IRISH MEDICINES BOARD ACTS 1995 AND 2006

MEDICINAL PRODUCTS(CONTROL OF PLACING ON THE MARKET)REGULATIONS,2007

(S.I. No.540 of 2007)

PA1380/003/001
Case No: 2064890

The Irish Medicines Board in exercise of the powers conferred on it by the above mentioned Regulations hereby grants to

Actavis Group PTC ehf

Reykjavikurvegi 76-78, **220 Hafnarfjordur**, **Iceland**

an authorisation, subject to the provisions of the said Regulations, in respect of the product

Fludarabine Phosphate Actavis 50 mg Powder For Solution For Injection or Infusion

The particulars of which are set out in Part I and Part II of the attached Schedule. The authorisation is also subject to the general conditions as may be specified in the said Regulations as listed on the reverse of this document.

This authorisation, unless previously revoked, shall continue in force from **24/07/2009** until **21/08/2013**.

Signed on behalf of the Irish Medicines Board this

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A person authorised in that behalf by the said Board.

Part II

Summary of Product Characteristics

1 NAME OF THE MEDICINAL PRODUCT

Fludarabine Phosphate Actavis 50 mg Powder For Solution For Injection or Infusion

2 QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50 mg fludarabine phosphate.
1 ml of reconstituted solution contains 25 mg fludarabine phosphate.

For a full list of excipients, see section 6.1

3 PHARMACEUTICAL FORM

Powder for solution for injection or infusion.
White or almost white lyophilisate.

4 CLINICAL PARTICULARS

4.1 Therapeutic Indications

Treatment of B-cell chronic lymphocytic leukaemia (CLL) in patients with sufficient bone marrow reserves.
First line treatment with Fludarabine Phosphate Actavis should only be initiated in patients with advanced disease, Rai stages III/IV (Binet stage C), or Rai stages I/II (Binet stage A/B) where the patient has disease related symptoms or evidence of progressive disease.

4.2 Posology and method of administration

Fludarabine Phosphate Actavis should be administered under the supervision of a qualified physician experienced in the use of antineoplastic therapy.

It is strongly recommended that Fludarabine Phosphate Actavis should be only administered intravenously. No cases have been reported in which paravenously administered fludarabine led to severe local adverse reactions. However, the unintentional paravenous administration must be avoided.

Adults
The recommended dose is 25 mg fludarabine phosphate/m² body surface given daily for 5 consecutive days every 28 days by the intravenous route. Each vial is to be made up in 2 ml water for injection. Each ml of the resulting reconstituted solution will contain 25 mg fludarabine phosphate. The required dose (calculated on the basis of the patient's body surface) of the reconstituted solution is drawn up into a syringe. For intravenous bolus injection this dose is further diluted in 10 ml of 0.9 % sodium chloride. Alternatively, for infusion, the required dose may be diluted in 100 ml 0.9 % sodium chloride and infused over approximately 30 minutes (see also section 6.6).
The optimal duration of treatment has not been clearly established. The duration of treatment depends on the treatment success and the tolerability of the drug.
It is recommended that Fludarabine Phosphate Actavis be administered up to the achievement of response (usually 6 cycles) and then the drug should be discontinued.

Hepatic impairment
No data are available concerning the use of fludarabine phosphate in patients with hepatic impairment. In this group of patients, Fludarabine Phosphate Actavis should be used with caution and administered if the perceived benefit outweighs any potential risk.

Renal impairment
The total body clearance of the principle plasma metabolite 2-F-ara-A shows a correlation with creatinine clearance, indicating the importance of the renal excretion pathway for the elimination of the compound. Patients with reduced kidney function demonstrated an increased total body exposure (AUC of 2F-ara-A). Limited clinical data are available in patients with impairment of renal function (creatinine clearance below 70 ml/min). Therefore, if renal impairment is clinically suspected, or in patients over the age of 70 years, creatinine clearance should be measured. If creatinine clearance is between 30 and 70 ml/min, the dose should be reduced by up to 50% and close haematological monitoring should be used to assess toxicity.Fludarabine Phosphate Actavis treatment is contraindicated, if creatinine clearance is < 30 ml/min.

Children
Fludarabine is not recommended for use in children, due to a lack of data on safety and efficacy.

4.3 Contraindications

Fludarabine Phosphate Actavis is contraindicated

- in those patients who are hypersensitive to the active substance or any of the excipients
- in renally impaired patients with creatinine clearance < 30 ml/min
- in patients with decompensated haemolytic anaemia
- during pregnancy and lactation.

4.4 Special warnings and precautions for use

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. This severe central nervous system toxicity occurred in 36 % of patients treated with doses approximately four times greater (96 mg/m²/day for 5 -7 days) than the dose recommended for treatment of CLL. In patients treated at doses in the range of the dose recommended for CLL, severe central nervous system toxicity occurred rarely (coma, seizures and agitation) or uncommonly (confusion). Patients should be closely observed for signs of neurological side effects.

The effect of chronic administration of fludarabine phosphate on the central nervous system is unknown. However, patients tolerated the recommended dose, in some studies for relatively long term treatment times, whereby up to 26 courses of therapy were administered.

In patients with impaired state of health, Fludarabine Phosphate Actavis should be given with caution and after careful risk/benefit consideration. This applies especially for patients with severe impairment of bone marrow function (thrombocytopenia, anaemia, and/or granulocytopenia), immunodeficiency or with a history of opportunistic infection.

Severe bone marrow suppression, notably anaemia, thrombocytopenia and neutropenia, has been reported in patients treated with fludarabine phosphate. In a Phase I study in solid tumour patients, the median time to nadir counts was 13 days (range, 3 - 25 days) for granulocytes and 16 days (range, 2 - 32) for platelets. 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.

Fludarabine Phosphate Actavis is a potent antineoplastic agent with potentially significant toxic side effects. Patients undergoing therapy should be closely observed for signs of haematological and non-haematological toxicity. Periodic assessment of peripheral blood counts is recommended to detect the development of anaemia, neutropenia and thrombocytopenia.

As with other cytotoxics, caution should be exercised with fludarabine phosphate, when further haematopoietic stem sampling is considered.

Transfusion-associated graft-versus-host disease (reaction by the transfused immunocompetent lymphocytes 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, patients who require blood transfusion and who are undergoing, or who have received, treatment with Fludarabine Phosphate Actavis should receive irradiated blood only.

Reversible worsening or flare up of pre-existing skin cancer lesions has been reported in some patients to occur during or after fludarabine phosphate therapy.

Tumour lysis syndrome associated with fludarabine phosphate treatment has been reported in CLL 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.

Irrespective of any previous history of autoimmune processes or Coombs test status, life-threatening and sometimes fatal autoimmune phenomena (e.g. autoimmune haemolytic anaemia, autoimmune thrombocytopenia, thrombocytopenic purpura, pemphigus, Evans' syndrome) 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 Actavis should be closely monitored for haemolysis.

Patients undergoing treatment with Fludarabine Phosphate Actavis should be closely monitored for signs of autoimmune haemolytic anaemia (decline in haemoglobin linked with haemolysis and positive Coombs test). Discontinuation of therapy with Fludarabine Phosphate Actavis is recommended in case of haemolysis. Blood transfusion (irradiated, see above) and adrenocorticoid preparations are the most common treatment measures for autoimmune haemolytic anaemia.

Since there are limited data for the use of fludarabine phoshpate in elderly persons (> 75 years), caution should be exercised with the administration of Fludarabine Phosphate Actavis in these patients.

No data are available concerning the use of fludarabine phosphate in children. Therefore, treatment with Fludarabine Phosphate Actavis in children is not recommended.

Females of child-bearing potential or males must take contraceptive measures during and at least for 6 months after cessation of therapy.

During and after treatment with Fludarabine Phosphate Actavis vaccination with live vaccines should be avoided.

A crossover from initial treatment with Fludarabine Phosphate to chlorambucil for non responders to fludarabine phosphate should be avoided because most patients who have been resistant to fludarabine phosphate have shown resistance to chlorambucil.

This medicinal product contains less than 1 mmol sodium (23 mg) per ml after reconstitution, i.e. essentially sodium free.

4.5 Interaction with other medicinal products and other forms of interaction

In a clinical investigation using fludarabine phosphate in combination with pentostatin (deoxycoformycin) for the treatment of refractory chronic lymphocytic leukaemia (CLL), there was an unacceptably high incidence of fatal pulmonary toxicity. Therefore, the use of Fludarabine Phosphate Actavis in combination with pentostatin is not recommended.

The therapeutic efficacy of fludarabine phosphate may be reduced by dipyridamole and other inhibitors of adenosine uptake.

A pharmacokinetic drug interaction was observed in CLL and AML patients during combination therapy with fludarabine phosphate and Ara-C. Clinical studies and *in vitro* experiments with cancer cell lines demonstrated elevated intracellular Ara-CTP levels in leukaemic cells in terms of intracellular peak concentrations as well as of intracellular exposure (AUC) in combination of fludarabine phosphate and subsequent Ara-C treatment. Plasma concentrations of Ara-C and the elimination rate of Ara-CTP were not affected.

4.6 Pregnancy and lactation

Pregnancy
Fludarabine Phosphate Actavis is contraindicated during pregnancy.

Women of child-bearing potential should be advised to avoid becoming pregnant and to inform the treating physician immediately should this occur.

Very limited human experience supports the findings of embryotoxicity studies in animals demonstrating an embryotoxic and/or teratogenic potential at the therapeutic dose. Preclinical data in rats demonstrated a transfer of fludarabine phosphate and/or metabolites through the foeto-placental barrier.

Lactation
Breast-feeding must be discontinued for the duration of Fludarabine Phosphate Actavis therapy. It is not known whether this drug is excreted in human milk. However, there is evidence from preclinical data that fludarabine phosphate and/or metabolites transfer from maternal blood to milk.

4.7 Effects on ability to drive and use machines

No studies on the effects on the ability to drive and use machines have been performed.

Fludarabine Phosphate Actavis may influence the ability to drive and use machines since fatigue, weakness, agitation, seizures and visual disturbances has been observed.

4.8 Undesirable effects

Adverse reactions are presented below according to the MedDRA system organ class and ranked under heading of frequency: Very common (≥1/10); common (≥1/100 to <1/10); uncommon (≥1/1,000 to ≤1/100); rare (≥1/10,000 to ≤ 1/1,000); very rare (≤1/10,000), not known (cannot be estimated form the available data).
The frequency of the commonly and uncommonly reported adverse events and those reactions which are more clearly related to the drug are based on clinical trial data regardless of the causal relationship with fludarabine phosphate. The rare events were mainly identified from the post-marketing experience. Fatalities as a consequence of serious adverse events have been reported.

The most common adverse events include myelosuppression (neutropenia, thrombocytopenia and anaemia), infection including pneumonia, fever, nausea, vomiting and diarrhoea. Other commonly reported events include fatigue, weakness, stomatitis, malaise, anorexia, oedema, chills, peripheral neuropathy, visual disturbances and skin rashes. Serious opportunistic infections have occurred in patients treated with fludarabine phosphate. Fatalities as a consequence of serious adverse events have been reported.

Cardiac disorders
Rare: Heart failure and arrhythmia.

Blood and lymphatic system disorders
Haematological events (neutropenia, thrombocytopenia, and anaemia) have been reported in the majority of patients treated with fludarabine phosphate. Myelosuppression may be severe and cumulative. The medicinal product´s prolonged negative effect on the decrease in the numbers of T-lymphocytes may lead to an increased risk of opportunistic infections, including those due to latent viral reactivation, e.g. Herpes zoster, Epstein-Barr Virus (EBV) or progressive multifocal leucoencephalopathy (see section 4.4). Evolution of EBV-infection/reactivation into EBV-associated lymphoproliferative disorders has been observed in immunocompromised patients.
Uncommon: Clinically significant autoimmune phenomena (see section 4.4).
Rare: Myelodysplastic syndrome (MDS) has been described in patients treated with fludarabine phosphate. The majority of these patients also received prior, concomitant or subsequent treatment with alkylating agents or irradiation. Monotherapy with fludarabine phosphate has not been associated with an increased risk for the development of MDS.

Nervous system
Common: Peripheral neuropathy.
Uncommon: Confusion.
Rare: Coma, agitation and seizures.

Eye disorders
Common: Visual disturbances
Rare: Optic neuritis, optic neuropathy and blindness.

Respiratory, thoracic and mediastinal disorders
Common: Pneumonia.
Uncommon: Pulmonary hypersensitivity reactions (pulmonary infiltrates/pneumonitis/fibrosis) associated with dyspnoea and cough.

Gastrointestinal disorders
Common: Gastrointestinal disturbances such as nausea and vomiting, diarrhoea, stomatitis, and anorexia.
Uncommon: Gastrointestinal bleeding, mainly related to thrombocytopenia.

Renal and urinary disorders
Rare: Haemorrhagic cystitis.

Skin and subcutaneous tissue disorders
Common: Skin rashes.
Rare: Stevens-Johnson syndrome or a toxic epidermal necrolysis (Lyell's syndrome).

Metabolism and nutrition disorders
Common: Oedema.
Uncommon: Tumour lysis syndrome. This complication may include hyperuricaemia, hyperphosphataemia, hypocalcaemia, metabolic acidosis, hyperkalaemia, haematuria, urate crystalluria, and renal failure. The onset of this syndrome may be heralded by flank pain and haematuria. Changes in hepatic and pancreatic enzyme levels.

General disorders and administration site conditions
Common: Infection, fever, fatigue, weakness, malaise, and chills.

4.9 Overdose

High doses of fludarabine phosphate have been associated with an irreversible central nervous system toxicity characterised by delayed blindness, coma, and death. High doses are also associated with severe thrombocytopenia and neutropenia due to bone marrow suppression. There is no known specific antidote for fludarabine phosphate overdosage. Treatment consists of drug discontinuation and supportive therapy.

5 PHARMACOLOGICAL PROPERTIES

5.1 Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic agents ATC-code L01B B05

Fludarabine Phosphate Actavis contains fludarabine phosphate, a water-soluble fluorinated nucleotide analogue of the antiviral agent vidarabine, "9 ß-D-" arabinofuranosyladenine (ara-A) that is relatively resistant to deamination by adenosine deaminase.

Fludarabine phosphate is rapidly dephosphorylated to 2F-ara-A which is taken up by cells and then phosphorylated intracellularly by deoxycytidine kinase to the active triphosphate, 2F-ara-ATP. This metabolite has been shown to inhibit ribonucleotide reductase, DNA polymerase α/δ and ε, DNA primase and DNA ligase thereby inhibiting DNA synthesis. Furthermore, partial inhibition of RNA polymerase II and consequent reduction in protein synthesis occur.

While some aspects of the mechanism of action of 2F-ara-ATP are as yet unclear, it is assumed that effects on DNA, RNA and protein synthesis all contribute to inhibition of cell growth with inhibition of DNA synthesis being the dominant factor. In addition, in vitro studies have shown that exposure of CLL lymphocytes to 2F-ara-A triggers extensive DNA fragmentation and cell death characteristic of apoptosis.

A phase III trial in patients with previously untreated B-chronic lymphocytic leukaemia comparing treatment with fludarabine phosphate vs. chlorambucil (40mg / m² q4 weeks) in 195 and 199 patients respectively showed the following outcome: statistically significant higher overall response rates and complete response rates after 1st line treatment with fludarabine phosphate compared to chlorambucil (61.1% vs. 37.6% and 14.9% vs. 3.4%, respectively); statistically significant longer duration of response (19 vs. 12.2 months) and time to progression (17 vs. 13.2 months) for the patients in the fludarabine phosphate group.

The median survival of the two patient groups was 56.1 months for fludarabine phosphate and 55.1 months for chlorambucil, a non-significant difference was also shown with performance status. The proportion of patients reported to have toxicities were comparable between fludarabine phosphate patients (89.7%) and chlorambucil patients (89.9%). While the difference in the overall incidence of haematological toxicities was not significant between the two treatment groups, significantly greater proportions of fludarabine phosphate patients experienced white blood cell ($p=0.0054$) and lymphocyte ($p=0.0240$) toxicities than chlorambucil patients. The proportions of patients who experienced nausea, vomiting, and diarrhoea were significantly lower for fludarabine phosphate patients ($p<0.0001$, $p<0.0001$, and $p=0.0489$, respectively) than chlorambucil patients. Toxicities of the liver were also reported for significantly ($p=0.0487$) less proportions of patients in the fludarabine phosphate group than in the chlorambucil group.

Patients who initially respond to fludarabine phosphate have a chance of responding again to fludarabine phosphate monotherapy.

A randomised trial of fludarabine phosphate vs. cyclophosphamide, adriamycin and prednisone (CAP) in 208 patients with CLL Binet stage B or C revealed the following results in the subgroup of 103 previously treated patients: the overall response rate and the complete response rate were higher with fludarabine phosphate compared to CAP (45% vs. 26% and 13% vs. 6%, respectively); response duration and overall survival were similar with fludarabine phosphate and CAP. Within the stipulated treatment period of 6 months the number of deaths was 9 (fludarabine phosphate) vs. 4 (CAP).

Post-hoc analyses using only data of up to 6 months after start of treatment revealed a difference between survival curves of fludarabine phosphate and CAP in favour of CAP in the subgroup of pretreated Binet stage C patients.

5.2 Pharmacokinetic properties

Plasma and urinary pharmacokinetics of fludarabine (2F-ara-A)

The pharmacokinetics of fludarabine (2F-ara-A) have been studied after intravenous administration by rapid bolus injection and short-term infusion as well as following continuous infusion of fludarabine phosphate (fludarabine phosphate, 2F-ara-AMP).

2F-ara-AMP is a water-soluble prodrug, which is rapidly and quantitatively dephosphorylated in the human organism to the nucleoside fludarabine (2F -ara-A). After single dose infusion of 25 mg 2F-ara-AMP per m² to cancer patients for 30 minutes 2F-ara-A reached mean maximum concentrations in the plasma of 3.5 - 3.7 µM at the end of the infusion. Corresponding 2F-ara-A levels after the fifth dose showed a moderate accumulation with mean maximum levels of 4.4 - 4.8 µM at the end of infusion. During a 5-day treatment schedule 2F-ara-A plasma trough levels increased by a factor of about 2. An accumulation of 2F-ara-A over several treatment cycles can be excluded. Postmaximum levels decayed in three disposition phases with an initial half-life of approx. 5 minutes, an intermediate half-life of 1 - 2 hours and a terminal half-life of approx. 20 hours.

An interstudy comparison of 2F-ara-A pharmacokinetics resulted in a mean total plasma clearance (CL) of 79 ± 40 ml/min/m² (2.2 ± 1.2 ml/min/kg) and a mean volume of distribution (Vss) of 83 ± 55 l/m² (2.4 ± 1.6 l/kg). Data showed a high interindividual variability. Plasma levels of 2F-ara-A and areas under the plasma level time curves increased linearly with the dose, whereas half-lives, plasma clearance and volumes of distribution remained constant independent of the dose indicating a dose linear behaviour. Occurrence of neutropenia and haematocrit changes indicated that the cytotoxicity of fludarabine phosphate depresses the haematopoiesis in a dose dependent manner.

2F-ara-A elimination is largely by renal excretion. 40 to 60 % of the administered i.v. dose was excreted in the urine.

Mass balance studies in laboratory animals with ^{3}H-2F-ara-AMP showed a complete recovery of radio-labelled substances in the urine. Another metabolite, 2F-ara-hypoxanthine, which represents the major metabolite in the dog, was observed in humans only to a minor extent. Individuals with impaired renal function exhibit a reduced total body clearance, indicating the need for a dose reduction. *In vitro* investigations with human plasma proteins revealed no pronounced tendency of 2F-ara-A protein binding.

Cellular pharmacokinetics of fludarabine triphosphate
2F-ara-A is actively transported into leukaemic cells, whereupon it is rephosphorylated to the monophosphate and subsequently to the di- and triphosphate. The triphosphate 2F-ara-ATP is the major intracellular metabolite and the only metabolite known to have cytotoxic activity. Maximum 2F-ara-ATP levels in leukaemic lymphocytes of CLL patients were observed at a median of 4 hours and exhibited a considerable variation with a median peak concentration of approx. 20 µM. 2F-ara-ATP levels in leukaemic cells were always considerably higher than maximum 2F-ara-A levels in the plasma indicating an accumulation at the target sites. In vitro incubation of leukaemic lymphocytes showed a linear relationship between extracellular 2F-ara-A exposure (product of 2F-ara-A concentration and duration of incubation) and intracellular 2F-ara-ATP enrichment. 2F-ara ATP elimination from target cells showed median half life values of 15 and 23 hours.

No clear correlation was found between 2F-ara-A pharmacokinetics and treatment efficacy in cancer patients.

5.3 Preclinical safety data

In acute toxicity studies, single doses of fludarabine phosphate produced severe intoxication symptoms or death at dosages about two orders of magnitude above the therapeutic dose. As expected for a cytotoxic compound, the bone marrow, lymphoid organs, gastrointestinal mucosa, kidneys and male gonads were affected.

Systemic toxicity studies following repeated administration of fludarabine phosphate showed also the expected effects on rapidly proliferating tissues above a threshold dose. The severity of morphological manifestations increased with dose levels and duration of dosing and the observed changes were generally considered to be reversible. In principle, the available experience from the therapeutic use of fludarabine phosphate points to a comparable toxicological profile in humans, although additional undesirable effects such as neurotoxicity were observed in patients (see section 4.8).

The results from animal embryotoxicity studies indicated a teratogenic potential of fludarabine phosphate. In view of the small safety margin between the teratogenic doses in animals and the human therapeutic dose as well as in analogy to other antimetabolites which are assumed to interfere with the process of differentiation, the therapeutic use of fludarabine phosphate is associated with a relevant risk of teratogenic effects in humans (see section 4.6).

Fludarabine phosphate has been shown to induce chromosomal aberrations in an *in vitro* cytogenetic assay, to cause DNA-damage in a sister chromatid exchange test and to increase the rate of micronuclei in the mouse micronucleus test *in vivo*, but was negative in gene mutation assays and in the dominant lethal test in male mice. Thus, the mutagenic potential was demonstrated in somatic cells but could not be shown in germ cells.

The known activity of fludarabine phosphate at the DNA-level and the mutagenicity test results form the basis for the suspicion of a tumorigenic potential. No animal studies which directly address the question of tumorigenicity have been conducted, because the suspicion of an increased risk of second tumours due to fludarabine phosphate therapy can exclusively be verified by epidemiological data.

According to the results from animal experiments following intravenous administration of fludarabine phosphate, no remarkable local irritation has to be expected at the injection site. Even in case of misplaced injections, no relevant local irritation was observed after paravenous, intraarterial, and intramuscular administration of an aqueous solution containing 7.5 mg fludarabine phosphate/ml.

6 PHARMACEUTICAL PARTICULARS

6.1 List of excipients

Mannitol
Sodium hydroxide (for pH adjustment).

6.2 Incompatibilities

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

6.3 Shelf Life

Vial before opening:
36 months

After reconstitution:
The physicochemical stability of the drug product after reconstitution in water for injections has been demonstrated for 8 hours at 25°C ± 2°C/ 60% ± 5 %RH and for 7 days at 5°C ± 3°C. From a microbiological point of view, the product should be used immediately. If not used immediately, in-use storage times and conditions prior to use are the responsibility of the user.

6.4 Special precautions for storage

Store below 25°C.
For storage after reconstitution or dilution, see Section 6.3.

6.5 Nature and contents of container

Colourless glass vial (type I) with bromobutylic rubber stopper and metallic cap (aluminium) with polypropylene disk.

Pack sizes
1 x 50 mg vial
5 x 50 mg vial

Not all pack sizes may be marketed.

6.6 Special precautions for disposal and other handling

Reconstitution
Fludarabine Phosphate Actavis should be prepared for parenteral use by aseptically adding sterile water for injection. When reconstituted with 2 ml of sterile water for injection, the powder should fully dissolve in 15 seconds or less. Each ml of the resulting solution will contain 25 mg of fludarabine phosphate, 25 mg of mannitol, and sodium hydroxide to adjust the pH to 7.7. The pH range for the final product is 7.2 - 8.2.

Dilution
The required dose (calculated on the basis of the patient's body surface) is drawn up into a syringe.
For intravenous bolus injection this dose is further diluted in 10 ml of 0.9 % sodium chloride. Alternatively, for infusion, the required dose may be diluted in 100 ml of 0.9 % sodium chloride (see section 4.2).

Inspection prior to use
The reconstituted solution is clear and colourless. It should be visually inspected before use.
Only clear and colourless solutions without particles should be used. Fludarabine Phosphate Actavis should not be used in case of a defective container.

Handling and disposal
Fludarabine Phosphate Actavis should not be handled by pregnant staff.

Procedures for proper handling should be followed according to local requirements for cytotoxic drugs. Caution should be exercised in the handling and preparation of the Fludarabine Phosphate Actavis solution. The use of latex gloves and safety glasses is recommended to avoid exposure in case of breakage of the vial or other accidental spillage.

If the solution comes into contact with the skin or mucous membranes, the area should be washed thoroughly with soap and water. In the event of contact with the eyes, rinse them thoroughly with copious amounts of water. Exposure by inhalation should be avoided.

The medicinal product is for single use only. Any unused product or waste material should be disposed of in accordance with local requirements for cytotoxic agents.

7 MARKETING AUTHORISATION HOLDER

Actavis Group PTC ehf
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220 Hafnarfjordur,
Iceland

8 MARKETING AUTHORISATION NUMBER

PA 1380/3/1

9 DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

Date of first authorisation: 22nd August 2008

10 DATE OF REVISION OF THE TEXT

July 2009