ARSENIC TRIOXIDE - AFT
Concentrated Solution for Injection for Infusion 10 mg/10 mL

1 NAME OF THE MEDICINE

Arsenic trioxide

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Arsenic trioxide – AFT: Each 10 mL glass ampoule contains 10 mg arsenic trioxide as the active ingredient.

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

3 PHARMCEUTICAL FORM

Arsenic trioxide – AFT is clear, colourless, concentrated solution for injection. It is a sterile solution for single use. The pH of Arsenic trioxide – AFT is between 7.0-8.5. It must be diluted before use for Intravenous Infusion.

4 CLINICAL PARTICULARS

4.1 THERAPEUTIC INDICATIONS

For the induction of remission and consolidation in patients with acute promyelocytic leukaemia (APL) who are refractory to, or have relapsed from, retinoid and anthracycline chemotherapy, and whose APL is characterised by the presence of the t(15:17) translocation or PML/RAR-alpha gene expression.

For the treatment of adults with newly-diagnosed low-to-intermediate risk acute promyelocytic leukemia (APL) in combination with tretinoin and whose APL is characterised by the presence of the t(15:17) translocation or PML/RAR-alpha gene expression.

4.2 DOSE AND METHOD OF ADMINISTRATION

Recommended Dosage for Newly Diagnosed Low-to-Intermediate-Risk Acute Promyelocytic Leukemia (APL)

A treatment course for patients with newly diagnosed low-to-intermediate-risk APL consists of 1 induction cycle and 4 consolidation cycles.

- For the induction cycle, the recommended dosage of arsenic trioxide is 0.15 mg/kg intravenously daily in combination with tretinoin until bone marrow remission but not to exceed 60 days (see Table 1)
- For the consolidation cycles, the recommended dosage of arsenic trioxide is 0.15 mg/kg intravenously daily 5 days p er week during weeks 1-4 of each 8-week cycle for a total of 4 cycles in combination with tretinoin (see Table 1). Omit tretinoin during weeks 5-6 of the fourth cycle of consolidation.

Table 1: Recommended Dose of Arsenic trioxide-AFT in Low-to-Intermediate Risk Patients

Induction (1 cycle)

Arsenic trioxide 0.15 mg/kg once daily intravenously	Until marrow remission but not to exceed 60 days
Tretinoin[a] 22.5 mg/m^2 twice daily orally	Until marrow remission but not to exceed 60 days

Consolidation (4 cycles)

	Week							
	1	2	3	4	5	6	7	8
Arsenic trioxide 0.15 mg/kg QD, iv	D[c] 1-5	D 1-5	D 1-5	D 1-5	--	--	--	--
Tretinoin[a] 22.5 mg/m^2 BID, po	D 1-7	D 1-7	--	--	D[b] 1-7	D[b] 1-7	--	--

[a]Rounded to the nearest 10 mg increment

[b]Omitted during the 4th cycle of consolidation

[c]D: Days

Differentiation syndrome prophylaxis consisting of prednisone 0.5 mg/kg daily from day 1 until the end of induction therapy with arsenic trioxide and tretinoin is recommended.

Recommended Dosage for Relapsed or Refractory APL

A treatment course for patients with relapsed or refractory APL consists of 1 induction cycle and 1 consolidation cycle.

- For the induction cycle, the recommended dosage of arsenic trioxide is 0.15 mg/kg /day intravenously daily until bone marrow remission or up to a maximum of 60 days.
- For the consolidation cycle, the recommended dosage of arsenic trioxide is 0.15 mg/kg/day intravenously daily for 25 doses over a period of up to 5 weeks. Begin consolidation 3 to 6 weeks after completion of induction cycle.

Monitoring and Dosage Modifications for Adverse Reactions

During induction monitor coagulation studies, blood counts, and chemistries at least 2-3 times per week through recovery. During consolidation, monitor coagulation studies, blood counts, and chemistries at least weekly.

Table 2 shows the dose modifications for adverse reactions due to arsenic trioxide when used alone or in combination with tretinoin.

Table 2: Dose Adjustments for Adverse Reactions of Arsenic Trioxide

Adverse Reaction	Dose Modification
Differentiation syndrome, defined by the presence of 2 or more of the following: • Unexplained fever • Dyspnea • Pleural and/or pericardial effusion • Pulmonary infiltrates • Renal failure • Hypotension • Weight gain greater than 5 kg (see Special Warnings and Precautions for Use)	• Temporarily withhold Arsenic trioxide-AFT. Consider holding tretinoin if symptoms are severe. • Administer dexamethasone 10 mg intravenously every 12 hours until the resolution of signs and symptoms for a minimum of 3 days. • Resume treatment when the clinical condition improves and reduce the dose of the withheld drug(s) by 50%. • Increase the dose of the withheld drug(s) to the recommended dosage after one week in the absence of recurrence of symptoms of differentiation syndrome. • If symptoms re appear, decrease arsenic trioxide and/or tretinoin to the previous dose.
QTc (Framingham formula) Prolongation greater than 450 msec for men or greater than 460 msec for women (see Special Warnings and Precautions for Use)	• Withhold Arsenic Trioxide and any medication known to prolong the QTc interval. • Correct electrolyte abnormalities. • After the QTc normalizes, and electrolyte abnormalities are corrected, resume treatment with Arsenic trioxide-AFT at a 50% reduced dose (0.075 mg/kg daily) for one week after resolution. • If the 50% reduced dose is tolerated for one week (in the absence of QTc prolongation), increase the dose of arsenic trioxide to 0.11 mg/kg /day for the next week (see Dose and Method of Administration) • The dose of Arsenic trioxide-AFT can be increased to 0.15 mg/kg /day in the absence of QTc prolongation during that 14-day dose-escalation period.
Hepatotoxicity, defined by 1 or more of the following: • Total bilirubin (TB) greater than 3 times the upper limit of normal (ULN) • Aspartate aminotransferase (AST) greater than 5 times the ULN • Alkaline phosphatase (AP) greater than 5 times the ULN (see Special Warnings and Precautions for Use)	• Withhold Arsenic trioxide-AFT and/or tretinoin. • Resume treatment at a 50% reduced dose of the withheld drug(s) when TB is less than 1.5 times the ULN and AP/AST are less than 3 times the ULN. • Increase the dose of the withheld drug(s) back to the recommended dosage after one week on the reduced dose in the absence of worsening of hepatotoxicity. • Discontinue the withheld drug(s) permanently if hepatotoxicity recurs.

Adverse Reaction	Dose Modification
Other severe or life threatening (grade 3-4) nonhematologic reactions (see Adverse Effects)	• Temporarily withhold Arsenic trioxide-AFT and tretinoin. • When the adverse reaction resolves to no more than mild (grade 1), resume arsenic trioxide and tretinoin reduced by 2 dose levels (see Table 3 below).
Moderate (grade 2) nonhematologic reactions (see Adverse Effects)	Reduce the dose of arsenic trioxide and/or tretinoin by 1 dose level (see Table 3 below).
Leukocytosis (WBC count greater than 10 Gi/L) (see Adverse Effects)	• Administer hydroxyurea: WBC: Hydroxyurea 10-50 Gi/L: 500 mg QID >50 Gi/L: 1000 mg QID • Hydroxyurea may be discontinued when the WBC declines below 10 Gi/L.
Myelosuppression, defined by 1 or more of the following: • absolute neutrophil count less than 1 Gi/L • platelets less than 50 Gi/L lasting more than 5 weeks (see Adverse Effects)	• Consider reducing the dose of arsenic trioxide and tretinoin by 1 dose level (see Table 3 below). • If myelosuppression lasts ≥ 50 days or occurs on 2 consecutive cycles, assess a marrow aspirate for remission status. In the case of molecular remission, resume arsenic trioxide and tretinoin at 1 dose level lower (see Table 3 below).

Table 3: Dose Reduction Levels for Hematologic and Nonhematologic Toxicities

Dose Level	Arsenic trioxide mg/kg intravenously once daily	Tretinoin* mg/m² orally twice daily
Starting level	0.15	22.5
-1	0.11	18.75
-2	0.10	12.5
-3	0.075	10

*Rounded to the nearest 10 mg increment

Preparation and administration

Reconstitution

Dilute Arsenic trioxide-AFT with 100 or 250 mL 5% Dextrose Injection, or 0.9% Sodium Chloride Injection, using proper aseptic technique, immediately after withdrawal from the vial.

Once diluted the solution should be used as soon as possible. Product is for single use in one patient only and contains no antimicrobial preservative. Discard any residue. If storage is necessary, the prepared solution should be stored refrigerated between 2°C and 8°C for no longer than 48 hours or below 25 °C for no longer than 24 hours before discarding.

Administration

Parenteral drug products should be inspected visually for particulate matter and discoloration prior to administration, whenever solution and container permit. Administer Arsenic trioxide-AFT as an intravenous infusion over 2 hours. The infusion duration may be extended up to 4 hours if acute vasomotor reactions are observed. A central venous catheter is not required.

Do not mix Arsenic trioxide-AFT with other medications.

Safe Handling Procedures

Arsenic trioxide-AFT is a cytotoxic drug. Follow applicable special handling and disposal procedures.

Incompatibilities

In the absence of incompatibility studies, this medicinal product must not be mixed with other medicinal products except those mentioned above.

4.3 CONTRAINDICATIONS

Arsenic trioxide – AFT is contraindicated in patients who are hypersensitive to arsenic or any of the excipients (see Section 6.1 List of Excipients).

4.4 SPECIAL WARNINGS AND PRECAUTIONS FOR USE

Arsenic trioxide – AFT should be administered under the supervision of a physician experienced in the management of patients with acute leukaemia.

APL differentiation syndrome

Some patients with APL treated with arsenic trioxide experience symptoms similar to a syndrome called retinoic acute promyelocytic leukaemia (RA-APL) syndrome or APL differentiation syndrome, characterised by fever, dyspnoea, weight gain, pulmonary infiltrates and pleural or pericardial effusions with or without leukocytosis. This syndrome can be fatal. The first signs that could suggest the development of the APL differentiation syndrome are unexplained fever, dyspnoea and/or weight gain, abnormal chest auscultatory findings or radiographic abnormalities. The management of the syndrome has not been fully studied, but high dose steroids have been used at the first suspicion of the APL differentiation syndrome and appear to mitigate signs and symptoms.

When arsenic trioxide is used in combination with tretinoin, prophylaxis with prednisone is recommended during the induction cycle.

If differentiation syndrome is suspected, temporarily withhold arsenic trioxide and immediately initiate dexamethasone 10 mg intravenously every 12 hours and hemodynamic monitoring until resolution of signs and symptoms for a minimum of 3 days.

ECG abnormalities

Arsenic trioxide can cause QT interval prolongation and complete atrioventricular block. QT prolongation can lead to a torsade de pointes-type ventricular arrhythmia, which can be fatal. The risk of torsade de pointes is related to the extent of QT prolongation, concomitant administration of QT prolonging drugs, a history of torsade de pointes, pre-existing QT interval prolongation, congestive heart failure, administration of potassium-depleting diuretics, or other conditions that result in hypokalaemia or hypomagnesaemia. One patient (also receiving amphotericin B) had torsade de pointes during induction therapy for relapsed APL with arsenic trioxide.

QT/QTc prolongation

QT prolongation should be expected during treatment with arsenic trioxide and torsades de pointes as well as complete heart block has been reported. Over 460 ECG tracings from 40 patients with refractory or relapsed APL treated with arsenic trioxide were evaluated for QTc prolongation. Sixteen of 40 patients (40%) had at least one ECG tracing with a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion. In these ECG evaluations, women did not experience more pronounced QT prolongation than men, and there was no correlation with age.

Complete AV block

Complete AV block has been reported with arsenic trioxide in the published literature including a case of a patient with APL.

ECG and Electrolytes: Monitoring Recommendations

Patients with congestive heart failure should not be administered arsenic trioxide, except when the benefit outweighs the risk. Prior to initiating therapy with Arsenic trioxide – AFT, a 12-lead ECG should be performed and serum electrolytes (potassium, calcium and magnesium) and creatinine should be assessed; pre-existing electrolyte abnormalities should be corrected and, if possible, drugs that are known to prolong the QT interval should be discontinued. For QTc greater than 500 msec, corrective measures should be completed and the QTc reassessed with serial ECGs prior to considering using arsenic trioxide. During therapy with arsenic trioxide, potassium concentrations should be kept above 4 mmol/L and magnesium concentrations should be kept above 0.8 mmol/L. Patients who reach an absolute QT interval > 500 msec should be reassessed and immediate action should be taken to correct concomitant risk factors, if any, while the risk/benefit of continuing versus suspending arsenic trioxide therapy should be considered. If syncope, rapid or irregular heart beat develops, the patient should be hospitalised for monitoring and serum electrolytes should be assessed. Arsenic trioxide therapy should be temporarily discontinued until the QTc interval regresses to below 460 msec, electrolyte abnormalities are corrected, and the syncope and irregular heartbeat cease. There are no data on the effect of arsenic trioxide on the QTc interval during the infusion.

Peripheral neuropathy

Peripheral neuropathy has been associated with the use of arsenic trioxide. In the largest case series (Soignet SL, 2001 – see Section 5.1 Pharmacodynamic Properties, Clinical trials) one patient (out of 40) experienced grade 3 neuropathy and required discontinuation of arsenic trioxide treatment. Patients should be monitored periodically for symptoms or signs of neuropathy. Patients on continuing arsenic trioxide treatment may be at greater risk.

Hepatotoxicity

In the clinical trials (APL0406 Trial), 44% of patients with newly diagnosed low to intermediate risk APL treated with Arsenic Trioxide in combination with tretinoin experienced elevated aspartate aminotransferase (AST), alkaline phosphatase, and/or serum bilirubin. These abnormalities resolved with temporary discontinuation of arsenic trioxide and/or tretinoin.

Long term liver abnormalities can occur in APL patients treated with arsenic trioxide in combination with tretinoin. In a published series, mild liver dysfunction and hepatic steatosis were seen in 15% and 43%, respectively, of patients at a median of 7 years (range 0-14 years) after treatment with arsenic trioxide in combination with tretinoin.

During treatment with arsenic trioxide monitor hepatic function tests at least twice weekly during induction and at least once weekly during consolidation. Withhold arsenic trioxide and/ or tretinoin if elevations in AST or alkaline phosphatase occur to greater than 5 times the upper limit of normal and/or elevation in serum total bilirubin occurs to greater than 3 times the upper limit of normal and resume at reduced dose upon resolution (see Dose and Method of Administration).

Hyperleukocytosis

Arsenic trioxide has been investigated in 40 relapsed or refractory APL patients, previously treated with an anthracycline and a retinoid regimen, in an open-label, single-arm, non-comparative study (Soignet SL, 2001). Patients received arsenic trioxide 0.15 mg/kg/day intravenously over 1 to 2 hours daily until the bone marrow was cleared of leukaemic cells or up to a maximum of 60 days. In this study in relapsed or refractory APL patients, treatment with arsenic trioxide was associated with the development of hyperleukocytosis ($\geq 10 \times 10^9$/L) in some patients. There did not appear to be a relationship between baseline white blood cell (WBC) counts and development of hyperleukocytosis nor did there appear to be a correlation between baseline WBC count and peak WBC counts. Hyperleukocytosis was never treated with additional chemotherapy and resolved on continuation of arsenic trioxide. WBC counts during consolidation were not as high as during induction treatment and were $< 10 \times 10^9$/L, except in one patient who had a WBC count of 22×10^9/L during consolidation. Twenty patients (50%) experienced leukocytosis; however, in all these patients, the WBC count was declining or had normalised by the time of bone marrow remission and cytotoxic chemotherapy or leukopheresis was not required.

Use in hepatic impairment

Since limited data are available across all hepatic impairment groups, caution is advised in the use of arsenic trioxide in patients with hepatic impairment. Monitor patients with severe hepatic impairment (Child-Pugh Class C) frequently for toxicity.

Use in renal impairment

Exposure of arsenic trioxide may be higher in patients with severe renal impairment. Monitor patients with severe renal impairment (creatinine clearance [CLcr] less than 30mL/min) frequently for toxicity; a dose reduction may be warranted. The use of arsenic trioxide in patients on dialysis has not been studied.

Use in the elderly

There is limited clinical data on the use of arsenic trioxide in the elderly population. Elderly patients have a greater risk of reduced renal function. Because renal excretion is the main route of elimination of arsenic, particular caution is needed in these patients.

Paediatric use

There are limited clinical data on the paediatric use of arsenic trioxide. Of 5 patients below the age of 18 years (age range: 5 to 16 years) who received a dose of 0.15 mg/kg/day for relapsed/refractory APL, 3 achieved a complete response.

Safety and effectiveness in paediatric patients below the age of 5 years has not been studied.

Effects on laboratory tests

The patient's electrolyte, haematologic and coagulation profiles should be monitored at least twice weekly, and more frequently for clinically unstable patients during the induction phase and at least weekly during the consolidation phase.

ECGs should be obtained weekly, and more frequently for clinically unstable patients, during induction and consolidation.

4.5 INTERACTIONS WITH OTHER MEDICINES AND OTHER FORMS OF INTERACTIONS

No assessments of drug interactions have been made. Caution is advised when Arsenic trioxide - AFT is used with medications that:

- can prolong the QT interval (e.g. certain antiarrhythmics, thioridazine);
- lead to electrolyte abnormalities (e.g. diuretics, amphotericin B)

Arsenic trioxide should not be used concomitantly with ziprasidone or pimozide because of potential additive effects on prolongation of the QT intervals.

4.6 FERTILITY, PREGNANCY AND LACTATION

Effects on fertility

The effects of arsenite on fertility have not been systematically studied. Men and women of childbearing potential must use effective contraception during treatment with Arsenic trioxide – AFT.

Use in pregnancy

Category X: Drugs which have such a high risk of causing permanent damage to the foetus that they should not be used in pregnancy or when there is a possibility of pregnancy.

Arsenic trioxide – AFT should not be given to patients who are pregnant. Pregnancy test prior to the treatment with arsenic trioxide should be considered.

In hamsters, rats and mice, parenteral administration of arsenite during the period of organogenesis produces malformations, including neural tube, eye, facial, genitourinary and skeletal defects, at respective single doses of *ca* 2-13 fold the clinical dose on a body surface area basis; no-effect dose levels were not established. Arsenite treatment of mice during gestation has also produced a widespread tumorigenic response in offspring. The effects of arsenic trioxide injection on human pregnancy are not known, but the results of the animal studies indicate that this treatment should not be given to pregnant women.

Use in lactation

It is not known whether arsenite and/or its metabolites are excreted in milk. Arsenic trioxide should not be administered to lactating women.

4.7 EFFECTS ON ABILITY TO DRIVE AND USE MACHINES

The effects of this medicine on a person's ability to drive and use machines were not assessed.

4.8 ADVERSE EFFECTS (UNDESIRABLE EFFECTS)

The following clinically significant adverse reactions are described elsewhere in the product information.

- Differentiation Syndrome (see Special Warnings and Precautions for Use)
- Cardiac Conduction Abnormalities (see Special Warnings and Precautions for Use)
- Encephalopathy (see Special Warnings and Precautions for Use)
- Hepatotoxicity (see Special Warnings and Precautions for Use)
- Carcinogenesis (see Special Warnings and Precautions for Use)

Clinical trials experience

Because clinical trials are conducted under widely varying conditions, adverse reaction rates observed in the clinical trials of a drug cannot be directly compared to rates in the clinical trials of another drug and may not reflect the rates observed in practice.

Newly Diagnosed Low-to-Intermediate Risk APL

The safety of arsenic trioxide in combination with tretinoin was evaluated in Study APL0406, a randomized trial comparing arsenic trioxide plus tretinoin (n=129) versus chemotherapy plus tretinoin (n=137) in patients with newly diagnosed APL. In the arsenic trioxide/tretinoin group, 98% of patients completed induction therapy and 89% completed at least three consolidation cycles. In the chemotherapy/tretinoin group, 96% completed induction therapy and 87% patients completed all three courses of consolidation therapy.

Serious adverse reactions reported in 25% of the patients on the arsenic trioxide/tretinoin arm and 24% on the chemotherapy/tretinoin arm. The serious adverse reactions reported in ≥ 2% of patients receiving arsenic trioxide/tretinoin were abnormal liver tests, differentiation syndrome, dyspnea, pneumonia, and other infections. Fatal adverse reactions were reported in 1 (1%) patient on the arsenic trioxide/tretinoin arm and 8 (6%) patients on the chemotherapy/tretinoin arm.

Arsenic trioxide/tretinoin was discontinued due to toxicity in 1 patient during induction and in 4 patients during the first three consolidation courses, whereas chemotherapy/tretinoin was discontinued due to toxicity in 4 patients during induction and in 6 patients during consolidation.

Selected hematologic and nonhematologic toxicities that occurred during induction or consolidation are presented in Table 4.

Table 4: Selected Adverse Reactions of Arsenic Trioxide in Combination with Tretinoin in Patients with Newly Diagnosed APL in Study APL0406

Adverse reaction	Induction (%)	Consolidation n (%)		
		1st	2nd	3rd
Thrombocytopenia > 15 days (Grade 3-4)				
ATO/ATRA	74 (58%)	6 (5%)	6 (5%)	8 (7%)
CHT/ATRA	120 (88%)	17 (14%)	77 (63%)	26 (22%)
Neutropenia > 15 days (Grade 3-4)				
ATO/ATRA	61 (48%)	8 (7%)	7 (6%)	5 (4%)
CHT/ATRA	109 (80%)	40 (32%)	90 (73%)	28 (24%)
Hepatic toxicity (Grade 3-4)				
ATO/ATRA	51 (40%)	5 (4%)	1 (1%)	0 (0%)
CHT/ATRA	4 (3%)	1 (1%)	0 (0%)	0 (0%)
Infection and fever of unknown origin				
ATO/ATRA	30 (23%)	10 (8%)	4 (3%)	2 (2%)
CHT/ATRA	75 (55%)	8 (6%)	46 (38%)	2 (2%)
Hypertriglyceridemia				
ATO/ATRA	29 (22%)	22 (18%)	17 (14%)	16 (14%)
CHT/ATRA	29 (22%)	19 (15%)	10 (8%)	13 (11%)
Hypercholesterolemia				
ATO/ATRA	14 (10%)	19 (16%)	19 (16%)	16 (14%)
CHT/ATRA	12 (9%)	12 (10%)	12 (10%)	11 (9%)
QT prolongation				
ATO/ATRA	11 (9%)	3 (2%)	3 (2%)	2 (2%)
CHT/ATRA	1 (1%)	0 (0%)	0 (0%)	0 (0%)
Gastrointestinal toxicity (Grade 3-4)				

Adverse reaction	Induction (%)	Consolidation n (%)		
		1st	2nd	3rd
ATO/ATRA	3 (2%)	0 (0%)	0 (0%)	0 (0%)
CHT/ATRA	25 (18%)	1 (1%)	6 (5%)	0 (0%)
Neurotoxicity*				
ATO/ATRA	1 (1%)	5 (4%)	6 (5%)	7 (6%)
CHT/ATRA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
Cardiac function (Grade 3-4)				
ATO/ATRA	0 (0%)	0 (0%)	0 (0%)	0 (0%)
CHT/ATRA	5 (4%)	0 (0%)	0 (0%)	0 (0%)

*Mostly cases of reversible peripheral neuropathy
ATO: Arsenic Trioxide; ATRA: Tretinoin ; CHT: chemotherapy

Relapsed or Refractory APL

Safety information was available for 52 patients with relapsed or refractory APL who participated in clinical trials of arsenic trioxide. Forty patients in the Study PLRXAS01 received the recommended dose of 0.15 mg/kg, of whom 28 completed both induction and consolidation treatment cycles. An additional 12 patients with relapsed or refractory APL received doses generally similar to the recommended dose.

Serious adverse reactions observed in the 40 patients with refractory or relapsed APL enrolled in Study PLRXAS01 included differentiation syndrome (n=3), hyperleukocytosis (n=3), QTc interval ≥ 500 msec (n=16, 1 with torsade de pointes), atrial dysrhythmias (n=2), and hyperglycemia (n=2).

Most patients experienced some drug related toxicity, most commonly leukocytosis, gastrointestinal (nausea, vomiting, diarrhea, and abdominal pain), fatigue, edema, hyperglycemia, dyspnea, cough, rash or itching, headaches, and dizziness. These adverse effects have not been observed to be permanent or irreversible nor do they usually require interruption of therapy.

The most common adverse reactions (> 30%) were nausea, cough, fatigue, pyrexia, headache, abdominal pain, vomiting, tachycardia, diarrhea, dyspnea, hypokalemia, leukocytosis, hyperglycemia, hypomagnesemia, insomnia, dermatitis, edema, QTc prolongation, rigors, sore throat, arthralgia, paresthesia, and pruritus.

Table 5 describes the adverse reactions in patients aged 5 to 73 years with APL who received arsenic trioxide at the recommended dose. Similar adverse reactions profiles were seen in the other patient populations who received arsenic trioxide.

Table 5: Adverse Reactions (≥ 5%) in Patients with Relapsed or Refractory APL who received Arsenic Trioxide in Study PLRXAS01

Body System Adverse reaction	Any grade adverse reactions		Grade ≥ 3 adverse reactions	
	n	%	n	%
Gastrointestinal disorders				
Nausea	30	75		

Body System Adverse reaction	Any grade adverse reactions		Grade ≥ 3 adverse reactions	
	n	%	n	%
Abdominal pain (lower & upper)	23	58	4	10
Vomiting	23	58		
Diarrhea	21	53		
Sore throat	14	35		
Constipation	11	28	1	3
Anorexia	9	23		
Appetite decreased	6	15		
Loose stools	4	10		
Dyspepsia	4	10		
Oral blistering	3	8		
Fecal incontinence	3	8		
Gastrointestinal hemorrhage	3	8		
Dry mouth	3	8		
Abdominal tenderness	3	8		
Diarrhea hemorrhagic	3	8		
Abdominal distension	3	8		
Respiratory				
Cough	26	65		
Dyspnea	21	53	4	10
Epistaxis	10	25		
Hypoxia	9	23	4	10
Pleural effusion	8	20	1	3
Post nasal drip	5	13		
Wheezing	5	13		
Decreased breath sounds	4	10		
Crepitations	4	10		
Rales	4	10		
Hemoptysis	3	8		
Tachypnea	3	8		
Rhonchi	3	8		
General disorders and administration site conditions				
Fatigue	25	63	2	5
Pyrexia (fever)	25	63	2	5
Edema - non-specific	16	40		
Rigors	15	38		
Chest pain	10	25	2	5

Body System Adverse reaction	Any grade adverse reactions		Grade ≥ 3 adverse reactions	
	n	%	n	%
Injection site pain	8	20		
Pain - non-specific	6	15	1	3
Injection site erythema	5	13		
Weight gain	5	13		
Injection site edema	4	10		
Weakness	4	10	2	5
Hemorrhage	3	8		
Weight loss	3	8		
Drug hypersensitivity	2	5	1	3
Nervous system disorders				
Headache	24	60	1	3
Insomnia	17	43	1	3
Paresthesia	13	33	2	5
Dizziness (excluding vertigo)	9	23		
Tremor	5	13		
Convulsion	3	8	2	5
Somnolence	3	8		
Coma	2	5	2	5
Cardiac disorders				
Tachycardia	22	55		
ECG QT corrected interval prolonged > 500 msec	16	40		
Palpitations	4	10		
ECG abnormal other than QT interval prolongation	3	8		
Metabolism and nutrition disorders				
Hypokalemia	20	50	5	13
Hypomagnesemia	18	45	5	13
Hyperglycemia	18	45	5	13
ALT increased	8	20	2	5
Hyperkalemia	7	18	2	5
AST increased	5	13	1	3
Hypocalcemia	4	10		
Hypoglycemia	3	8		
Acidosis	2	5		
Hematologic disorders				
Leukocytosis	20	50	1	3

Body System Adverse reaction	Any grade adverse reactions		Grade ≥ 3 adverse reactions	
	n	%	n	%
Anemia	8	20	2	5
Thrombocytopenia	7	18	5	13
Febrile neutropenia	5	13	3	8
Neutropenia	4	10	4	10
Disseminated intravascular coagulation	3	8	3	8
Lymphadenopathy	3	8		
Skin and subcutaneous tissue disorders				
Dermatitis	17	43		
Pruritus	13	33	1	3
Ecchymosis	8	20		
Dry skin	6	15		
Erythema - non-specific	5	13		
Increased sweating	5	13		
Facial edema	3	8		
Night sweats	3	8		
Petechiae	3	8		
Hyperpigmentation	3	8		
Non-specific skin lesions	3	8		
Urticaria	3	8		
Local exfoliation	2	5		
Eyelid edema	2	5		
Musculoskeletal, connective tissue, and bone disorders				
Arthralgia	13	33	3	8
Myalgia	10	25	2	5
Bone pain	9	23	4	10
Back pain	7	18	1	3
Neck pain	5	13		
Pain in limb	5	13	2	5
Psychiatric disorders				
Anxiety	12	30		
Depression	8	20		
Agitation	2	5		
Confusion	2	5		
Vascular disorders				
Hypotension	10	25	2	5
Flushing	4	10		

Body System Adverse reaction	Any grade adverse reactions		Grade ≥ 3 adverse reactions	
	n	%	n	%
Hypertension	4	10		
Pallor	4	10		
Infections and infestations				
Sinusitis	8	20		
Herpes simplex	5	13		
Upper respiratory tract infection	5	13	1	3
Bacterial infection - non-specific	3	8	1	3
Herpes zoster	3	8		
Nasopharyngitis	2	5		
Oral candidiasis	2	5		
Sepsis	2	5	2	5
Reproductive system disorders				
Vaginal hemorrhage	5	13		
Intermenstrual bleeding	3	8		
Ocular disorders				
Eye irritation	4	10		
Blurred vision	4	10		
Dry eye	3	8		
Painful red eye	2	5		
Renal and urinary disorders				
Renal failure	3	8	1	3
Renal impairment	3	8		
Oliguria	2	5		
Incontinence	2	5		
Ear disorders				
Earache	3	8		
Tinnitus	2	5		

Other Clinically Relevant Adverse Reactions

Leukocytosis: Arsenic trioxide can induce proliferation of leukemic promyelocytes resulting in a rapid increase in white blood cell count. Leukocytosis greater than 10 Gi/L developed during induction therapy in 43% patients receiving Arsenic Trioxide/tretinoin for newly-diagnosed low to intermediate risk APL and in 50% of patients receiving arsenic trioxide monotherapy for relapsed/refractory APL. In the relapsed/refractory setting, a relationship did not exist between baseline WBC counts and development of hyperleukocytosis nor baseline WBC counts and peak WBC counts.

Post-marketing Experience

The following adverse reactions have been identified during post-approval use of arsenic trioxide. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate the frequency or establish a causal relationship to drug exposure.

Cardiac disorders: Ventricular extrasystoles in association with QT prolongation, ventricular tachycardia in association with QT prolongation, including torsade de pointes, atrioventricular block, and congestive heart failure.

Ear and labyrinth disorders: Deafness

Hematologic disorders: Pancytopenia, bone marrow necrosis

Infections: Herpes zoster

Investigations: Gamma glutamyltransferase increased

Musculoskeletal and connective tissue disorders: Bone pain, myalgia, rha bdomyolysis

Neoplasms benign, malignant and unspecified: Melanoma, pancreatic cancer, squamous cell carcinoma

Nervous system disorders: Peripheral neuropathy, paresis, seizures, confusion, encephalopathy, Wernicke's encephalopathy, posterior reversible encephalopathy syndrome

Skin and subcutaneous tissue disorders: Toxic epidermal necrolysis

Reporting suspected adverse effects

Reporting suspected adverse reactions after registration of the medicinal product is important. It allows continued monitoring of the benefit-risk balance of the medicinal product. Healthcare professionals are asked to report any suspected adverse reactions.

4.9 OVERDOSE

Treatment of overdose

If symptoms of serious acute arsenic toxicity appear, the drug should be immediately discontinued and chelation therapy should be considered. Other anti-arsenical treatment may be considered.

5 PHARMACOLOGICAL PROPERTIES

5.1 PHARMACODYNAMIC PROPERTIES

Mechanism of action

The precise molecular and cellular mechanisms underlying the pharmacodynamics of arsenic trioxide in acute promyelocytic leukaemia (APL) are uncertain. Arsenic trioxide can induce partial differentiation and apoptosis of leukaemic cells *in vitro*. There is also evidence that its other known pharmacological effects (degradation of specific APL fusion transcripts, anti-proliferation, inhibition of angiogenesis) may contribute to efficacy in APL.

Clinical trials

Cardiac Electrophysiology

In a single arm trial of Arsenic trioxide (0.15 mg/kg daily), 16 of 40 patients (40%) had a QTc interval greater than 500 msec. Prolongation of the QTc was observed between 1 and 5 weeks after arsenic trioxide infusion, and then returned towards baseline by the end of 8 weeks after arsenic trioxide infusion.

5.2 PHARMACOKINETIC PROPERTIES

The inorganic, lyophilized form of arsenic trioxide, when placed into solution, immediately forms the hydrolysis product arsenious acid (As^{III}). As^{III} is the pharmacologically active species of arsenic trioxide. Monomethylarsonic acid (MMA^{V}), and dimethylarsinic acid (DMA^{V}) are the main pentavalent metabolites formed during metabolism, in addition to arsenic acid (As^{V}) a product of As^{III} oxidation.

The pharmacokinetics of arsenical species ([As^{III}], [As^{V}], [MMA^{V}], [DMA^{V}]) were determined in 6 APL patients following once daily doses of 0.15 mg/kg for 5 days per week. Over the total single dose range of 7 to 32 mg (administered as 0.15 mg/kg), systemic exposure (AUC) appears to be linear.

Peak plasma concentrations of arsenious acid (As^{III}), the primary active arsenical species were reached at the end of infusion (2 hours). Plasma concentration of As^{III} declined in a biphasic manner with a mean elimination half-life of 10 to 14 hours and is characterized by an initial rapid distribution phase followed by a slower terminal elimination phase. The daily exposure to As^{III} (mean AUC_{0-24}) was 194 ng·hr/mL (n=5) on Day 1 of Cycle 1 and 332 ng·hr/mL (n=6) on Day 25 of Cycle 1, which represents an approximate 2-fold accumulation.

The primary pentavalent metabolites, MMA^{V} and DMA^{V}, are slow to appear in plasma (approximately 10 24 hours after first administration of arsenic trioxide), but, due to their longer half-life, accumulate more upon multiple dosing than does As III The mean estimated terminal elimination half-lives of the metabolites MMA^{V} and DMA^{V} are 32 hours and 72 hours, respectively. Approximate accumulation ranged from 1.4- to 8-fold following multiple dosing as compared to single dose administration. As^{V} is present in plasma only at relatively low levels.

Distribution

The volume of distribution (V_{ss}) for As^{III} is large (mean 562 L, N=10) indicating that As^{III} is widely distributed throughout body tissues. V ss is also dependent on body weight and increases as body weight increases.

Elimination

Metabolism

Much of the As^{III} is distributed to the tissues where it is methylated to the less cytotoxic metabolites, monomethylarsonic acid (MMA^{V}) and dimethylarsinic acid (DMA^{V}) by methyltransferases primarily in the liver. The metabolism of arsenic trioxide also involves oxidation of As^{III} to As^{V}, which may occur in numerous tissues via enzymatic or

nonenzymatic processes. As^{V} is present in plasma only at relatively low levels following administration of arsenic trioxide.

Excretion

Approximately 15% of the administered arsenic trioxide dose is excreted in the urine as unchanged As^{III}. The methylated metabolites of As^{III} (MMA^{V}, DMA^{V}) are primarily excreted in the urine. The total clearance of As^{III} is 49 L/h and the renal clearance is 9 L/h. Clearance is not dependent on body weight or dose administered over the range of 7-32 mg.

Specific populations

Patients with renal impairment

The effect of renal impairment on the pharmacokinetics of As^{III}, As^{V}, and the pentavalent metabolites MMA^{V} and DMA^{V} was evaluated in 20 patients with advanced malignancies. Patients were classified as having normal renal function (creatinine clearance [CrCl] > 80 mL/min, n=6), mild renal impairment (CrCl 50-80 mL/min, n=5), moderate renal impairment (CrCl 30-49 mL/min, n=6), or severe renal impairment (Cr Cl < 30 mL/min, n=3). Following twice weekly administration of 0.15 mg/kg over a 2-hour infusion, the mean $AUC_{0-\infty}$ for As^{III} was comparable among the normal, mild and moderate renal impairment groups. However, in the severe renal impairment group, the mean $AUC_{0-\infty}$ for As^{III} was approximately 4 8% higher than that in the normal group.

Systemic exposure to MMA^{V} and DMA^{V} tended to be larger in patients with renal impairment; however, the clinical consequences of this increased exposure are not known. As^{V} plasma levels were generally below the limit of assay quantitation in patients with impaired renal function. The use of arsenic trioxide in patients on dialysis has not been studied.

Patients with Hepatic Impairment

The effect of pharmacokinetics of As^{III}, As^{V}, and the pentavalent metabolites MMA^{V} and DMA^{V} was evaluated following administration of 0.25-0.50 mg/kg of arsenic trioxide in patients with hepatocellular carcinoma. Patients were classified as having normal hepatic function (n=4), mild hepatic impairment (Child Pugh class A, n=12), moderate hepatic impairment (Child Pugh class B, n=3), or severe hepatic impairment (Child Pugh class C, n=1). No clear trend toward an increase in systemic exposure to As^{III}, As^{V}, MMA^{V} or DMA^{V} was observed with decreasing level of hepatic function as assessed by dose normalized (per mg dose) AUC in the mild and moderate hepatic impairment groups. However, the one patient with severe hepatic impairment had mean dose normalized AUC_{0-24} and C_{max} values 40% and 70% higher, respectively, than those patients with normal hepatic function. The mean dose normalized trough plasma levels for both MMA^{V} and DMA^{V} in this severely hepatically impaired patient were 2.2-fold and 4.7-fold higher, respectively, than those in the patients with normal hepatic function.

Pediatric Patients

Following IV administration of 0.15 mg/kg/day of arsenic trioxide in 10 APL patients (median age = 13.5 years, range 4 20 years), the daily exposure to As^{III} (mean AUC_{0-24h}) was 317 ng·hr/mL on Day 1 of Cycle 1.

Drug Interaction Studies

No formal assessments of pharmacokinetic drug-drug interactions between arsenic trioxide and other drugs have been conducted. The methyltransferases responsible for metabolizing arsenic trioxide are not members of the cytochrome P450 family of isoenzymes. *In vitro* incubation of arsenic trioxide with human liver microsomes showed no inhibitory activity on substrates of the major cytochrome P450 (CYP) enzymes such as 1A2, 2A6, 2B6, 2C8, 2C9, 2C19, 2D6, 2E1, 3A4/5, and 4A9/11. The pharmacokinetics of drugs that are substrates for these CYP enzymes are not expected to be affected by concomitant treatment with arsenic trioxide.

5.3 PRECLINICAL SAFETY DATA

Carcinogenesis, Mutagenesis, Impairment of Fertility

Carcinogenicity studies have not been conducted with arsenic trioxide.

Arsenic trioxide and trivalent arsenite salts have not been demonstrated to be mutagenic to bacteria, yeast, or mammalian cells. Arsenite salts are clastogenic *in vitro* (human human lymphocytes, Chinese hamster ovary cells, Chinese hamster V79 lung cells). Trivalent arsenic was genotoxic in the chromosome aberrations assay and micronucleus bone marrow assay in mice.

The effect of arsenic on fertility has not been adequately studied in humans. Decreased testicular weight and impaired spermatogenesis have been reported in animal studies. Male Wistar rat pups were administered 1.5 mg/kg sodium arsenite solution via the intraperitoneal route from postnatal days 1 to 14 and testes were collected for evaluation on postnatal days 1 5, 21, and 50. Results of this study revealed an altered morphology of the seminiferous tubules along with degeneration of spermatogenic cells, increased number of sperm with abnormal morphology, and decreased sperm counts. In beagle dogs administered intravenous arsenic trioxide for 90 days, reduced inner cell layers within seminiferous tubules and significantly decreased numbers of spermatocytes, spermatozoa, and sperm cells were observed at doses of 1 mg/kg/day and higher. The 1 mg/kg/day dose is approximately 3 times the recommended human daily dose on a mg/m^2 basis.

6 PHARMACEUTICAL PARTICULARS

6.1 LIST OF EXCIPIENTS

Arsenic trioxide – AFT contains sodium hydroxide and water for injections. Hydrochloric acid is added for pH adjustment. Arsenic trioxide – AFT contains no antimicrobial preservative.

6.2 INCOMPATIBILITIES

Incompatibilities were either not assessed or not identified as part of the registration of this medicine.

6.3 SHELF LIFE

The expiry date can be found on the packaging.

6.4 SPECIAL PRECAUTIONS FOR STORAGE

Store below 30°C. Cytotoxic. Proper safe handling and disposal should be observed by medical staff.

6.5 NATURE AND CONTENTS OF CONTAINER

Arsenic trioxide – AFT (10 mg/ 10 mL) is presented in 10 mL glass ampoules in packs of 10 ampoules.

6.6 SPECIAL PRECAUTIONS FOR DISPOSAL

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

6.7 PHYSICOCHEMICAL PROPERTIES

The molecular weight of the compound is 197.84. The molecular formula is As_2O_3.

CAS number

1327-53-3

7 MEDICINE SCHEDULE (POISONS STANDARD)

S4 – Prescription only medicine

8 PRODUCT OWNER

AFT Pharmaceuticals Ltd.

129 Hurstmere Road

Takapuna, Auckland, New Zealand

9 DATE OF REVISION

January 2024