Date

Fludarabine

Version: 2.0

ELEMENTS FOR A PUBLIC SUMMARY

VI.2.1 Overview of disease epidemiology

Although the incidence of (chronic lymphoid leukaemia, CLL) in Western countries is similar to that of the United States, the true incidence is unknown and is likely higher, and many cases are not reported. CLL is extremely rare in Asian countries (ie, China, Japan). The incidence of CLL is higher among whites than blacks. The incidence of CLL is higher in males than in females. CLL is a disease that primarily affects the elderly.

The prognosis of patients with CLL varies widely at diagnosis. Prognosis depends on the disease stage at diagnosis as well as the presence or absence of high-risk markers. Patients with CLL present with a wide range of symptoms and signs. Onset is insidious, and it is not unusual for CLL to be discovered incidentally. The transformation of CLL into an aggressive large B-cell lymphoma is seen in approximately 3-10% of cases Treatment remains challenging and prognosis poor, with median survival in months.

Richter syndrome or Richter transformation refers to the transformation of CLL into an aggressive large B-cell lymphoma and is seen in approximately 3-10% of cases.
Patients with CLL do not need to be treated with chemotherapy until they become symptomatic or display evidence of rapid progression of disease. Chemotherapy regimens include nucleoside analogues, alkylating agents, and biologics, often in combination. Infectious complications have been known to be a major cause of morbidity and mortality in CLL (Muhammad A Mir, 2013).

VI.2.2 Summary of treatment benefits

The treatment and its duration depend on the treatment success and the tolerability of the drug. It is recommended that fludarabine phosphate be administered up to the achievement of response and then the drug should be discontinued.

Doses should be adjusted for patients with reduced renal function. Close haematological monitoring should be used to assess toxicity. The treatment is contraindicated, if creatinine clearance is <30 ml/min.

VI.2.3 Unknown relating to treatment benefits

No data are available concerning the use of fludarabine phosphate in patients with hepatic impairment, and it should be used with caution and administered if the perceived benefit outweighs any potential risk.

Fludarabine is not recommended for use in children and adolescents below age 18, due to a lack of data on safety and efficacy. And since there are limited data for the use of fludarabine in elderly persons (>75 years), caution should be exercised with the administration of fludarabine in these patients

VI.2.4 Summary of safety concerns

Risk	What is known	Preventability
Myelosuppression Bone marrow is the spongy tissue inside some of your bones. It contains immature cells, called stem cells. The stem cells can develop into the red blood cells that carry oxygen through your body, the white blood cells that fight infections, and the platelets that help with blood clotting. If you have a bone marrow disease, there are problems with the stem cells or how they develop. Leukemia is a cancer in which the bone marrow produces abnormal white blood cells. With aplastic anemia, the bone marrow doesn't make red blood cells.	Severe bone marrow suppression, notably anaemia, thrombocytopenia and neutropenia, has been reported in patients treated with fludarabine phosphate. In a Phase I intravenous study in adult solid tumour patients. Most patients had haematological impairment at baseline either as a result of disease or as a result of prior myelosuppressive therapy. Cumulative myelosuppression may be seen. While chemotherapy-induced myelosuppression is often reversible, administration of fludarabine phosphate requires careful haematological monitoring.	While myelosuppression usually is reversible, careful he-matologic monitoring is necessary during fludarabine therapy. Depending on the severity of hematologic toxicity, dosage adjustment, interruption of therapy, and/or transfusions may be necessary. Recovery of neutrophil and platelet count usually is complete within 5–7 weeks after discontinuance of fludarabine therapy, but occasionally may require longer periods. Bone marrow fibrosis has occurred rarely
Autoimmune disorder Your body's immune system protects you from disease and infection. But if you have an autoimmune disease, your immune system attacks healthy cells in your body by mistake. Autoimmune diseases can affect many parts of the body.	Irrespective of any previous history of autoimmune processes or Coombs test status, life-threatening and sometimes fatal autoimmune phenomena have been reported to occur during or after treatment with fludarabine phosphate. The majority of patients experiencing haemolytic anaemia developed a recurrence in the haemolytic process after rechallenge with fludarabine phosphate. Patients treated with fludarabine phosphate should be closely monitored for signs of haemolysis	It is not known if administration of corticosteroids is bene-ficial for management of these hemolytic episodes. Patients receiving fludarabine should be evaluated and monitored closely for hemolysis

Neurotoxicity Neurologic diseases are disorders of the brain, spinal cord and nerves throughout your body. Together they control all the workings of the body. Neurotoxicity has been associated with an irreversible central nervous system toxicity characterised by delayed blindness, coma, and death	The effect of chronic administration of fludarabine phosphate on the central nervous system is unknown. Patients should be closely observed for signs of neurologic effects. When used at high doses in dose-ranging studies in patients with acute leukaemia, fludarabine phosphate was associated with severe neurological effects, including blindness, coma and death. Patients treated at doses in the range of the dose recommended for chronic lymphocytic leukameia, severe central nerv-ous system toxicity occurred rarely (coma, seizures and agitation) or uncommonly (confusion) (	While some clinicians recommended during early studies with the drug that even patients receiving relatively low dosages (e.g., those currently recommended for chronic lymphocytic leukaemia) be monitored closely with fre-quent neurologic evaluation and tests for possible neurotoxic effects, most clinicians currently suggest that such evaluation would not be cost-effective and that visual changes generally can be monitored as evidence of neu-rotoxicity
Transfusion-associated graft versus host disease Transfusion-associated graft versus host disease is a rare complication of blood transfusion, in which the donor T lymphocytes mount an immune response against the recipient's lymphoid tissue. Donor lymphocytes are usually identified as foreign and destroyed by the recipient's immune system. However, in situations where the immune system is not able to destroy the donor lymphocytes, the result is graft versus host disease.	Transfusion-associated graft-versus-host disease (re-action by the transfused immunocompetent lympho-cytes to the host) has been observed after transfusion of non-irradiated blood in patients treated with fludarabine phosphate. Fatal outcome as a consequence of this disease has been reported with a high frequency. Therefore, to minimize the risk, patients who require blood transfusion and who are undergoing, or who have received, treatment with fludarabine phosphate should receive irradiated blood only.	Prevention can be achieved either by complete removal of T-lymphocytes from donors blood or by abolishing their proliferating potentials. Available methods of leuko-depletion are not effective in preventing TA-GVHD. Only effective way is to inactivate T-lymhocytes. This can be achieved by irradiating blood product with gamma or X-ray irradiation. The concerns about malignant transformation of cells or re-activation of intracellular viruses have not been proved so far. Newer technologies for T-cell in-activation, which are not based on irradiation, are currently under trial.
Skin cancer Skin cancer is a malignant growth on the outer layer of the skin. A malignant growth is one that has the potential to cause death. Skin cancers are often divided into two general groups: malignant melanomas and non-melanoma cancers.	The worsening or flare up of pre-existing skin cancer lesions as well as new onset of skin cancer have been reported in some patients to occur during or after fludarabine phosphate therapy.	Patients who have lymphoma-associated skin cancer should undergo aggressive treatment approaches to de-crease the chances of recurrence and skin cancer-associated morbidity and mortality. Preventive

		strategies, such as early detection, sun-protective behavior, frequent dermatologic examinations and education directed toward the patient with lymphoma, may not only prevent the development of aggressive skin cancer, but also have a higher rate of successfully treating early forms of skin cancer in this high-risk patient population
Tumor lysis syndrome Tumor lysis syndrome is a group of metabolic complications that can occur after treatment of cancer	Tumour lysis syndrome has been reported in patients with large tumour burdens. Since fludarabine phosphate can induce a response as early as the first week of treatment, precautions should be taken in those patients at risk of developing this complication.	Early recognition of signs and symptoms of patients at risk for tumor lysis syndrome, including identification of abnormal clinical and laboratory values, can lead to suc-cessful prevention of the otherwise life-threatening complications of the condition
Reproductive toxicity An adverse effect on many aspect of male or female sexual structure or function, which would interfere with the production of development of normal offspring which could be reared to sexual maturity, capable in turn of reproducing the species.	Fludarabine phosphate should not be used during pregnancy unless clearly necessary (e.g. life-threatening situation, no alternative safer treatment available without compromising the therapeutic bene-fit, treatment cannot be avoided). It has the potential to cause fetal harm Pre-scribers may only consider the use of fludarabine, if the potential benefits justify the potential risks to the foetus.	Women should avoid becoming pregnant while on fludarabine therapy. Women of childbearing potential must be apprised of the potential hazard to the foetus

Important potential risks

Important potential risks	Myelosuppression
	Autoimmune disorders
	Neurotoxicity
	Transfusion-associated graft-versus-host disease
	Skin cancer
	Tumour lysis syndrome
	Reproductive toxicity

Important missing information

Important missing information	Limited information is available on the use of fludarabine in elderly populations.

VI.2.5 Summary of risk minimization measures by safety concerns

No additional risk minimization measures are considered needed in relation the identified safety concerns.

VI.2.6 Planned post authorization development plan

No post-authorization safety or efficacy studies are on-going or are planned to be conducted for flurabine.

VI. 2.7 Sammanfattning av uppdateringar i riskhanteringsplan

Avsevärda uppdateringar i riskhanteringsplan

Versionnummer	Datum	Säkerhetsfrågor	Anmärkning
1.0	05-03-2013	Initial version	
2.0	05-04-2013	Additional risks added: • Transfusion-associated graft-versus-host disease • Skin cancer • Tumour lysis syndrome • Reproductive toxicity Update to section VI.2 Elements for a Public summary	