EU-RISK MANAGEMENT PLAN FOR EVOLTRA® (CLOFARABINE)

Data Lock Point (DLP)	**28-DEC-2023**
RMP Version number	**Version 10.0**
Date of final sign-off	**20-FEB-2024**

Table 1 - RMP version to be assessed as part of this application

Rationale for submitting an updated RMP	This update is submitted following the assessment report on the 17th annual re-assessment, in the frame of the procedure EMEA/H/C/000613/S/0078.
Summary of significant changes in this RMP	Updates of RMP Part II Module SI: Epidemiology of the indication(s) and target population(s) and Module SV: Post-authorization with respect to revised DLP. **Pharmacovigilance Plan:** Update to include the remaining general SOB 44 as category 2 additional pharmacovigilance activity. **Annexes:** Annex 2 is updated to include general SOB 44 as category 2 additional pharmacovigilance activity.

DLP: Data Lock Point; RMP: Risk Management Plan; SOB: Specific Obligation.

Table 2 - Other RMP versions under evaluation

RMP Version number	Submitted on	Submitted within
Not applicable	Not applicable	Not applicable

RMP: Risk Management Plan.

Table 3 - Details of the currently approved RMP

Version number	9.0
Approved with procedure	EMEA/H/C/000613/II/0069
Date of approval (opinion date)	03-Sep-2020

RMP: Risk Management Plan.

Table 4 - QPPV name and signature

QPPV name	Armelle Donohoe[a], M.Sc
QPPV signature	Electronic signature on file

a Deputy QPPV by delegation from Heike Schoepper, QPPV for Sanofi.

QPPV: Qualified Person Responsible for Pharmacovigilance.

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ABBREVIATIONS

AE:	Adverse Event
ALL:	Acute Lymphoblastic Leukemia
ALT:	Alanine Transaminase
AML:	Acute Myelogenous/Myeloid Leukemia
ANC:	Absolute Neutrophil Count
ASR:	Age Standardized Rate
AST:	Aspartate Transaminase
ATC:	Anatomical Therapeutic Chemical
AUC:	Area Under Curve
BSA:	Body Surface Area
BSA:	Body Surface Area
CI:	Confidence Interval
CLL:	Chronic Lymphoblastic Leukemia
CML:	Chronic Myelogenous Leukemia
CRLF2:	Cytokine Receptor Like Factor 2
DLP:	Data Lock Point
DLT:	Dose Limiting Toxicity
DNA:	Deoxyribonucleic Acid
dNTP:	Deoxynucleotide Triphosphate
EC:	European Community
ECHO:	Echocardiogram
EEA:	European Economic Area
EPAR:	European Public Assessment Report
EU:	European Union
GBD:	Global Burden of Disease
GCP:	Good Clinical Practices
GVP:	Good Pharmacovigilance Practices
HSCT:	Hematopoietic Stem Cell Transplantation
IKZF1:	IKAROS Family Zinc Finger 1
INN:	International Nonproprietary Name
ISS:	Integrated Summary of Safety
IU:	International Unit
IV:	Intravenous
LVEF:	Left Ventricular Ejection Fraction
MAH:	Marketing Authorization Holder
MDS:	Myelodysplastic Syndrome
MTD:	Maximum Tolerated Dose
MUGA:	Multigated Acquisition
OCT2:	Organic Cation Transporter 2
PBRER:	Periodic Benefit-Risk Evaluation Report
PEG:	Polyethylene Glycol
PL:	Package Leaflet
QPPV:	Qualified Person Responsible for Pharmacovigilance

RMP:	Risk Management Plan
SmPC:	Summary of Product Characteristics
SOB:	Specific Obligation
ULN:	Upper Limit of Normal
USA:	United States of America
WHO:	World Health Organization

RISK MANAGEMENT PLAN - PART I: PRODUCT (S) OVERVIEW

Table 5 - Product Overview

Active substance(s) (INN or common name)	Clofarabine
Pharmacotherapeutic group(s) (ATC Code)	Antineoplastic, antimetabolites (L01BB06)
Marketing Authorization Holder	Sanofi B.V.
Medicinal products to which this RMP refers	1
Invented name(s) in the EEA	EVOLTRA ®
Marketing authorization procedure	Centralized
Brief description of the product	Chemical class: Clofarabine is a purine nucleoside anti-metabolite.
	Summary of mode action: Clofarabine is a purine nucleoside anti metabolite. Its antitumour activity is believed to be due to 3 mechanisms: • Deoxyribonucleic acid polymerase α inhibition resulting in termination of DNA chain elongation and/or DNA synthesis/repair. • Ribonucleotide reductase inhibition with reduction of cellular dNTP pools. • Disruption of mitochondrial membrane integrity with the release of cytochrome C and other proapoptotic factors leading to programmed cell death even in non-dividing lymphocytes.
	Important information about its composition: Each 20 mL vial contains 180 mg of sodium chloride.
Hyperlink to the product information	The current Product Information (EMEA/H/C/000613/IAIN/0079 and EMEA/H/C/000613/II/0077) was approved in Mar-2023 and submitted on 25-Apr-2023 (closing seq 134).
Indication(s) in the EEA	Current: Treatment of ALL in pediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. Safety and efficacy have been assessed in studies of patients ≤21 years old at initial diagnosis.
	Proposed: Not applicable

Dosage in the EEA	Current: Children and adolescent (≥1 year old): The recommended dose in monotherapy is 52 mg/m^2 of BSA administered by intravenous infusion over 2 hours daily for 5 consecutive days. Treatment cycles should be repeated every 2 to 6 weeks (from the starting day of the previous cycle) following recovery of normal hematopoiesis (ie, ANC ≥0.75 X 10^9/L) and return to baseline organ function. A 25% dose reduction may be warranted in patients experiencing significant toxicities.
	Proposed: Not applicable
Pharmaceutical form(s) and strength(s)	Current: Concentrate for solution for infusion (1 mg/mL).
	Proposed: Not applicable
Is/will the product (be) subject to additional monitoring in the EU?	Yes

ALL: Acute Lymphoblastic Leukemia; ANC: Absolute Neutrophil Count; ATC: Anatomical Therapeutic Chemical; BSA: Body Surface Area; DNA: Deoxyribonucleic Acid; dNTP: Deoxynucleotide Triphosphate; EEA: European Economic Area; EU: European Union; INN: International Nonproprietary Name; RMP: Risk Management Plan.

RISK MANAGEMENT PLAN - PART II MODULE SI: EPIDEMIOLOGY OF THE INDICATION(S) AND TARGET POPULATION(S)

Clofarabine (EVOLTRA in EU, CLOLAR® in United States of America [USA] and Canada) is indicated for the treatment of ALL in pediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. Safety and efficacy have been assessed in studies of patients ≤21 years old at initial diagnosis.

The epidemiology of the ALL in pediatric patients is summarized in Table 6.

Table 6 - Epidemiology of the ALL in pediatric patients

Indication	ALL in pediatric patients
Incidence	Acute Lymphoblastic Leukemia constitutes12% of all leukemia cases. (1) The estimated worldwide all-age incidence ASR of ALL was 1.96 (95% CI: 1.64-2.17) per 100 000 population, based on the 2019 global population data from the GBD project (the most recent available estimates). (2) In the USA, the incidence was significantly lower at 0.90 (0.78-1.03). The estimated worldwide incidence of ALL has been relatively consistent over the most recent two decades. **WHO Geographic Regions** Expanding the analysis to WHO geographic regions reveals substantial variability in ALL incidence ASRs across different regions. The highest 2019 rates were estimated for the European Region at 3.92 (3.41-4.53) and the Western Pacific Region at 3.49 (2.52-4.06), both significantly higher than the Region of the Americas at 1.60 (1.35-1.87) and the Eastern Mediterranean Region at 1.03 (0.79-1.29). Additionally, lower rates were observed in the African Region at 0.51 (0.38-0.64) and the South-East Asia Region at 0.50 (0.41-0.62).
Prevalence	The estimated worldwide all-age prevalence ASR of ALL was 12.30 (10.30-13.73) per 100 000 population, based on the 2019 global population data from the GBD project (the most recent available estimates). (2) In the USA, the prevalence was significantly lower at 4.41 (3.81-5.07). The estimated worldwide prevalence of ALL has been relatively consistent over the most recent two decades. **WHO Geographic Regions** There is substantial variability in the ASR prevalence of ALL across different WHO geographical regions. The highest rates in 2019 per 100 000 population were estimated for the European Region at 29.70 (95% CI: 25.58-34.72) and the Western Pacific Region at 25.19 (18.28-29.48), both significantly higher than the Region of the Americas at 7.05 (5.83-8.29) and the Eastern Mediterranean Region at 3.67 (2.75-4.48). This was followed by lower rates in the African Region at 1.32 (0.96-1.69) and the Southeast Asia Region at 1.32 (1.09-1.64). Acute Lymphoblastic Leukemia stands as the most prevalent malignancy diagnosed in children, constituting nearly one-third of all pediatric cancers. The overall cure rates for children with ALL have now reached approximately 80%. (1) (3) Consequently, pediatric patients facing relapse or refractory cases after undergoing a minimum of two prior treatments constitute a rare patient population, likely numbering around 6 per million children.
Demographics of the population in the authorized indication	**Demographics of the target population** **Age** Table 6a (below) presents the estimated incidence and prevalence of ALL per 100 000 population in pediatric age groups worldwide. These data were derived from the 2019 global population data provided by the GBD project, representing the most recent available estimates. (2) Generally, the rates observed were higher for pediatric cases, with a significant increase noted in early neonates (0 to 6 days).

Table 6a: The estimated incidence and prevalence of ALL per 100 000 population in pediatric age groups globally and in the USA. The data are derived from the 2019 global population data provided by the GBD project

	Global		USA	
	Incidence	**Prevalence**	**Incidence**	**Prevalence**
0 to 6 days (early neonatal)	11.96 (8.0–16.30)	54.01 (39.64-69.78)	3.40 (2.44–4.64)	23.13 (16.29-32.04)
7 to 27 days (late neonatal)	3.02 (2.01–4.19)	14.13 (10.20-18.29)	0.60 (0.41–0.81)	4.06 (2.74–5.61)
28 to 364 days (post neonatal)	2.98 (2.06–3.92)	14.78 (10.51-19.29)	0.70 (0.50–0.97)	4.78 (3.34–6.63)
1 to 4 years	2.01 (1.58–2.49)	11.50 (9.21-14.23)	0.98 (0.66–1.42)	6.66 (4.40–9.90)
5 to 9 years	1.80 (1.51-2.06)	9.13 (7.75-10.54)	1.13 (0.94-1.40)	7.35 (5.95-9.42)
10 to 14 years	1.13 (0.99-1.28)	4.89 (4.22-5.52)	0.89 (0.75-1.07)	5.13 (4.13-6.42)
15 to 19 years	1.35 (1.13-1.53)	7.53 (6.29-8.57)	1.00 (0.82-1.21)	6.03 (4.82-7.48)

ALL: Acute Lymphoblastic Leukemia; GBD: Global Burden of Disease; USA: United States of America.

Studies from the USA have shown a significant increase in ALL incidence for Hispanic White children (annual percent change Hispanic 1.08 [0.59, 1.58]), but no significant increase was observed for non-Hispanic White, Black, or Asian children. (4)

Sex

Analyzing the GBD, 2019 data revealed that the global incidence of ASRs of ALL for males, 2.18 (1.73-2.49), were not significantly different from females, 1.75 (1.34-2.08). Similarly, the global prevalence ASRs of ALL for males, 13.15 (10.36-15.07), and females, 11.49 (8.75-13.79), were not significantly different. (2) A slight male predominance is observed in most countries due to the divergence of rates after 65 years of age when the rate among males increases more rapidly. Among children <15 years of age, ALL was the main subtype of leukemia ranging 61% to 84% for boys and 57% to 82% for girls. (5)

Ethnicity and racial groups

Most racial and ethnic subpopulations in the USA exhibited similar (incidence and prevalence rates) based on the data from the 2019 global population data provided by the GBD project. (2) However, among them, the age-specific Non-Hispanic White group (1.56 [1.35-1.79] and 8.59 [7.42-10.02]) and Non-Hispanic American Indian or Alaskan Native group (1.80 [1.39-2.35] and 9.94 [7.61-13.20]) had significantly higher rates compared to the Non-Hispanic Asian or Pacific Islander group (0.90 [0.73-1.13] and 4.97 [3.98-6.35]).

The research findings indicate that children under 20 years of age from the Hispanic White population in the USA are more likely to be diagnosed with ALL compared to children of other races/ethnicities. The age-adjusted incidence rates per 100 000 from 2009 to 2013 were 4.89 for Hispanic White, 3.44 for non-Hispanic White, 1.83 for non-Hispanic Black, and 2.97 for non-Hispanic Asian children. Moreover, there was an increase in ALL incidence among older Hispanic White children, with a 2% per year rise for ages 10-14 years and a 3% per year increase for ages 15-19 years, observed from 1992 to 2013. This increasing trend was not observed for older children of other races/ethnicities. (4)

Risk factors for the disease

Evidence suggests that the various risk factors may be associated with the development of ALL, including:

Environmental Risk Factors:

- Low doses of ionizing radiation during early childhood.
- Exposure to pesticides during maternal preconception/pregnancy.
- Presence of extremely low-frequency electromagnetic fields in individuals living near nuclear facilities.
- Exposure to petroleum, benzene, solvents, and domestic paint during early childhood. (6)

Patient-Related: Specific immunophenotype, genetic abnormalities in leukemia cells, such as deletions or sequence mutations of genes IKZF1, CRLF2, erythroblast transformation-specific related gene, and

Indication	ALL in pediatric patients
	Philadelphia-like ALL, certain genetic disorders, such as Down syndrome, and having a brother or sister with ALL. **Treatment-Related:** Time elapsed from the diagnosis, therapy adherence, minimal residual disease persistence following therapy, and socioeconomic factors may act as a risk factor for higher mortality. (7) In addition, comorbidities and risk factors related to comorbidities include venous thromboembolism (8), infections during treatment (9), and obesity may act as risk factors for higher mortality.
Main existing treatment options	Standard treatment of relapsed childhood ALL with bone marrow involvement may include the following: • Combination chemotherapy with or without targeted therapy (bortezomib). • Stem cell transplant, using stem cells from a donor. Standard treatment of relapsed childhood ALL without bone marrow involvement may include the following: • Systemic chemotherapy and intrathecal chemotherapy with radiation therapy to the brain and/or spinal cord for cancer that impacts the brain and spinal cord only. • Combination chemotherapy and radiation therapy for cancer that is in the testicles only. • Stem cell transplant for cancer that has recurred in the brain and/or spinal cord. Some of the treatments being studied in clinical trials for relapsed childhood ALL include: • A new regimen of combination chemotherapy and targeted therapy (blinatumomab). • A new type of chemotherapy treatment. • Chimeric antigen receptor T-cell therapy.
Natural history of the indicated condition in the untreated population including mortality and morbidity	In the absence of treatment, ALL is a rapidly fatal disease with a median survival time of <3 months. (10) Typically, symptoms arise in pediatric patients only a few weeks before diagnosis indicating that much of the natural history of the latent form of the disease may be clinically silent. (11) Pediatric ALL is genetically heterogeneous, in which specific chromosomal abnormalities are strong prognostic indicators of treatment outcomes, especially risk of relapse. For example, pediatric patients whose disease exhibits a high level of hyperdiploidy, the *TEL-AML1* translocation, or *TCF3-PBX1* translocation have survival rates >85%, whereas patients with the *BCR-ABL1* translocation have survival rates that were historically on the order of 35% to 40%. (12) Acute Lymphoblastic Leukemia cure rates have improved dramatically with treatment to >80% among pediatric patients, and 40% to 50% among adults. (13) Over the course of a 60-year period (1958 to 2018) at a single pediatric center in Poland, the probability of 5-year overall survival increased from 1.2% to 90.7%, event-free survival increased from 1.2% to 86.6%, and relapse risk decreased from 98.8% to 9.9%. (14) However, the prognosis among patients with relapsed or refractory ALL, regardless of age or treatment, is extremely poor. Acute Lymphoblastic Leukemia remains one of the leading causes of death due to disease in children. (12)
Important co-morbidities	Acute Lymphoblastic Leukemia is the most common childhood malignancy, boasting a 5-year event-free survival rate of 80%. (15) However, the management of ALL in adults and children introduces significant comorbidities due to treatments, primarily chemotherapy supplemented with radiation therapy, including: **General Side Effects:** Nausea and vomiting may, in turn, lead to nutritional challenges in the long term. Mucositis, hair loss, and neuropathy may also develop. Treatment-induced anemia may cause fatigue, weakness, and pale skin. Intensive treatments may impact normal growth and development in children, leading to emotional and psychological challenges, including stress, anxiety, and depression. A study reported that 13% of young adult survivors of childhood ALL experienced moderate/high levels of overall unmet needs. (16) **Specific Organ Complications:** Treatment modalities for ALL may lead to cardiovascular issues, renal complications, and hepatic dysfunction. • **Cardiovascular Complications**: Approximately 75% of survivors face chronic health conditions negatively impacting cardiovascular morbidity and mortality. (15) Those treated for ALL are more prone to obesity, increasing the risk of cardiovascular and metabolic comorbidities. (15) A prospective study revealed that 43% of pediatric ALL patients developed obesity within 12 months of chemotherapy, and 26% experienced high blood pressure. (16) • **Bleeding, Bruising, and Thromboembolism**: Treatment interference with blood clotting leads to increased bleeding and bruising tendencies. Specific risk factors for thromboembolism include treatment with

Indication	ALL in pediatric patients
	Escherichia coli asparaginase, concomitant steroids, the presence of central venous lines, and thrombophilic abnormalities. (17) • **Infections**: Patients undergoing chemotherapy face an increased risk of infections due to weakened immune systems. Septicemia is an important cause of treatment-related mortality and treatment failure in pediatric ALL. In a study from China, out of 4080 patients recruited 527 cases with septicemia were identified, accounting for 12.9% (11.9%-13.9%). (18)

ALL: Acute Lymphoblastic Leukemia; ASR: Age-Standardized Rate; CI: Confidence Interval; CRLF2: Confidence Interval; GBD: Global Burden of Disease; IKZF1: IKAROS Family Zinc Finger 1 USA: United States of America; WHO: World Health Organization.

RISK MANAGEMENT PLAN – PART II MODULE SII: NON-CLINICAL PART OF THE SAFETY SPECIFICATION

Table 7 - Key safety findings from non-clinical studies and relevance to human usage

Key Safety Findings	Relevance to human usage
Toxicity	
• Reproductive/developmental toxicity studies *Developmental toxicity:* Increased incidence of malformation and variations (gross external, soft tissue) skeletal and retarded ossification.	These findings are considered relevant to human use and are reflected in the SmPC. Teratogenicity was considered as an important potential risk. In the EU-RMP version 9.0, this risk has been removed from the list of safety concerns.
Male/female fertility: The potential effects of clofarabine on male and female fertility and post-natal development have not been evaluated in non-clinical studies. Studies in mice, rats and dogs have demonstrated dose-related adverse effects on male reproductive organs (seminiferous tubule and testicular degeneration and/or atrophy) at doses between approximately 0.14 and 3 times the recommended human dose. Ovarian atrophy or degeneration was observed in mice at a dose approximately 4 times the recommend human dose.	These findings are considered relevant to human use and are reflected in the SmPC. It is advised that females of childbearing potential and sexually active males use effective methods of contraception during clofarabine treatment. Infertility was considered as an important potential risk. In the EU-RMP version 9.0, this risk has been removed from the list of safety concerns.
• Genotoxicity Clastogenic activity was observed in the in vitro mammalian cell chromosome aberration assay (Chinese hamster ovary cells) in a non-activated test system and in the in vivo rat micronucleus assay.	Based on the pharmacodynamic mechanism of action, clofarabine is suggested to cause congenital malformations when administered during pregnancy. Clofarabine should not be used during pregnancy unless the clinical condition of the woman requires treatment with clofarabine. There are no adequate clinical data for the use clofarabine in pregnant women. Teratogenicity was considered as an important potential risk. In the EU-RMP version 9.0, this risk has been removed from the list of safety concerns.
Safety pharmacology	
Cardiovascular effects Histological evidence of cardiotoxicity characterized by myocardial degeneration primarily in the left atrium, left ventricle in a band subjacent to the endocardial surface and the interventricular septum was observed in rat toxicity studies at dose levels approximately 3 times higher than the recommended human dose of 52 mg/m^2.	Left ventricular dysfunction is occasionally observed following clofarabine exposure in humans. Several of these patients also experienced prior exposure to the cardiotoxic anthracyclines. Cardiotoxicity was considered as an important identified risk. In the EU-RMP version 9.0, this risk has been removed from the list of safety concerns.
Renal effects Histologic evidence of glomerulonephropathy was reported in rats in a 6-month multicycle toxicity study at dose levels approximately 1.4 and 3 times higher than the recommended human dose. The lesion was never severe and was unlikely to have had a marked effect on the health of affected animals. This change was not associated with functional	Pre-clinical data suggest a potential but limited effect on the kidney. Nephrotoxicity was considered as an important potential risk. In the EU-RMP version 9.0, this risk has been removed from the list of safety concerns.

Key Safety Findings	Relevance to human usage
renal changes in serum chemistry or appreciable protein leakage.	
Hepatic effects Persistent elevations in ALT and AST were observed in mice at doses (225 mg/m^2/day for 7 days) approximately 4-fold higher than the recommended human dose. Clofarabine administered intravenously for 5 consecutive days in single-or 6-month multi-cycle studies in rats and dogs was not associated with increases in serum ALT, AST or bilirubin levels. However, a mild increase in ALT, AST, and bilirubin was observed when clofarabine was administered orally for 21 consecutive days at doses of 180 mg/m^2/day and higher in rats and 11.2 mg/m^2/day and higher in dogs. Histologic evidence of adverse hepatic changes in rats was observed in rats at doses approximately 0.7 to 3 times the clinical dose. Single-cell hepatocyte degeneration and necrosis (a hallmark of cellular apoptosis) and karyomegaly/cytomegaly (disruption of cellular replication) were prominent histologic features. The histologic changes are likely related to the superimposition of degenerative and regenerative hepatocyte changes as a result of the cycles of treatment with clofarabine.	Most common reported events in patients are hyperbilirubinemia and transient elevated transaminases. Hepatotoxicity was considered as an important identified risk. In the EU-RMP version 9.0, this risk has been removed from the list of safety concerns.
Other toxicity-related information or data	
Mechanism for drug interactions The primary route of clofarabine elimination is through the kidneys (approximately 76% excreted unchanged in urine). The urinary excretion of clofarabine is complex and involves glomerular filtration and tubular secretion and reabsorption. Inhibition studies with cimetidine in rats have shown that tubular secretion of clofarabine occurs through OCT2. The potential pharmacokinetic effects associated with the combined administration of clofarabine with other compounds that utilize the OCT2 transporter (eg, cimetidine) has not been adequately studied in animals.	As the effects of the drugs utilizing the same transporter as clofarabine for their renal elimination have not been studied, drug interaction with commonly used co-medications was considered missing information. In the EU-RMP version 9.0, this missing information has been removed from the list of safety concerns.

ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; EU: European Union; OCT2: Organic Cation Transporter 2; RMP: Risk Management Plan; SmPC: Summary of Product Characteristics.

No additional non-clinical data have been collected on the use of clofarabine in any special populations.

Based on non-clinical studies; cardiotoxicity and hepatotoxicity were identified as important identified risks; teratogenicity, infertility and nephrotoxicity were identified as important potential risks; and drug interaction with commonly used co-medications was considered as missing information. In the EU-RMP version 9.0, all important risks and missing information have been removed from the list of safety concerns.

RISK MANAGEMENT PLAN – PART II MODULE SIII: CLINICAL TRIAL EXPOSURE

Completed clofarabine clinical studies in pediatric ALL or acute myelogenous/myeloid leukemia (AML)

An overview of pediatric studies is provided in Table 8. The company has performed studies in the registered indication (relapsed or refractory ALL in pediatric patients), and likewise in relapsed or refractory AML in the pediatric population. The use of clofarabine as a single agent, as well as a combination of clofarabine with other antineoplastic agents has been investigated.

Seven (7) studies have been undertaken in the pediatric population: 5 pediatric studies using clofarabine as single agent and 2 combination studies. All studies have been completed.

Table 8 - Company sponsored clinical studies in pediatric ALL or AML

Study identifier/location	Study phase/diagnosis	Objective of study	Treatment dosage	Number of patients	Study status
Pediatric studies - Completed					
ID99-383[a] MDACC United States of America	Phase I ALL/AML	To determine the MTD of single agent clofarabine.	1-2 hour IV infusion daily 11.25 to 70 mg/m²/day x 5 days	25 (17 ALL; 8 AML)	Completed
CLO212[a] Genzyme United States of America	Phase II Relapsed or refractory ALL	To determine the efficacy of single agent clofarabine.	2 hour IV infusion daily 52 mg/m²/day x 5 days	62 (61 treated)	Completed
CLO222[a] Genzyme United States of America	Phase II Relapsed or refractory AML	To determine the efficacy of single agent clofarabine.	2 hour IV infusion daily 52 mg/m²/day x 5 days	43 (42 treated)	Completed
BIOV-111 (conducted by Bioenvision, Limited) European Union	Phase II Relapsed or refractory ALL	To determine the efficacy of single agent clofarabine.	2 hour IV infusion 52 mg/m²/day x 5 days	74 (71 treated)	Completed
CLO218 00205 (CLO218) Genzyme United States of America	Phase I/II Relapsed or refractory AML/ALL Phase II: only ALL patients	To determine the MTD and DLT of clofarabine in combination with etoposide and cyclophosphamide.	Clofarabine 20-40 mg/m²/day 2 hour IV infusion daily x 5 days; Etoposide 75-100 mg/m²/day 2 hour IV infusion daily x 5 days; Cyclophosphamide 340-440 mg/m²/day 30-60 min IV infusion daily x 5 days	50 patients enrolled Phase I: 25 patients enrolled (20 ALL, 5 AML) Phase II: 25 patients enrolled (ALL only)	Phase I: completed; Phase II: completed

Study identifier/location	Study phase/diagnosis	Objective of study	Treatment dosage	Number of patients	Study status
CLO05908	Phase I Relapsed or refractory ALL	Single-agent therapy; multi-center, open label dose escalation safety study of clofarabine in Japanese pediatric patients	Daily x 5 at 30 mg/m^2/day or 52 mg/m^2/day IV infusion	7 (7 treated)	Completed
CLO08808	Phase I, 1st relapse ALL	Combination therapy; multi-center, open label pilot study to assess the safety and tolerability of incorporating clofarabine into an intensive chemotherapy regimen of etoposide, cyclophosphamide, pegylated *Escherichia coli* asparaginase, and vincristine in pediatric patients with ALL in first relapse.	Daily x 5 Days 1-5: IV infusions Clofarabine: 40 mg/m^2/day; Etoposide: 100 mg/m^2/day; Cyclophosphamide: 440 mg/m^2/day Day 15: IV PEG-asparaginase: 2500 IU/m^2 Day 15 and 22: IV vincristine: 1.5 mg/m^2	8 (8 treated) Cohort #1: (n = 6) Cohort #2: (n = 2)	Cohort #1: completed Cohort #2: completed

a Study included in the ISS.

ALL: Acute Lymphoblastic Leukemia; AML: Acute Myelogenous/Myeloid Leukemia; DLT: Dose Limiting Toxicity; ISS: Integrated Summary of Safety; IU: International Unit; IV: Intravenous; MTD: Maximum Tolerated Dose; PEG: Polyethylene Glycol.

Completed clinical studies in adult AML, ALL, solid tumors, myelodysplastic syndrome (MDS) and chronic lymphoblastic leukemia (CLL)

An overview of all 10 adult studies is provided in Table 9. The company has been investigating the efficacy of clofarabine in adults and elderly population in solid tumors, acute leukemia (AML and ALL), CLL, and MDS. All 10 studies have been completed.

Table 9 - Company sponsored studies in adult in solid tumors, AML, ALL, CLL, and MDS

Study identifier/location	Study phase/diagnosis	Objective of study	Treatment dosage	Number of patients	Study status
DM93-036 MDACC United States of America	Phase I Solid tumor, lymphoma, acute and chronic leukemia,	To determine the MTD of single agent clofarabine.	1 hour IV infusion daily x 5. Patients received 2, 4, 7.5, 11.25, 15, 22.5, 30, 40 and	51	Completed

Study identifier/location	Study phase/diagnosis	Objective of study	Treatment dosage	Number of patients	Study status
	other hematologic malignancy		55 mg/m²/day to determine MTD.		
CLO151 Genzyme United States of America	Phase I Advanced solid tumors	To determine MTD and DLT of single agent clofarabine.	Intravenous infusion over at least 2 hour for 3 weeks (days 1, 8, and 15) followed by 1 week of rest. Patients received 4, 6, 10, 14, 18, 22, 27.5, 34, 42.5, 53, 66, 82.5, 103, 129, and 148 mg/m²/week	78 enrolled (75 treated)	Completed
CLO141 MDACC United States of America	Phase I/II First relapse or first salvage of primary refractory AML or ALL; high-risk MDS; or with CML blast phase as front line therapy or in first salvage	To determine MTD and DLT of clofarabine in combination with cytarabine (Ara-C).	Phase I: Clofarabine IV infusion at 15 mg/m²/day, with subsequent dose escalation to 22.5 mg/m²/day, then 30 mg/m²/day, and then further 25% increase until the MTD was identified. Phase II: 40 mg/m²/day dose was chosen. For both Phase I and II, Ara-C induction dose was fixed at 1 g/m²/day.	32	Completed
DM99-225 MDACC United States of America	Phase II CLL refractory to fludarabine and alkylator therapy.	To estimate the efficacy of single agent clofarabine.	4 mg/kg IV infusion over 60 minutes on days 1-5 every 4 weeks	12 planned 11 enrolled before termination due to lack of efficacy.	Completed
ID00-038 MDACC United States of America	Phase II Relapsed or refractory AML/ALL MDS/CML	To determine the activity and toxicity of single agent clofarabine.	40 mg/m² IV over 1 hour daily x 5 days	64[a] enrolled, (62 treated)	Completed
CLO221 Genzyme	Phase II Relapsed or refractory AML	To demonstrate a complete response rate	Induction: Clofarabine 40 mg/m²/day as	41 (40 treated)	Completed

Study identifier/location	Study phase/diagnosis	Objective of study	Treatment dosage	Number of patients	Study status
United States of America		≥40% of single agent clofarabine.	a 1-hour IV infusion for 5 days for up to 2 cycles Consolidation phase: Clofarabine 30 mg/m^2/day for 5 days as a 1-hour IV infusion; cycles repeated every 28 days		
BIOV121	Phase II Untreated AML Older patients with AML for whom intensive chemotherapy is not considered suitable.	To determine the overall response rate	30 mg/m^2/day over 1 hour IV infusion x 5 days. In protocol amendment 3, the dose for the second and subsequent cycles was reduced to 20 mg/m^2 daily.	69 enrolled (66 treated)	Completed
CLO243 Genzyme United States of America	Phase II Previously untreated adult patients ≥60 years old with AML for whom standard induction chemotherapy is unlikely to be of benefit.	To assess the overall remission rate of single agent clofarabine.	Induction: Clofarabine 30 mg/m^2/day for 5 days IV infusion Subsequent cycles: Clofarabine 20 mg/m^2/day for 5 days IV infusion	116 (112 analyzed)	Completed
CLO341 Genzyme United States of America	Phase III randomized, double-blind, placebo-controlled study Adult patients ≥55 years old Relapsed or refractory AML	To assess the efficacy of clofarabine in combination with cytarabine compared with cytarabine alone.	Induction and re-induction: Patients will receive either placebo administered as a 1-hour IV infusion or clofarabine 40 mg/m^2 as a 1-hour IV infusion followed 3 hour later (from the end of infusion) by cytarabine 1 g/m^2 administered as a 2 hour IV infusion for 5 consecutive days.	Planned 376 316 treated	Completed

Study identifier/location	Study phase/diagnosis	Objective of study	Treatment dosage	Number of patients	Study status
CLOAML 10508 Japan	Phase I Adults with newly diagnosed or relapsed or refractory AML	Assess the safety, tolerability and pharmacokinetics of clofarabine intravenously administered at 20, 30, and 40 mg/m^2/day on a 5-daily dose schedule to Japanese adult patients.	Cohort 1 were to receive 20 mg/m^2/day of clofarabine once daily for 5 consecutive days, the subjects in cohort 2 were to receive 30 mg/m^2/day, and the subjects in cohort 3 were to receive 40 mg/m^2/day.	24 planned 14 analyzed	Completed

a Protocol ID00-038 enrolled 64 patients, but data available for analysis (to Ilex) were only for 16 patients.
ALL: Acute Lymphoblastic leukemia; AML: Acute Myelogenous/Myeloid Leukemia; CLL: Chronic Lymphoblastic Leukemia; CML: Chronic Myelogenous Leukemia; DLT: Dose Limiting Toxicity; IV: Intravenous; MDS: Myelodysplastic Syndrome; MTD: Maximum Tolerated Dose.

Other formulation in adult patients with MDS

In addition, 3 company sponsored studies were initiated with an oral formulation of clofarabine in adult patients with MDS. An overview of these 3 studies is provided in Table 10.

Table 10 - Company sponsored studies of oral formulation of clofarabine in adults with MDS

Protocol	Title	Phase	Status	No. patients enrolled
CLO152	A Phase I, dose-escalation and pharmacokinetic study of oral clofarabine administered daily for 5 days in adult patients with refractory solid tumors.	Phase I	Completed	24 (23 treated)
CLOMDS 02507	A Phase IIa, open-label, dose confirmation study of oral clofarabine in previously treated adult patients with MDS.	Phase IIa	Completed	36 (24 patients at 25 mg, 8 patients at 35 mg and 4 patients at 55 mg)
CLOMDS 01206	A Phase I, open-label, 2-part, multi-centre, dose-finding and food effect study of oral clofarabine in previously treated adult patients with MDS.	Phase I	Discontinued per study design (both patients had DLT).	2

DLT: Dose Limiting Toxicity; MDS: Myelodysplastic Syndrome.

Clinical trial exposure

Company sponsored studies in Intravenous formulation

- In the pediatric population with ALL or AML, a total of 264 subjects were exposed to clofarabine in the 7 completed studies and as of 28 December 2012.
- In the adult population with AML, ALL, solid tumors, MDS and CLL, 626 subjects were exposed to clofarabine in the 10 completed studies.

Company sponsored studies in Oral formulation:

- In the 3 studies conducted in adults with MDS with an oral formulation, 61 patients have been exposed to clofarabine. No patients have been exposed to oral clofarabine since August 2014 when all studies were completed.

The gender and age distributions of all populations evaluated in 20 company sponsored clinical studies are shown in Table 11.

Table 11 - Company sponsored studies - exposure by age group and gender

Study identifier	Male (n)	Female (n)	Age median (years)	Age range (years)
Pediatric ALL or AML				
ID99-383	15	10	12	1-19
CLO212	37	24	12	1-20
CLO218 (Phase I)	15	10	9	2-21
CLO218 (Phase II)	16	9	14	1-21
CLO222	27	15	12.5	2-22
BIOV-111	45	26	10	0-22
CLO05908	4	3	10	3-16
CLO08808	2	6	9.5	4-23
Adult AML, solid tumors, MDS and CLL				
DM93-036	22	29	48	19-78
CLO151	43	32	64	24-79
CLO141	19	13	59.5	18-84
DM99-225	7	4	See footnote[a]	
ID00-038	5	3	57	22-73
CLO221	22	18	63	19-78
CLO243	52	60	71	60-88
CLO341[b]	215	105	67	55-86
BIOV121	33	33	71	64-81
CLOAML10508	10	4	67.5	59-72

Study identifier	Male (n)	Female (n)	Age median (years)	Age range (years)
Oral formulation in adults with MDS				
CLO152	11	12	64	45-81
CLOMDS02507	20	16	70.5	41-82
CLOMDS01206	1	1	69.5	66-73

a Study included in ISS.

b Total of enrolled patients (enrolled 320 of which 161 patients treated with clofarabine).

ALL: Acute Lymphoblastic Leukemia; AML: Acute Myelogenous/Myeloid Leukemia; CLL: Chronic Lymphoblastic Leukemia; ISS: Integrated Summary of Safety; MDS: Myelodysplastic Syndrome.

RISK MANAGEMENT PLAN - PART II MODULE SIV: POPULATIONS NOT STUDIED IN CLINICAL TRIALS

SIV.1 EXCLUSION CRITERIA IN PIVOTAL CLINICAL STUDIES WITHIN THE DEVELOPMENT PROGRAMME

Exclusion criteria that occurred in most studies are listed in Table 12. Most of the exclusion criteria that occurred in all studies were part of Good Clinical Practice (GCP) and/or were exclusions that will also be part of standard medical practice.

Table 12 - Important exclusion criteria in pivotal studies in the development programme

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
Hepatic co-morbidity	Direct hepatic toxicity is typical for other purine analogues. Pre-clinical safety data indicated that hepatic effects were observed in rats following chronic administration of clofarabine. These likely represent the superimposition of degenerative and regenerative changes as a result of treatment cycles and were not associated with changes in serum chemistry. Histological evidence of hepatic effects was seen in dogs following acute administration of high doses but was also not accompanied by changes in serum chemistry. Although not definitively established, patients with pre-existing liver disease including active hepatitis B and C, cirrhosis or other liver disease manifest by serum bilirubin of over 1.5 may be at higher risk for liver adverse reactions when treated with clofarabine. Patients with prior HSCT may also be at a higher risk of hepatic abnormalities after treatment with clofarabine. The product labeling states that there is no experience in patients with hepatic impairment (serum bilirubin >1.5 x ULN plus AST and ALT >5 x ULN) and the liver is a potential target organ for toxicity. Therefore, clofarabine is contraindicated in patients with severe hepatic impairment and should be used with caution in patients with mild to moderate hepatic impairment.	Tolerability and pharmacokinetics in hepatic impairment was considered as missing information. In the EU-RMP version 9.0, this missing information has been removed from the list of safety concerns.	Not applicable
Renal co-morbidity	Pre-clinical safety data indicated that glomerulonephropathy was reported in rats at exposure levels 3 to 5-fold higher than the clinical AUC after 6 dosing cycles of clofarabine. It was characterized by minor thickening of the glomerular basement membrane with only slight tubular damage and was not associated with changes in serum chemistry. There are limited data on the use of clofarabine in patients with renal dysfunction. The pharmacokinetics of clofarabine has not been formally studied in patients with renal insufficiency. As part of a Clinical Specific	Tolerability and pharmacokinetics in renal impairment was considered as missing information. In the EU-RMP version 9.0, this missing information has been removed from the list of safety concerns.	Not applicable

Exclusion criteria	Reason for exclusion	Is it considered to be included as missing information?	Rationale
	Obligation-12 to conduct an investigation of clofarabine pharmacokinetics and toxicity in patients with renal impairment a population pharmacokinetic analysis and analysis of safety data from clinical studies were performed. The product labeling states that the limited data available indicate that clofarabine may accumulate in patients with decreased creatinine clearance, clofarabine is contraindicated in patients with severe renal insufficiency and should be used with caution in patients with mild to moderate renal insufficiency. Patients with moderate renal impairment (creatinine clearance 30 to <60 mL/min) require a 50% dose reduction		
Cardiac co-morbidity	Preclinical safety data indicated that cardiac effects were observed in rats consistent with cardiomyopathy and contributed to signs of cardiac failure after repeated cycles of treatment. The incidence of these toxicities was dependent on both the dose of clofarabine administered and the duration of treatment. Clofarabine has not been studied in patients with cardiac dysfunction. Patients had to have adequate cardiac function (LVEF ≥40% on MUGA scan or similar radionuclide angiographic scan; or left ventricular fractional shortening ≥22% on echocardiography exam; or LVEF ≥40% on echocardiography exam) in the performed company sponsored studies. In the pediatric investigator sponsored study population, 49.6% of patients experienced at least 1 cardiac disorder AE. Sanofi-Genzyme consulted with a board-certified pediatric cardiologist, who reviewed ECHO reports and clinical source documents from the pediatric investigator sponsored study population, to assess the effect of clofarabine on cardiac function in these patients. The cardiologist concluded that although direct cardiotoxicity of clofarabine could not be completely ruled out, most of the patients who had mild-to-moderate left ventricular systolic dysfunction also had other factors that were possibly responsible for the left ventricular systolic dysfunction. It is currently recommended that the use of clofarabine in patients with cardiac dysfunction should be undertaken only with caution. The product labeling states that patients with cardiac disease and those taking medicinal products known to affect blood pressure or cardiac function should be closely monitored during treatment with clofarabine.	Tolerability and pharmacokinetics in cardiac impairment was considered as missing information. In the EU-RMP version 9.0, this missing information has been removed from the list of safety concerns.	Not applicable

AE: Adverse Event; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; AUC: Area Under Curve; ECHO: Echocardiogram; EU: European Union; HSCT: Hematopoietic Stem Cell Transplantation; LVEF: Left Ventricular Ejection Fraction; MUGA: Multigated Acquisition; RMP: Risk Management Plan: ULN: Upper Limit of Normal.

SIV.2 LIMITATIONS TO DETECT ADVERSE REACTIONS IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Acute lymphoblastic leukemia and acute myelogenous/myeloid leukemia in pediatric patients are rare indications.

The overall size of the clofarabine safety population is commensurate with the size of the target population.

Cumulative subject exposure until 28 December 2019 for clofarabine in company sponsored clinical studies is estimated to be 951 subjects exposed to clofarabine alone or in combination with other chemotherapy agents since the developmental international birth date.

While the number of patients is adequate to evaluate efficacy and common adverse reactions, uncommon and rare adverse reactions cannot be reliably detected on the low numbers of patients studied.

Long term and delayed toxicity should be also discussed regarding the duration of the treatment and the survival duration of the targeted population.

The number of patients from clinical trials is summarized in [Part II SIII]

SIV.3 LIMITATIONS IN RESPECT TO POPULATIONS TYPICALLY UNDER-REPRESENTED IN CLINICAL TRIAL DEVELOPMENT PROGRAMMES

Table 13 - Exposure of special populations included or not in clinical trial development programmes

Type of special population	Exposure
Pregnant or breast-feeding women	Studies in animals have shown reproductive toxicity including teratogenicity. There are no data on the use of clofarabine in pregnant women. Females of childbearing potential and sexually active males are advised to use effective methods of contraception during treatment. It is unknown whether clofarabine or its metabolites are excreted in human breast milk. The excretion of clofarabine in milk has not been studied in animals. Dose related toxicities on male reproductive organs have been observed in mice, rats and dogs, and toxicities on female reproductive organs have been observed in mice.
Patients with relevant co-morbidities • Patients with hepatic impairment • Patients with renal impairment	There is no experience in patients with hepatic impairment (serum bilirubin >1.5 x ULN plus AST and ALT >5 x ULN) and the liver is a potential target organ for toxicity. The limited data available indicate that clofarabine may accumulate in patients with decreased creatinine clearance.
Populations with relevant different racial and/or ethnic origin	A separate analysis relating clinical outcomes to race, or ethnic origin has not been performed.
Other • Age	Although clofarabine is only registered for the treatment of pediatric patients (up to 21 years old) with ALL, adults and elderly with AML have been included in studies especially designed for adult age groups.

ALL: Acute Lymphoblastic Leukemia; AML: Acute Myelogenous/Myeloid Leukemia; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; ULN: Upper Limit of Normal.

RISK MANAGEMENT PLAN - PART II MODULE SV: POST-AUTHORIZATION EXPERIENCE

SV.1 POST-AUTHORIZATION EXPOSURE

SV.1.1 Method used to calculate exposure

Internal sales have been used as the source for sales data retrieval.

- The calculation of patient exposure has been standardized to represent the average patient. This was done using the approved dosing posology of 52 mg/m^2 for five days for one cycle. An average BSA of 1.53 was selected to represent the median between the average adult BSA and the average pediatric BSA. Using these calculations, the average patient would receive approximately 400 mg, equivalent to 20 vials for one cycle.
- The total counting units (in number of vials) for parenteral formulation were divided by the estimated average dose of 20 vials to calculate the total patients exposed to clofarabine.

SV.1.2 Exposure

Based on the above methodology, the cumulative exposure to clofarabine has been estimated to be 16 634 patients during the period 01 January 2012 through 31 December 2023.

As detailed, usage data are not available, presentation of patient exposure by age, sex and indication is not possible.

This estimated global exposure data has been extracted from the Periodic Benefit Risk Evaluation Report (PBRER) for the period 29 December 2020 to 28 December 2023 and is presented in Table 14.

Table 14 - Cumulative clofarabine exposure per global region

Region	Total Patients
Europe	4782
North America	9012
Rest of the world	2840
Total number of patients	**16 634**

RISK MANAGEMENT PLAN – PART II MODULE SVI: ADDITIONAL EU REQUIREMENTS FOR THE SAFETY SPECIFICATION

SVI.1 Potential for misuse for illegal purposes

Potential for misuse for illegal purposes is considered very low given the controlled environment and administration by medical or paramedical staff.

RISK MANAGEMENT PLAN – PART II MODULE SVII: IDENTIFIED AND POTENTIAL RISKS

SVII.1 IDENTIFICATION OF SAFETY CONCERNS IN THE INITIAL RMP SUBMISSION

This section is not applicable as the initial RMP version 1.0 for clofarabine was submitted prior to the implementation of the Good Pharmacovigilance Practices (GVP) Module V Rev. 2.

SVII.1.1 Risks not considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.1.2 Risks considered important for inclusion in the list of safety concerns in the RMP

Not applicable

SVII.2 NEW SAFETY CONCERNS AND RECLASSIFICATION WITH A SUBMISSION OF AN UPDATED RMP

In the RMP version 9.0, the previous list of safety concerns had been revised in accordance with the GVP Module V Rev. 2. As a result, all important risks and missing information have been removed from the list of safety concerns for the reasons described below:

- The important identified risks of "bone marrow failure (myelosuppression)"; "infection (septic shock, sepsis, bacteremia, pneumonia, herpes zoster, herpes simplex, *Clostridium difficile* colitis, oral candidiasis)"; "hepatotoxicity"; "veno-occlusive disease"; "cardiotoxicity"; "tumor lysis syndrome"; "systemic inflammatory response syndrome and capillary leak syndrome"; "Stevens-Johnson syndrome and toxic epidermal necrolysis"; "pancreatitis"; "rash"; "enterocolitis, including neutropenic colitis, caecitis and *C. difficile* colitis"; "hemorrhage, including cerebral, gastrointestinal and pulmonary hemorrhage"; "hepatitis" and "hepatic failure" are well known and appropriately managed by highly-qualified physicians experienced in treating patients with acute leukemias. These safety concerns are appropriately addressed in the Product Information with recommendations fully integrated into standard clinical practice (such as monitoring of hepatic function or monitoring of blood and platelets counts or monitoring for signs and symptoms of tumor lysis syndrome).
- The important potential risks of "nephropathy toxic"; "teratogenicity"; "infertility" and "off-label use in pediatric acute myelogenous/myeloid leukemia, in ALL patients with less than two prior regimens, or in combination with other drugs" are well known and appropriately managed by highly-qualified physicians experienced in treating patients with acute leukemias are appropriately addressed in the Product Information with recommendations fully integrated into standard clinical practice (such as monitoring of renal function for the risk of nephropathy toxic). There is no reasonable expectation that any

future pharmacovigilance activities beyond routine pharmacovigilance could further characterize the risk of off-label use in pediatric patients.

For the missing information of “safety of use for more than 3 cycles”, “drug interactions with commonly used co-medications”, “tolerability and pharmacokinetics in renal impairment”, “tolerability and pharmacokinetics in hepatic impairment”, “tolerability and pharmacokinetics in cardiac impairment” and “pregnancy”; there is no reasonable expectation that any future pharmacovigilance activities beyond routine pharmacovigilance could further characterize this missing information.

SVII.3 DETAILS OF IMPORTANT IDENTIFIED RISKS, IMPORTANT POTENTIAL RISKS, AND MISSING INFORMATION

Following the revision of the list of safety concerns in accordance with the GVP Module V Rev. 2, no important risks or missing information were considered to be relevant to the RMP.

Therefore, this section is not applicable.

RISK MANAGEMENT PLAN – PART II MODULE SVIII: SUMMARY OF THE SAFETY CONCERNS

Summary of the safety concerns

Important identified risk	None
Important potential risk	None
Missing information	None

RISK MANAGEMENT PLAN – PART III: PHARMACOVIGILANCE PLAN (INCLUDING POST-AUTHORIZATION SAFETY STUDIES)

III.1 ROUTINE PHARMACOVIGILANCE ACTIVITIES

The safety profile of clofarabine will continue to be further characterized in real clinical conditions of use through postmarketing safety surveillance, encompassing analysis of spontaneous reporting of adverse drug reactions in periodic safety reports and signal detection.

III.2 ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Additional pharmacovigilance in the postmarketing setting includes SOB 44 of providing yearly updates on any new information concerning efficacy and safety of the product in paediatric patients with ALL who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response.

Table 15 - Additional pharmacovigilance activities (category 1 to 3) summary

Specific obligation (SOB) 44 (Cat. 2)
Study short name and title Specific obligation of providing yearly updates on any new information concerning efficacy and safety of the product in pediatric patients with ALL who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response.
Rationale and study objectives Rationale: This being an approval under exceptional circumstances and pursuant to Article 14(8) of Regulation (EC) No 726/2004, the MAH shall conduct, within the stated timeframe, the SOB. Study objectives: The primary objective of this SOB is to provide new information concerning efficacy and safety of the product in pediatric patients with ALL who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response.
Study design Not applicable
Study populations Pediatric patients with ALL who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response.
Milestones Specific Obligation Annual Report

ALL: Acute Lymphoblastic Leukemia; EC: European Community; MAH: Marketing Authorization Holder; SOB: Specific Obligation.

III.3 SUMMARY TABLE OF ADDITIONAL PHARMACOVIGILANCE ACTIVITIES

Table 16 - Ongoing and planned additional pharmacovigilance activities

Study Status	Summary of objectives	Safety concerns addressed	Milestones	Due dates
Category 1 - Imposed mandatory additional pharmacovigilance activities which are conditions of the marketing authorization (key to benefit risk)				
Not applicable				
Category 2 - Imposed mandatory additional pharmacovigilance activities which are Specific Obligations in the context of a conditional marketing authorization or a marketing authorization under exceptional circumstances (key to benefit risk)				
SOB 44 The MAH shall provide yearly updates on any new information concerning efficacy and safety of the product in pediatric patients with ALL who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. Ongoing	The primary objective of this SOB is to provide new information concerning efficacy and safety of the product in pediatric patients with ALL who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response	Any new information concerning efficacy and safety of the product in pediatric patients	Specific Obligation annual report	Yearly
Category 3 - Required additional pharmacovigilance activities (by the competent Authority)				
Not applicable				

ALL: Acute Lymphoblastic Leukemia; MAH: Marketing Authorization Holder; SOB: Specific Obligation

RISK MANAGEMENT PLAN PART IV: PLANS FOR POST-AUTHORIZATION EFFICACY STUDIES

No imposed post-authorization efficacy studies as a condition of the marketing authorization or which are specific obligations in the context of conditional marketing authorization or marketing authorization under exceptional circumstances are planned or ongoing for clofarabine.

RISK MANAGEMENT PLAN - PART V: RISK MINIMIZATION MEASURES (INCLUDING EVALUATION OF THE EFFECTIVENESS OF RISK MINIMIZATION ACTIVITIES)

V.1 ROUTINE RISK MINIMIZATION MEASURES

This section describes the routine risk minimization measures by safety concern. Since the list of safety concerns in this RMP update has been revised in accordance with the GVP Module V Rev. 2, and since all safety concerns have been removed, this section is no longer applicable.

Routine risk minimization measures, in the form of legal status and product information (SmPC and package leaflet [PL]), continue to be in place for clofarabine.

V.2 ADDITIONAL RISK MINIMIZATION MEASURES

This section describes the additional risk minimization measures by safety concern. Since the list of safety concerns in this RMP update has been revised in accordance with the GVP Module V Rev. 2, and since all safety concerns have been removed, this section is no longer applicable.

Routine risk minimization measures, in the form of legal status and product information (SmPC and PL) are considered sufficient to manage the safety concerns of clofarabine.

V.3 SUMMARY OF RISK MINIMIZATION MEASURES

Not applicable

RISK MANAGEMENT PLAN – PART VI: SUMMARY OF THE RISK MANAGEMENT PLAN

Summary of risk management plan for EVOLTRA (Clofarabine)

This is a summary of the risk management plan (RMP) for EVOLTRA. The RMP details important risks of EVOLTRA, how these risks can be minimized, and how more information will be obtained about EVOLTRA's risks and uncertainties (missing information).

EVOLTRA's summary of product characteristics (SmPC) and its package leaflet (PL) give essential information to healthcare professionals and patients on how EVOLTRA should be used.

This summary of the RMP for EVOLTRA should be read in the context of all this information including the assessment report of the evaluation and its plain-language summary, all of which is part of the European Public Assessment Report (EPAR).

Important new safety concerns or changes to the current concerns will be included in updates of EVOLTRA's RMP.

I. THE MEDICINE AND WHAT IT IS USED FOR

EVOLTRA is authorized for treatment of acute lymphoblastic leukemia (ALL) in pediatric patients who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response. Safety and efficacy have been assessed in studies of patients ≤21 years old at initial diagnosis. It contains clofarabine as the active substance and it is given by intravenous route.

Further information about the evaluation of EVOLTRA's benefits can be found in EVOLTRA's EPAR, including in its plain-language summary, available on the European Medicines Agency (EMA) website, under the medicine's webpage:

https://www.ema.europa.eu/en/documents/overview/evoltra-epar-summary-public_en.pdf

II. RISKS ASSOCIATED WITH THE MEDICINE AND ACTIVITIES TO MINIMIZE OR FURTHER CHARACTERIZE THE RISKS

There are no important risks or missing information considered as relevant for EVOLTRA's RMP.

II.A List of important risks and missing information

Table 17 - List of important risks and missing information

Important identified risk	None
Important potential risk	None
Missing information	None

II.B Summary of important risks

Not applicable

II.C Post-authorization development plan

II.C.1 *Studies which are conditions of the marketing authorization*

The following study is condition of the marketing authorization for EVOLTRA.

Table 18 - Studies which are conditions of the marketing authorization

Specific obligation (SOB) 44 (Category 2) **The MAH shall provide yearly updates on any new information concerning efficacy and safety of the product in paediatric patients with ALL who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response.**
Purpose of the study This study is being conducted to provide new information concerning efficacy and safety of the product in pediatric patients with ALL who have relapsed or are refractory after receiving at least two prior regimens and where there is no other treatment option anticipated to result in a durable response.

ALL: Acute Lymphoblastic Leukemia; MAH: Marketing Authorization Holder; SOB: Specific Obligation.

II.C.2 *Other studies in post-authorization development plan*

There are no studies required for EVOLTRA.

REFERENCES

1. Redaelli A, Laskin BL, Stephens JM, Botteman MF, Pashos CL. The clinical and epidemiological burden of chronic lymphocytic leukaemia. Eur J Cancer Care (Engl). 2004 Jul;13(3):279-87.

2. Institute for Health Metrics and Evaluation (IHME). GBD Compare Data Visualization [Internet]. Seattle, WA: IHME, University of Washington; 2019 [cited 2024 Jan 10]. Available from http://vizhub.healthdata.org/gbd-compare

3. Pui CH, Robison LL, Look AT. Acute lymphoblastic leukaemia. Lancet. 2008 Mar 22;371(9617):1030-43.

4. Barrington-Trimis JL, Cockburn M, Metayer C, Gauderman WJ, Wiemels J, McKean-Cowdin R. Trends in childhood leukemia incidence over two decades from 1992 to 2013. Int J Cancer. 2017 Mar 1;140(5):1000-8.

5. Miranda-Filho A, Pineros M, Ferlay J, Soerjomataram I, Monnereau A, Bray F. Epidemiological patterns of leukaemia in 184 countries: a population-based study.Lancet Haematol. 2018 Jan;5(1):e14-24.

6. Onyije FM, Olsson A, Baaken D, Erdmann F, Stanulla M, Wollschlager D, et al. Environmental Risk Factors for Childhood Acute Lymphoblastic Leukemia: An Umbrella Review. Cancers (Basel). 2022 Jan 13;14(2):382

7. Ceppi F, Cazzaniga G, Colombini A, Biondi A, Conter V. Risk factors for relapse in childhood acute lymphoblastic leukemia: prediction and prevention. Expert Rev Hematol. 2015 Feb;8(1):57-70.

8. Mateos MK, Trahair TN, Mayoh C, Barbaro PM, Sutton R, Revesz T, et al., Risk factors for symptomatic venous thromboembolism during therapy for childhood acute lymphoblastic leukemia. Thromb Res. 2019 Jun;178:132-8.

9. Silva RA, de Mendonça RM, dos Santos Aguiar S, Yajima JC, Marson FA, Brandalise SR, et al. Induction therapy for acute lymphoblastic leukemia: incidence and risk factors for bloodstream infections. Supportive Care in Cancer. 2022 Jan;30(1):695-702.

10. Cripe LD. Adult acute leukemia. Curr Probl Cancer. 1997 Jan-Feb;21(1):1-64.

11. Greaves M. A natural history for pediatric acute leukemia. Blood. 1993 Aug 15;82(4):1043-51.

12. Lo Nigro L. Biology of childhood acute lymphoblastic leukemia. J Pediatr Hematol Oncol. 2013 May;35(4):245-52.

13. Douer D. Will novel agents for ALL finally change the natural history? Best Pract Res Clin Haematol. 2014 Sep-Dec;27(3-4):247-58.

14. Demidowicz E, Pogorzała M, Lecka M, Zolnowska H, Marjanska A, Kubicka M, et.al. Outcome of Pediatric Acute Lymphoblastic Leukemia: Sixty Years of Progress. Anticancer Res. 2019 Sep;39(9):5203-7.

15. Iughetti L, Bruzzi P, Predieri B, Paolucci P. Obesity in patients with acute lymphoblastic leukemia in childhood. Ital J Pediatr. 2012 Jan 27;38:4.

16. Larouche V, Bellavance C, Tibout P, Bergeron S, Simonyan D, Gagne J. Screening for asymptomatic diabetes and metabolic comorbidities in pediatric patients during therapy for acute lymphoblastic leukemia. J Pediatr Endocrinol Metab. 2021 Apr 12;34(5):627-32.

17. Zia AN, Chitlur M. Management of thrombotic complications in acute lymphoblastic leukemia. Indian J Pediatr. 2013 Oct;80(10):853-62.

18. Zhu Y, Yang R, Cai J, Yu J, Tang Y, Chen Y, et al. Septicemia after chemotherapy for childhood acute lymphoblastic leukemia in China: A multicenter study CCCG-ALL-2015. Cancer Med. 2020 Mar;9(6):2113-21.

RISK MANAGEMENT PLAN - PART VII: ANNEXES

ANNEX 4 SPECIFIC ADVERSE DRUG REACTION FOLLOW-UP FORMS

Not Applicable

ANNEX 6 DETAILS OF PROPOSED ADDITIONAL RISK MINIMIZATION ACTIVITIES

Not Applicable