89%, виходячи з площі під кривою. Середній об'єм розподілу після внутрішньовенного введення становить 76 ± 26 л. Середній очевидний підшкірний кліренс становить 167 ± 49 л/год, а середній період напіввиведення після підшкірного введення становить 41 ± 8 хвилин.

Опубліковані дослідження показують, що виведення з сечею є основним шляхом виведення азацитидину та його метаболітів. Після внутрішньовенного введення радіоактивного азацитидину 5 хворим на рак кумулятивне виділення із сечею становило 85 % радіоактивної дози. Екскреція фекаліями становила <1% введеної радіоактивності протягом 3 днів. Середнє виведення радіоактивності з сечею після підшкірного введення 14С-азацитидину становило 50%. Середній період напіввиведення загальної радіоактивності (азацитидину та його метаболітів) був подібним після внутрішньовенного та підшкірного введення, приблизно 4 години.

Особливі групи населення

Вплив ниркової або печінкової недостатності, статі, віку або раси на фармакокінетику азацитидину не вивчався.

ПОКАЗАННЯ ТА ВИКОРИСТАННЯ:

Дорослі пацієнти з усіма підтипами мієлодиспластичних синдромів (МДС)

Азацитидин показаний для лікування пацієнтів із такими підтипами франко-американсько-британського (ФАБ) мієлодиспластичного синдрому: рефрактерна анемія (РА) або рефрактерна анемія з кільчастими сидеробластами (якщо супроводжується нейтропенією або тромбоцитопенією або потребує переливання крові), рефрактерна анемія з надлишком бластів РАНБ (РАНБ), рефрактерна анемія з надлишком бластів у трансформації (РАНБт) і хронічний мієломоноцитарний лейкоз (ХММЛ).

ДОЗУВАННЯ ТА ЗАСТОСУВАННЯ:

Перший цикл лікування

Початкова доза, що рекомендується, для першого циклу лікування для всіх пацієнтів незалежно від вихідних гематологічних лабораторних показників становить 75 мг/м2 підшкірно або внутрішньовенно, щодня протягом 7 днів. Пацієнтам слід провести премедикацію проти нудоти та блювання.

Подальші цикли лікування

Цикли потрібно повторювати кожні 4 тижні. Дозу можна збільшити до 100 мг/м2, якщо після 2 циклів лікування не спостерігається сприятливого ефекту та якщо не виникло інших токсичних реакцій, крім нудоти та блювоти. Рекомендується, щоб пацієнти проходили курс лікування мінімум від 4 до 6 циклів. Однак, повна або часткова відповідь може вимагати додаткових циклів лікування. Лікування можна продовжувати до тих пір, поки продовжує бути корисним для пацієнта.

Пацієнтів потрібно контролювати щодо гематологічної реакції та ниркової токсичності, а також затримки або зниження дози, як описано нижче.

Коригування дозування залежно від лабораторних гематологічних показників

Для пацієнтів із вихідним рівнем (початок лікування) лейкоцитів > 3,0 x 109/л, нейтрофілів > 1,5 x 109/л і тромбоцитами > 75,0 x 109/л, коригуйте дозу таким чином, виходячи з найнижчого рівня для будь-якого даного циклу.

Кількість у надирі		% Доза в наступному циклі
Нейтрофіли ($x10^9$/л)	Тромбоцити ($x10^9$/л)	
<0.5	<25.0	50%
0.5-1.5	25.0-50.0	67%
>1.5	>50.0	100%

Для пацієнтів, у яких вихідний рівень лейкоцитів < 3,0 x 109/л, нейтрофілів < 1,5 x 109/л або тромбоцитів < 75,0 x 109/л, коригування дози має ґрунтуватися на найнижчій кількості та клітинності біопсії кісткового мозку на момент найнижчого рівня, як зазначено нижче, якщо не спостерігається явне покращення диференціювання (відсоток зрілих гранулоцитів вищий, а ANC вищий, ніж на початку цього курсу) під час наступного циклу, у цьому випадку дозу поточного лікування слід продовжувати.

Зниження кількості лейкоцитів або тромбоцитів у % від вихідного рівня	Кістковий мозок Клітинність біопсії під час надиру		
	30-60	15-30	<15
	% Доза в наступному циклі		
50 - 75	100	50	33
>75	75	50	33

Якщо досягнутий найнижчий рівень (надир), визначений у таблиці вище, наступний курс лікування потрібно провести через 28 днів після початку попереднього курсу, за умови, що кількість лейкоцитів і тромбоцитів на >25% перевищує найнижчу і зростає. Якщо до 28-го дня не спостерігається збільшення на >25% вище найнижчого рівня, кількість потрібно переоцінювати кожні 7 днів. Якщо збільшення на 25% не спостерігається до 42 дня, то пацієнта потрібно лікувати 50% запланованої дози.

Коригування дозування на основі функції нирок та електролітів сироватки

Якщо відбувається незрозуміле зниження рівня бікарбонату в сироватці крові до <20 мекв/л, дозу потрібно зменшити на 50% під час наступного курсу. Аналогічно, якщо спостерігається незрозуміле підвищення АСК або сироваткового креатиніну, наступний цикл потрібно відкласти, доки значення не повернуться до нормальних або вихідних показників, а дозу потрібно зменшити на 50% під час наступного лікування.

Приготування препарату Експреза для введення:

Експреза є цитотоксичним препаратом, і, як і з іншими потенційно токсичними сполуками, необхідно бути обережними під час роботи та приготування суспензії Експреза.

Якщо відновлений розчин Експреза потрапив на шкіру, негайно і ретельно промийте його водою з милом. При попаданні на слизові оболонки ретельно промити водою.

Флакон Експреза є одноразовим і не містить консервантів. Невикористані частини кожного флакона необхідно утилізувати належним чином. Не зберігайте невикористані частини для подальшого застосування.

Інструкція для підшкірного введення:

Експреза необхідно відновлювати в асептичних умовах за допомогою 4мл стерильної води для ін'єкцій. Розчинник потрібно вводити повільно у флакон. Енергійно струсіть або покрутіть флакон до отримання однорідної суспензії. Суспензія буде каламутною. Отримана суспензія міститиме 25 мг/мл азацитидину. Не фільтруйте суспензію після відновлення. Це може видалити активну речовину.

Підготовка до негайного підшкірного введення:

Дози більше 4 мл потрібно розділити порівну на 2 шприци. Препарат можна зберігати при кімнатній температурі до 1 години, але його необхідно ввести протягом 1 години після розчинення.

Підготовка до відстроченого підшкірного введення:

Відновлений препарат можна зберігати у флаконі або набрати в шприц. Дози більше 4 мл слід розділити порівну на 2 шприци. Препарат необхідно негайно охолодити. Коли Експреза відновлюють за допомогою води для ін'єкцій, яка не була охолоджена, відновлений продукт можна зберігати в охолоджених умовах (2°C – 8°C, 36°F – 46°F) до 8 годин. Коли Експреза відновлюють за допомогою охолодженої (2°C – 8°C, 36°F – 46°F) води для ін'єкцій, відновлений продукт можна зберігати в охолоджених умовах (2°C – 8°C, 36°F – 46°F). °F) до 22 годин. Після вилучення з охолоджених умов суспензії можна дати збалансуватися до кімнатної температури протягом 30 хвилин до введення.

Підшкірне введення:

Для отримання однорідної суспензії вміст дозуючого шприца необхідно повторно суспендувати безпосередньо перед введенням. Щоб повторно суспендувати, енергійно покатайте шприц між долонями, поки не отримаєте однорідну каламутну суспензію.

Суспензію **Експреза** вводять підшкірно. Дози більше 4 мл потрібно розподілити порівну на 2 шприци та ввести в 2 окремі місця. Міняйте місця для кожної ін'єкції (стегно, живіт або плече). Нові ін'єкції потрібно робити щонайменше на 1 дюйм від старого місця і ніколи не робити в місце, яке є чутливим, ураженим, червоним або твердим.

Стабільність суспензії:

Препарат **Експреза**, відновлений неохолодженою водою для ін'єкцій для підшкірного введення, можна зберігати до 1 години при 25°C (77°F) або до 8 годин при температурі від 2°C до 8°C (36°F і 46°F); після розчинення в охолодженій (2°C – 8°C, 36°F – 46°F) воді для ін'єкцій його можна зберігати протягом 22 годин при температурі від 2°C до 8°C (36°F та 46°F).

Інструкція для внутрішньовенного введення:

Відновіть відповідну кількість флаконів Експреза для досягнення бажаної дози. Розведіть кожен флакон 10 мл стерильної води для ін'єкцій. Енергійно струсіть або покатайте флакон, поки всі тверді речовини не розчиняться. Отриманий розчин міститиме азацитидину 10 мг/мл. Розчин повинен бути прозорим. Лікарський засіб для парентерального введення потрібно візуально перевіряти на наявність частинок і зміну кольору перед введенням, якщо це дозволяють розчин і упаковка.

Відберіть необхідну кількість розчину Експреза для отримання потрібної дози і введіть його в 50-100 мл інфузійний пакет з розчином хлориду натрію 0,9% або лактованим розчином Рінгера.

Несумісність внутрішньовенних розчинів
Експреза несумісний з 5% розчинами декстрози, Геспаном або розчинами, що містять бікарбонат. Ці розчини можуть підвищити швидкість розпаду азацитидину, тому їх потрібно уникати.

Внутрішньовенне введення:
Розчин Експреза вводиться внутрішньовенно. Введіть загальну дозу протягом 10-40 хвилин. Введення має бути завершено протягом 1 години після розчинення вмісту флакона Експреза

Стабільність розчину:
Препарат Експреза, відновлений для внутрішньовенного введення, можна зберігати при 25°C (77°F), але введення має бути завершено протягом 1 години після розчинення

ЛІКАРСЬКІ ФОРМИ ТА ДІЇ:
Експреза для ін'єкцій поставляється у вигляді ліофілізованого порошку у одноразових флаконах по 100 мг.

ПРОТИПОКАЗАННЯ
Поширені злоякісні пухлини печінки
Експреза протипоказаний пацієнтам із поширеними злоякісними пухлинами печінки.

Підвищена чутливість до азацитидину або манітолу
Експреза протипоказаний пацієнтам з відомою гіперчутливістю до азацитидину або манітолу.

ПОПЕРЕДЖЕННЯ ТА ЗАХОДИ:

Анемія, нейтропенія і тромбоцитопенія
Азацитидин пов'язаний з анемією, нейтропенією та тромбоцитопенією. Перед кожним циклом дозування потрібно проводити повний аналіз крові для контролю реакції та токсичності. Після введення рекомендованої дози для першого циклу дозу для наступних циклів потрібно зменшити або відстрочити залежно від найнижчого рівня (надиру) та гематологічної реакції.

Важка попередня печінкова недостатність
Азацитидин потенційно є гепатотоксичним у пацієнтів із тяжкою наявною печінковою недостатністю, тому щодо пацієнтів із захворюваннями печінки необхідна обережність. Повідомлялося, що у пацієнтів із значним пухлинним навантаженням внаслідок метастатичного захворювання спостерігається прогресуюча печінкова кома та смерть під час лікування азацитидином, особливо у пацієнтів із вихідним рівнем альбуміну <30 г/л. Азацитидин протипоказаний пацієнтам із поширеними злоякісними пухлинами печінки.
Безпека та ефективність азацитидину у пацієнтів з МДС та печінковою недостатністю не вивчалися.

Печінкові патології
У пацієнтів, які отримували внутрішньовенне введення азацитидину в комбінації з іншими хіміотерапевтичними засобами для лікування станів без МДС, повідомлялося про порушення функції нирок від підвищення рівня креатиніну в сироватці крові до ниркової недостатності та смерті. Крім того, у 5 пацієнтів з ХМЛ, які отримували азацитидин та етопозид, розвинувся нирковий тубулярний ацидоз, що визначається як зниження рівня бікарбонату в сироватці крові до <20 мекв/л у зв'язку з лужною сечею та гіпокаліємією (сироватковий калій <3 мекв/л). Якщо спостерігається незрозуміле зниження рівня бікарбонату в сироватці крові <20 мекв/л або підвищення АСК або сироваткового креатиніну, дозу потрібно зменшити або зберегти.
Пацієнтів з нирковою недостатністю потрібно ретельно спостерігати на предмет токсичності, оскільки азацитидин та його метаболіти виводяться нирками.
Безпека та ефективність азацитидину у пацієнтів з МДС та нирковою недостатністю не вивчалися.

Моніторинг лабораторних досліджень
Перед кожним циклом необхідно проводити повний аналіз крові для контролю реакції та токсичності. Перед початком лікування необхідно провести функціональний тест печінки та креатинін сироватки крові.

Використання під час вагітності
Азацитидин може завдати шкоди плоду при введенні вагітній жінці. Жінкам репродуктивного віку потрібно рекомендувати уникати вагітності під час лікування **азацитидином.**

Використання у чоловіків
Чоловікам потрібно рекомендувати не мати дітей під час лікування азацитидином.

ПОБІЧНІ РЕАКЦІЇ
Побічні реакції, описані в інших розділах маркування: анемія, нейтропенія, тромбоцитопенія, підвищення рівня креатиніну в сироватці крові, ниркова недостатність, нирковий тубулярний ацидоз, гіпокаліємія, печінкова кома.

Побічні реакції, які виникають найбільш часто (підшкірне або внутрішньовенне введення): нудота, анемія, тромбоцитопенія, блювання, лихоманка, лейкопенія, діарея, еритема в місці ін'єкції, закреп, нейтропенія, екхімоз, петехії, озноб, слабкість та гіпокаліємія.

Найчастіші побічні реакції (>2%), що призводять до клінічного втручання (підшкірне або внутрішньовенне введення):
Припинення: лейкопенія, тромбоцитопенія, нейтропенія.
Доза, що приймається: лейкопенія, нейтропенія, тромбоцитопенія, пірексія, пневмонія, фебрильна нейтропенія.
Знижена доза: лейкопенія, нейтропенія, тромбоцитопенія.

Побічні реакції в клінічних дослідженнях
У клінічних дослідженнях із підшкірним введенням азацитидину – нейтропенія, тромбоцитопенія, анемія, нудота, блювання, діарея, закреп та еритема/реакція у місці ін'єкції мали тенденцію до збільшення частоти при застосуванні вищих доз азацитидину. Побічні реакції, які мали тенденцію бути більш вираженими протягом перших 1-2 циклів лікування з підшкірним введенням порівняно з пізнішими циклами, включали тромбоцитопенію, нейтропенію, анемію, нудоту, блювоту, еритему/біль/синці/реакції в місці ін'єкції, закреп, петехії, запаморочення, гіпокаліємія та безсоння.

Побічні реакції були подібними у дослідженнях з внутрішньовенним та підшкірним введенням. Побічні реакції, які, мабуть, були специфічно пов'язані з внутрішньовенним шляхом введення, включали реакції в місці інфузії (наприклад, еритема або біль) і реакції в місці катетера (наприклад, інфекція, еритема або кровотеча).

Порушення з боку системи крові та лімфатичної системи: агранулоцитоз, недостатність кісткового мозку, панцитопенія, спленомегалія.

Серцеві порушення: фібриляція передсердь, серцева недостатність, застійна серцева недостатність, зупинка дихання, застійна кардіоміопатія.

Порушення зору: очна кровотеча.

Шлунково-кишкові розлади: дивертикуліт, шлунково-кишкові кровотечі, мелена, перириректальний абсцес.

Загальні розлади та зміни у місці введення: крововилив у місці введення катетера, погіршення загального фізичного здоров'я, синдром системної запальної реакції.

Гепатобіліарні порушення: холецистит.

Порушення з боку імунної системи: анафілактичний шок, гіперчутливість.

Інфекції та інвазії: абсцес кінцівки, бактеріальна інфекція, целюліт, бластомікоз, інфекція в місці ін'єкції, клебсієлозний сепсис, нейтропенічний сепсис, стрептококовий фарингіт, клебсієлозна пневмонія, сепсис, септичний шок, стафілококова бактеріємія, стафілококова інфекція, токсоплазмоз.

Порушення обміну речовин і харчування: зневоднення.

З боку кістково-м'язової системи та сполучної тканини: посилюються болі в кістках, м'язова слабкість, біль у шиї.

Доброякісні, злоякісні та неуточнені новоутворення: лейкемія шкіри.

Порушення з боку нервової системи: крововилив у мозок, судоми, внутрішньочерепні крововиливи.

Порушення з боку нирок та сечовипускання: біль у попереку, ниркова недостатність.

З боку органів дихання, грудної клітки та середостіння: кровохаркання, інфільтрація легенів, пневмоніт, респіраторний дистрес.

З боку шкіри та підшкірної клітковини: гангренозна піодермія, свербіж, ущільнення шкіри.

Хірургічні та лікувальні процедури: холецистектомія.

Судинні порушення: ортостатична гіпотензія.

ВЗАЄМОДІЯ ЛІКАРСЬКИХ ЗАСОБІВ
Дослідження взаємодії між азацитидином та іншими препаратами не проводилися.

ВИКОРИСТАННЯ В СПЕЦІАЛЬНИХ ГРУПАХ НАСЕЛЕННЯ
Вагітність
Вагітність Категорія D
Азацитидин може завдати шкоди плоду при введенні вагітній жінці. Клінічних досліджень із застосуванням азацитидину у вагітних жінок не проводилося.

Матері, які годують
Клінічні дослідження у матерів, які годують, не проводилися. Азацитидин або його метаболіти можуть виділятися у грудне молоко.

Педіатричне використання
Безпека та ефективність азацитидину у педіатричних пацієнтів не вивчалися.

Геріатричне використання
Відомо, що азацитидин та його метаболіти значною мірою виводяться нирками, тому доцільно контролювати функцію нирок у пацієнтів з порушенням функції нирок.

Стать
Клінічно значущих відмінностей у безпеці та ефективності залежно від статі не було.

Раса
Дані щодо безпеки, ефективності та фармакокінетичного порівняння серед представників різних рас відсутні.

ПЕРЕДОЗУВАННЯ
Передозування азацитидином може викликати діарею, нудоту та блювання після одноразового внутрішньовенного введення приблизно 290 мг/м². У разі передозування пацієнта слід контролювати за допомогою відповідного аналізу крові та надавати підтримуючу терапію за рекомендаціями лікаря. Немає відомого специфічного антидоту для азацитидину.

ЯК ПОСТАЧАЄТЬСЯ/ ЗБЕРІГАННЯ ТА ПОВОДЖЕННЯ
Як постачається
Експреза (азацитидин для ін'єкцій) постачається у вигляді ліофілізованого порошку у флаконах по 100 мг одноразового застосування, упакованих у картонні коробки по 1 флакону.

Зберігання
Зберігати при температурі нижче 25°C.

Поводження та утилізація
Потрібно застосовувати процедури належного поводження та утилізації протипухлинних препаратів. Було опубліковано кілька інструкцій з цього питання. Немає загальної згоди щодо того, що всі процедури, рекомендовані в інструкціях, є необхідними або доречними.

® Зареєстрована торгова марка.

Виготовлено в Індії:
НАТКО
ФАРМА ЛІМІТЕД,

Зареєстрований офіс: НАТКО ХАУС, РОУД № 2,
БАНЖАРА ХІЛЛС, ХАЙДАРАБАД-500 034.

372725

VA/19294/01/01
dtd 08.04.2022

For the usage of an Oncologist/ a Hospital / a Cancer Institutions only

372225

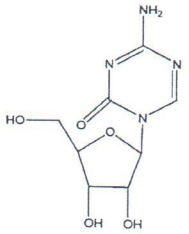
Azacitidine for Injection

Xpreza®

एक्सप्रिजा

DESCRIPTION

XPREZA (Azacitidine for Injection) contains Azacitidine I.P., which is a pyrimidine nucleoside analog of cytidine. Azacitidine is 4-amino-1-β-D-ribofuranosyl-s-triazin-2(1H)-one. The structural formula is as follows:



The empirical formula is $C_8H_{12}N_4O_5$. The molecular weight is 244. Azacitidine is a white to off- white solid. Azacitidine was found to be insoluble in acetone, ethanol, and methyl ethyl ketone; slightly soluble in ethanol/water (50/50), propylene glycol, and polyethylene glycol; sparingly soluble in water, water saturated octanol, 5% dextrose in water, N-methyl-2-pyrrolidone, normal saline and 5% Tween 80 in water; and soluble in dimethylsulfoxide (DMSO).

The finished product is supplied in a sterile form for reconstitution as a suspension for subcutaneous injection or reconstitution as a solution with further dilution for intravenous infusion. Each lyophilized vial of Xpreza contains 100 mg of Azacitidine I.P. and 100 mg mannitol as a sterile lyophilized powder.

CLINICAL PHARMACOLOGY

Mechanism of Action

Azacitidine is a pyrimidine nucleoside analog of cytidine. Azacitidine is believed to exert its antineoplastic effects by causing hypomethylation of DNA and direct cytotoxicity on abnormal hematopoietic cells in the bone marrow. The concentration of azacitidine required for maximum inhibition of DNA methylation *in vitro* does not cause major suppression of DNA synthesis. Hypomethylation may restore normal function to genes that are critical for differentiation and proliferation. The cytotoxic effects of azacitidine cause the death of rapidly dividing cells, including cancer cells that are no longer responsive to normal growth control mechanisms. Non-proliferating cells are relatively insensitive to azacitidine.

Pharmacokinetics

The pharmacokinetics of azacitidine were studied in 6 MDS patients following a single 75 mg/m² subcutaneous (SC) dose and a single 75 mg/m² intravenous (IV) dose. Azacitidine is rapidly absorbed after SC administration; the peak plasma azacitidine concentration of 750 ± 403 ng/ml occurred in 0.5 hour. The bioavailability of SC azacitidine relative to IV azacitidine is approximately 89%, based on area under the curve. Mean volume of distribution following IV dosing is 76 ± 26 L. Mean apparent SC clearance is 167 ± 49 L/hour and mean half-life after SC administration is 41 ± 8 minutes.

Published studies indicate that urinary excretion is the primary route of elimination of azacitidine and its metabolites. Following IV administration of radioactive azacitidine to 5 cancer patients, the cumulative urinary excretion was 85% of the radioactive dose. Fecal excretion accounted for <1% of administered radioactivity over 3 days. Mean excretion of radioactivity in urine following SC administration of 14C-azacitidine was 50%. The mean elimination half-lives of total radioactivity (azacitidine and its metabolites) were similar after IV and SC administrations, about 4 hours.

Special Populations

The effects of renal or hepatic impairment, gender, age, or race on the pharmacokinetics of azacitidine have not been studied.

INDICATIONS AND USAGE:

Adult patients with all subtypes of Myelodysplastic Syndromes (MDS)

Azacitidine is indicated for treatment of patients with the following French-American-British (FAB) myelodysplastic syndrome subtypes: refractory anemia (RA) or refractory anemia with ringed sideroblasts (if accompanied by neutropenia or thrombocytopenia or requiring transfusions), refractory anemia with excess blasts (RAEB), refractory anemia with excess blasts in transformation (RAEB-T), and chronic myelomonocytic leukemia (CMMoL).

DOSAGE AND ADMINISTRATION:

First Treatment Cycle

The recommended starting dose for the first treatment cycle, for all patients regardless of baseline hematology laboratory values, is 75 mg/m² subcutaneously or intravenously, daily for 7 days. Patients should be premedicated for nausea and vomiting.

Subsequent Treatment Cycles

Cycles should be repeated every 4 weeks. The dose may be increased to 100 mg/m² if no beneficial effect is seen after 2 treatment cycles and if no toxicity other than nausea and vomiting has occurred. It is recommended that patients be treated for a minimum of 4 to 6 cycles. However, complete or partial response may require additional treatment cycles. Treatment may be continued as long as the patient continues to benefit.

Patients should be monitored for hematologic response and renal toxicities, and dosage delay or reduction as described below.

Dosage Adjustment Based on Hematology Laboratory Values

For patients with baseline (start of treatment) WBC ≥ 3.0 x10⁹/L, ANC ≥ 1.5 x10⁹/L, and platelets ≥ 75.0 x 10⁹/L, adjust the dose as follows, based on nadir counts for any given cycle.

Nadir Counts		% Dose in the Next Course
ANC (x10⁹/L)	Platelets (x10⁹/L)	
<0.5	<25.0	50%
0.5 –1.5	25.0-50.0	67%
>1.5	>50.0	100%

For patients whose baseline counts are WBC < 3.0 x 10⁹/L, ANC < 1.5 x 10⁹/L, or platelets < 75.0 x 10⁹/L, dose adjustments should be based on nadir counts and bone marrow biopsy cellularity at the time of the nadir as noted below, unless there is clear improvement in differentiation (percentage of mature granulocytes is higher and ANC is higher than at onset of that course) at the time of the next cycle, in which case the dose of the current treatment should be continued.

WBC or Platelet Nadir % decrease in counts from baseline	Bone Marrow Biopsy Cellularity at Time of Nadir		
	30-60	15-30	<15
	% Dose in the Next Course		
50 – 75	100	50	33
>75	75	50	33

If a nadir as defined in the table above has occurred, the next course of treatment should be given 28 days after the start of the preceding course, provided that both the WBC and the platelet counts are >25% above the nadir and rising. If a >25% increase above the nadir is not seen by day 28, counts should be reassessed every 7 days. If a 25% increase is not seen by day 42, then the patient should be treated with 50% of the scheduled dose.

Dosage Adjustment Based on Renal Function and Serum Electrolytes

If unexplained reductions in serum bicarbonate levels to <20 mEq/L occur, the dosage should be reduced by 50% on the next course. Similarly, if unexplained elevations of BUN or serum creatinine 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.

Preparation of Xpreza for administration:

Xpreza is a cytotoxic drug and, as with other potentially toxic compounds, caution should be exercised when handling and preparing Xpreza suspensions.

If reconstituted Xpreza 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.

The Xpreza vial is single-use and does not contain any preservatives. Unused portions of each vial should be discarded properly. Do not save any unused portions for later administration.

Instructions for Subcutaneous Administration:

Xpreza should be reconstituted aseptically with 4 mL sterile water for injection. The diluent should be injected slowly into the vial. Vigorously shake or roll the vial until a uniform suspension is achieved. The suspension will be cloudy. The resulting suspension will contain azacitidine 25 mg/mL. Do not filter the suspension after reconstitution. It may remove the active substance.

Preparation for Immediate Subcutaneous Administration:

Doses greater than 4 mL should be divided equally into 2 syringes. The product may be held at room temperature for up to 1 hour, but must be administered within 1 hour after reconstitution.

Preparation for Delayed Subcutaneous Administration:

The reconstituted product may be kept in the vial or drawn into a syringe. Doses greater than 4 mL should be divided equally into 2 syringes. The product must be refrigerated immediately. When Xpreza is reconstituted using water for injection that has not been refrigerated, the reconstituted product may be held under refrigerated conditions (2°C - 8°C, 36°F - 46°F) for up to 8 hours. When Xpreza is reconstituted using refrigerated (2°C - 8°C, 36°F - 46°F) water for injection, the reconstituted product may be stored under refrigerated conditions (2°C - 8°C, 36°F - 46°F) for up to 22 hours. After removal from refrigerated conditions, the suspension may be allowed to equilibrate to room temperature for up to 30 minutes prior to administration.

Subcutaneous Administration:

To provide a homogeneous suspension, the contents of the dosing syringe must be re-suspended immediately prior to administration. To re-suspend, vigorously roll the syringe between the palms until a uniform, cloudy suspension is achieved.

Xpreza suspension is administered subcutaneously. Doses greater than 4 mL should be divided equally into 2 syringes and injected into 2 separate sites. Rotate sites for each injection (thigh, abdomen, or upper arm). New injections should be given at least one inch from an old site and never into areas where the site is tender, bruised, red, or hard.

Suspension Stability:

Xpreza reconstituted with non-refrigerated water for injection for subcutaneous administration may be stored for up to 1 hour at 25°C (77°F) or for up to 8 hours between 2°C and 8°C (36°F and 46°F); when reconstituted with refrigerated (2°C - 8°C, 36°F - 46°F) water for injection, it may be stored for 22 hours between 2°C and 8°C (36°F and 46°F).

Instructions for Intravenous Administration:

Reconstitute the appropriate number of Xpreza vials to achieve the desired dose. Reconstitute each vial with 10 mL sterile water for injection. Vigorously shake or roll the vial until all solids are dissolved. The resulting solution will contain azacitidine 10 mg/mL. The solution should be clear. Parenteral drug product should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit.

Withdraw the required amount of Xpreza solution to deliver the desired dose and inject into a 50 -100 mL infusion bag of either 0.9% Sodium Chloride Injection or Lactated Ringer's Injection.

Intravenous Solution Incompatibility
Xpreza is incompatible with 5% Dextrose solutions, Hespan, or solutions that contain bicarbonate. These solutions may increase the rate of degradation of Azacitidine and should be avoided.

Intravenous Administration:
Xpreza solution is administered intravenously. Administer the total dose over a period of 10 - 40 minutes. The administration must be completed within 1 hour of reconstitution of the Xpreza vial.

Solution Stability:

Xpreza reconstituted for intravenous administration may be stored at 25°C (77°F), but administration must be completed within 1 hour of reconstitution

DOSAGE FORMS AND STRENGTHS:
Xpreza for injection is supplied as lyophilized powder in 100 mg single-use vials.

CONTRAINDICATIONS

Advanced Malignant Hepatic Tumors

Xpreza is contraindicated in patients with advanced malignant hepatic tumors

Hypersensitivity to Azacitidine or Mannitol
Xpreza is contraindicated in patients with a known hypersensitivity to azacitidine or mannitol.

WARNINGS AND PRECAUTIONS:

Anemia, Neutropenia and Thrombocytopenia
Azacitidine is associated with anemia, neutropenia and thrombocytopenia. Prior to each dosing cycle Complete blood counts should be performed to monitor response and toxicity. After administration of the recommended dosage for the first cycle, dosage for subsequent cycles should be reduced or delayed based on nadir counts and hematologic response.

Severe Pre-existing Hepatic Impairment
Azacitidine is potentially hepatotoxic in patients with severe pre-existing hepatic impairment, caution is needed in patients with liver disease. Patients with extensive tumor burden due to metastatic disease have been reported to experience progressive hepatic coma and death during azacitidine treatment, especially in such patients with baseline albumin <30 g/L. Azacitidine is contraindicated in patients with advanced malignant hepatic tumors.

Safety and effectiveness of Azacitidine in patients with MDS and hepatic impairment have not been studied.

Renal Abnormalities
Renal abnormalities ranging from elevated serum creatinine to renal failure and death have been reported in patients treated with intravenous azacitidine in combination with other chemotherapeutic agents for non MDS conditions. In addition, renal tubular acidosis, defined as a fall in serum bicarbonate to <20 mEq/L in association with an alkaline urine and hypokalemia (serum potassium <3 mEq/L) developed in 5 patients with CML treated with azacitidine and etoposide. If unexplained reductions in serum bicarbonate <20 mEq/L or elevations of BUN or serum creatinine occur, the dosage should be reduced or held.

Patients with renal impairment should be closely monitored for toxicity since azacitidine and its metabolites are excreted by the kidneys.

Safety and effectiveness of Azacitidine in patients with MDS and renal impairment have not been studied.

Monitoring Laboratory Tests
Prior to each cycle Complete blood counts should be performed to monitor response and toxicity. Liver function test and serum creatinine must be conducted prior to initiation of therapy.

Use in Pregnancy

Azacitidine may cause fetal harm when administered to a pregnant woman. Women of childbearing potential should be advised to avoid pregnancy during treatment with **Azacitidine.**

Use in Males
Men should be advised not to father a child while receiving treatment with Azacitidine.

ADVERSE REACTIONS
Adverse Reactions Described in Other Labelling Sections: anemia, neutropenia, thrombocytopenia, elevated serum creatinine, renal failure, renal tubular acidosis, hypokalemia, hepatic coma.

Most Commonly Occurring Adverse Reactions (SC or IV Route): nausea, anemia, thrombocytopenia, vomiting, pyrexia, leukopenia, diarrhea, injection site erythema, constipation, neutropenia, ecchymosis, petechiae, rigors, weakness and hypokalemia.

Adverse Reactions Most Frequently (>2%) Resulting in Clinical Intervention (SC or IV Route):
Discontinuation: leukopenia, thrombocytopenia, neutropenia.
Dose Held: leukopenia, neutropenia, thrombocytopenia, pyrexia, pneumonia, febrile neutropenia.
Dose Reduced: leukopenia, neutropenia, thrombocytopenia.

Adverse Reactions in Clinical Trials
In clinical studies with SC administration of Azacitidine, - neutropenia, thrombocytopenia, anemia, nausea, vomiting, diarrhea, constipation, and injection site erythema/reaction tended to increase in incidence with higher doses of Azacitidine. Adverse reactions that tended to be more pronounced during the first 1 to 2 cycles of SC treatment compared with later cycles included thrombocytopenia, neutropenia, anemia, nausea, vomiting, injection site erythema/pain/bruising/reaction, constipation, petechiae, dizziness, anxiety, hypokalemia, and insomnia.

Adverse reactions were similar between the IV and SC studies. Adverse reactions that appeared to be specifically associated with the IV route of administration included infusion site reactions (e.g. erythema or pain) and catheter site reactions (e.g. infection, erythema, or hemorrhage).

Blood and lymphatic system disorders: agranulocytosis, bone marrow failure, pancytopenia splenomegaly.

Cardiac disorders: atrial fibrillation, cardiac failure, cardiac failure congestive, cardio respiratory arrest, congestive cardiomyopathy.

Eye disorders: eye haemorrhage.
Gastrointestinal disorders: diverticulitis, gastrointestinal hemorrhage, melena, perirectal abscess.

General disorders and administration site conditions: catheter site hemorrhage, general physical health deterioration, systemic inflammatory response syndrome.

Hepatobiliary disorders: cholecystitis.

Immune system disorders: anaphylactic shock, hypersensitivity.

Infections and infestations: abscess limb, bacterial infection, cellulitis, blastomycosis, injection site infection, Klebsiella sepsis, neutropenic sepsis, pharyngitis streptococcal, pneumonia Klebsiella, sepsis, septic shock, Staphylococcal bacteremia, Staphylococcal infection, toxoplasmosis.

Metabolism and nutrition disorders: dehydration.

Musculoskeletal and connective tissue disorders: bone pain aggravated, muscle weakness, neck pain.

Neoplasms benign, malignant and unspecified: leukemia cutis.

Nervous system disorders: cerebral hemorrhage, convulsions, intracranial haemorrhage.

Renal and urinary disorders: loin pain, renal failure.

Respiratory, thoracic and mediastinal disorders: hemoptysis, lung infiltration, pneumonitis, respiratory distress.

Skin and subcutaneous tissue disorders: pyoderma gangrenosum, rash pruritic, skin induration.

Surgical and medical procedures: cholecystectomy.

Vascular disorders: orthostatic hypotension.

DRUG INTERACTIONS
No drug-drug interactions studies were conducted between azacitidine and other agents.

USE IN SPECIFIC POPULATIONS
Pregnancy
Pregnancy Category D
Azacitidine may cause fetal harm when administered to a pregnant woman. No clinical studies were conducted with azacitidine in pregnant women.

Nursing Mothers
No clinical studies have been conducted in nursing mother. Azacitidine or its metabolites may be excreted in human milk.

Pediatric Use
Safety and effectiveness of azacitidine in pediatric patients have not been studied.

Geriatric Use
Azacitidine and its metabolites are known to be substantially excreted by the kidney, it is advisable to monitor renal function in patients with impaired renal function.

Gender
There were no clinically relevant differences in safety and efficacy based on gender.

Race
Data on safety, efficacy and pharmacokinetic comparison among different races are not available

OVERDOSAGE
Overdose with azacitidine may cause diarrhea, nausea, and vomiting after receiving a single IV dose of approximately 290 mg/m². In the event of overdosage, the patient should be monitored with appropriate blood counts and should receive supportive treatment, as advised by the physician. There is no known specific antidote for azacitidine.

HOW SUPPLIED/STORAGE AND HANDLING
How Supplied
Xpreza (Azacitidine for injection) is supplied as a lyophilized powder in 100 mg single-use vials packaged in cartons of 1 vial.

Storage
Store below 25ºC.

Handling and Disposal
Procedures for proper handling and disposal of anticancer drugs should be applied. Several guidelines on this subject have been published. There is no general agreement that all of the procedures recommended in the guidelines are necessary or appropriate.

® Registered Trade Mark

Made in India by:
NATCO PHARMA LIMITED,
Regd. Office: NATCO HOUSE, ROAD No. 2,
BANJARA HILLS, HYDERABAD-500 034.

372725

UA/19294/01/01
Lij 08.04.2022

1.3 Summary of product characteristics, labelling and instructions for medical use:

1.3.1 Summary of Product Characteristics (SPC)

Enclosed

NATCO PHARMA LIMITED
SUMMARY OF PRODUCT CHARACTERISTICS OF
AZACITIDINE for INJECTION 100 mg/ Vial

1. NAME OF THE MEDICINAL PRODUCT

Azacitidine for injection 100 mg/mL powder for injection

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

The sterile single-use vial contains azacitidine 100 mg and mannitol 100 mg.

Azacitidine for Injection is supplied in a sterile form for reconstitution as suspension for subcutaneous injection or reconstitution as a solution with further dilutions for intravenous infusion. Vials of Azacitidine for Injection contain 100 mg of azacitidine and 100 mg of mannitol as a sterile lyophilized powder.

For the full list of excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Azacitidine for injection is a lyophilized powder in 100 mg single-use vials packaged in cartons of 1 vial

4. CLINICAL PARTICULARS

4.1 Therapeutic indications

Azacitidine for injection 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 for injection 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 description below may be necessary.

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 ≤ 50.0 x 10^9/L and/or absolute neutrophil count (ANC) ≤ 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 ≥ nadir count + (0.5 x [baseline count – nadir count]).

Patients without reduced baseline blood counts (i.e. White Blood Cells (WBC) ≥ 3.0 x 10^9/l and ANC ≥ 1.5 x 10^9/l, and platelets ≥ 75.0 x 10^9/l) prior to the first treatment.

If haematological toxicity is observed following Azacitidine for injection 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 counts		Dose in the next cycle, if recovery* is not achieved within 14 days (%)
ANC (x 10^9/L)	Platelets (x 10^9/L)	
≤ 1.0	≤ 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 for injection treatment, if the decrease in WBC or ANC or platelets from that prior to treatment is ≤ 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 for injection 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 ≤ 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* ≤ 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 for injection is contraindicated in patients with advanced malignant hepatic tumours (see sections 4.3 and 4.4).

Paediatric population

The safety and efficacy of Azacitidine for injection 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 for injection 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 medical 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

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 and men must have to use effective contraception during and up to 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/delete 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). Men should be advised not to father a child while receiving treatment and must use effective contraception during and up to 3 months after treatment. 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 for injection 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	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 *
Blood and lymphatic system disorders	Febrile Neutropenia*, neutropenia, Leukopenia, Thrombocytopenia, anamia	pancytopenia*, bone marrow failure			
Immune system disorders			Hypersensitivity reactions		
Metabolism and nutrition disorders	anorexia decreased appetite, hypokalemia	dehydration		tumourlysis 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		Hypertension*, hypotension, orthostatic hypotension, haematoma			
Respiratory Thoracic and mediastinal disorders	Dyspnoea, epistaxis	pleural effusion, dyspnoea exertional, pharyngolaryngeal pain		Interstitial lung disease	
Gastrointestinal disorders	Diarrhoea, vomiting constipation, abdominal pain (includes upper and abdominal discomfort)	Gastrointestinal Haemorrhage*, (includes mouth haemorrhage), haemorrhoidal haemorrhage, 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		
Musculoskeletal and connective tissue disorders	arthralgia, musculoskeletal pain (includes back, bone and pain in extremity)	Myalgia, 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, haemotoma, 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				

Description of selected adverse reactions

Haematologic adverse reactions

The most commonly reported (≥ 10%) haematological adverse reactions associated with azacitidine treatment include anamia, 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 (0.8 %) and intracranial hacmorrhage (0.5 %) 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 (0.25 %) 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 injection 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 for injection during the course of the clinical study. The overall safety profile was consistent with that of the adult population.

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

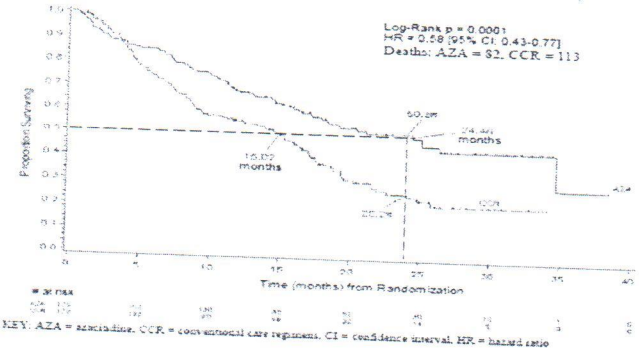
Azacitidine is believed to exert its antineoplastic effects by multiple mechanisms including cytotoxicity on abnormal haematopoietic cells in the bone marrow and hypomethylation of DNA. The cytotoxic effects of azacitidine may result from multiple mechanisms, including inhibition of DNA, RNA and protein 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 for injection were studied in an international, multicentre, 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 for injection. 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 for injection 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 for injection 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 ($p < 0.0001$).



The survival benefits of Azacitidine for injection 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 for injection 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 for injection treatment was also associated with a reduction in cytopenias, and their related symptoms. Azacitidine for injection 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).

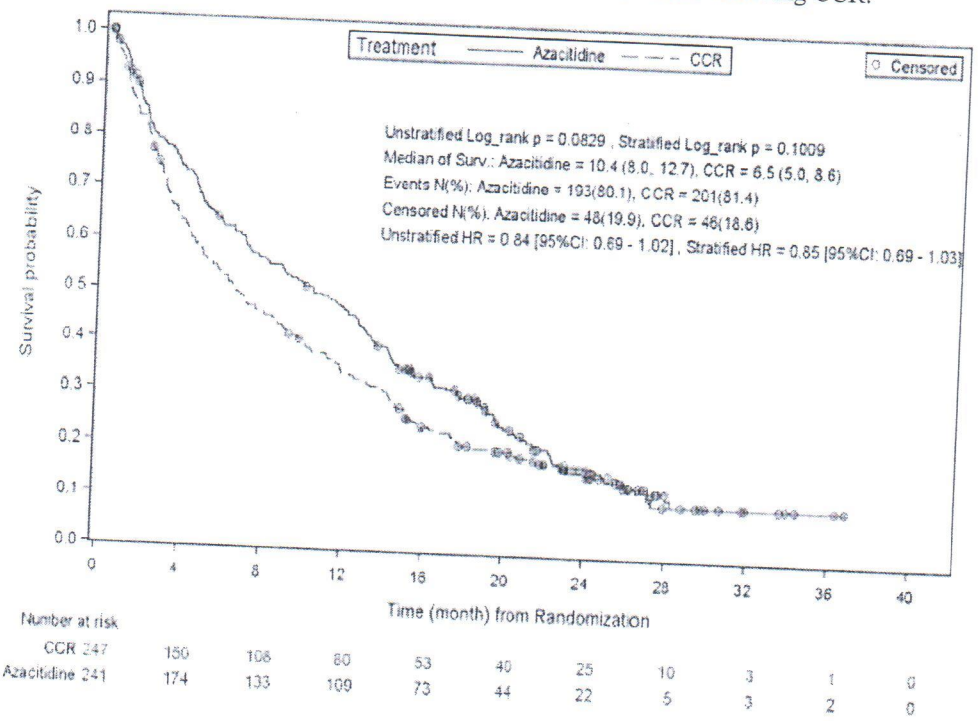
The efficacy and safety of Azacitidine for injection was studied in an international, multicentre, controlled, open-label, parallel group Phase 3 study in patients 65 years and older with newly diagnosed de novo or secondary AML with > 30% bone marrow blasts according to the WHO classification, who were not eligible for HSCT. Azacitidine for injection plus BSC ($n = 241$) was compared to CCR. CCR consisted of BSC alone ($n = 45$), lowdose cytarabine plus BSC ($n = 158$), or standard intensive chemotherapy with cytarabine andanthracycline 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 for injection. 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 for injection 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 for injection 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 for injection and 247 CCR), Azacitidine for injection 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 for injection versus 34.3% in patients receiving CCR.



The Cox PH model adjusted for pre-specified baseline prognostic factors defined a HR for azacitidine for injection 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 for injection 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 and ≥ 75 years], gender, race, ECOG performance status [0 or 1 and 2] , baseline cytogenetic risk [intermediate and poor], geographic region, WHO classification of AML [including AML with myelodysplasia-related changes], baseline WBC count [≤ 5 x10^9/L and > 5 x 10^9/L], baseline bone marrow blasts [≤ 50% and > 50%] and prior history of MDS), there was a trend in OS benefit in favour of Azacitidine for injection . 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 for injection 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 for injection 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 for injection compared to CCR.

Azacitidine for injection 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 for injection 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 for injection group and was not reached in the CCR group.

Of the patients in the azacitidine for injection 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 for injection 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 study 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 for injection.

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 for injection 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 for injection 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 for injection 75 mg/m^2, 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 for injection, 7 (43.8%) patients had a sustained platelet response (counts $\geq 100 \times 10^9$/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 for injection 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 for injection 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 15 Azacitidine for injection 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 for injection 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 administration 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 (t½) 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 14C-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 for injection rapidly reached C_{max} within 0.083 hours in both MDS and JMML populations. The geometric mean C_{max} were 1797.5 and 1066.3 ng/mL, and the geometric mean $AUC_{0-\infty}$ 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 for injection was higher in MDS subjects; however, moderate to high between-patient variability was noted for both AUC and C_{max}.

The geometric mean $t_{½}$ 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 for injection intravenously in Study AZA-2002-BA-002. Mean C_{max} and AUC_{0-t} of azacitidine for injection 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 C_{max} and AUC_{0-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 C_{max}, with a median time of 0.090 hours post-intravenous administration and declined with a geometric mean $t_{1/2}$ 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 exposers 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 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

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: 18 months.

Shelf life after reconstitution:

Suspension Stability: Azacitidine for injection reconstituted with non-refrigerated water for injection for subcutaneous administration may be stored for up to 1 hour at 25°C (77°F) or for up to 8 hours between 2°C and 8°C (36°F and 46°F); when reconstituted with refrigerated (2°C - 8°C, 36°F - 46°F) water for injection, it may be stored for 22 hours between 2°C and 8°C (36°F and 46°F).

Solution Stability: Azacitidine for injection reconstituted for intravenous administration may be stored at 25°C (77°F), but administration must be completed within 1 hour of reconstitution.

6.4 Special precautions for storage

Unopened vials
This medicinal product shall be stored below 30°C.

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

6.5 Nature and contents of container

Azacitidine for Injection, 100 mg/Vial will be packaged in 50 mL Clear Lyophilization Vials with a 20 mm double slotted grey rubber stoppers and 20 mm flip-off white cap.

Pack size: 1 vial

6.6 Special precautions for disposal and other handling

Recommendations for safe handling

Azacitidine for injection 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 for injection 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;
2. 5 mL injection syringe(s) with needle(s). 2. 4 mL of water for injections should be drawn into the syringe, making sure to purge any air trapped within the syringe.
3. The needle of the syringe containing the 4 mL of 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). 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
75 mg/m_2 (100%)	135 mg	2 vials	5.4 mL
37.5 mg/m_2 (50%)	67.5 mg	1 vial	2.7 mL
25 mg/m_2 (33%)	45 mg	1 vial	1.8 mL

Method of administration

Reconstituted azacitidine for injection should be injected subcutaneously (insert the needle at a 45-90o 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.

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

7. DATE OF REVISION OF THE TEXT

Nil

Reference: Vidaza: Marketing Authorisation Holder and Manufacturer: Bristol-Myers Squibb Pharma EEIG, Plaza 254, Blanchardstown Corporate Park 2, Dublin 15, D15 T867 Ireland.

Azacitidine for injection 100 mg / Vial:
Manufactured by:
NATCO PHARMA LIMITED
Kothur- 509 228, India

March 2022