ADIS DRUG PROFILE

Drugs 2003; 63 (21): 2317-2323
0012-6667/03/0021-2317/$33.00/0

Oral Fludarabine

Greg L. Plosker and *David P. Figgitt*

Adis International Limited, Auckland, New Zealand

Contents

Abstract

▲ Fludarabine is an antimetabolite antineoplastic agent used in the treatment of various haematological malignancies, particularly B-cell chronic lymphocytic leukaemia (CLL).

▲ An oral formulation of fludarabine has recently become available in the majority of European countries for the treatment of patients with relapsed or refractory B-cell CLL after initial treatment with an alkylating agent-based regimen. It is the first oral formulation of a purine analogue available for clinical use in B-cell CLL.

▲ Pharmacokinetic studies evaluating the bioavailability of oral fludarabine indicate that an oral dose of 40 mg/m^2/day would provide similar systemic drug exposure to the standard intravenous dose of 25 mg/m^2/day.

▲ A phase II study evaluated the clinical efficacy of six to eight cycles of oral fludarabine 40 mg/m^2/day for 5 days of each 28-day cycle in 78 patients with previously treated B-cell CLL. Depending on the criteria used, the overall response rate was 46.2% (20.5% complete response [CR], 25.6% partial response [PR]) or 51.3% (17.9% CR, 33.3% PR). These results were similar to the 48% overall response rate reported in a similar historical control group treated with intravenous fludarabine.

▲ Myelosuppression (WHO grade 3 or 4) was the most frequently reported adverse effect with oral fludarabine therapy. Other common adverse effects included infection and gastrointestinal disturbances, although these were usually of mild to moderate severity (WHO grade 1 or 2). Overall, the tolerability profile of oral fludarabine is similar to that of the intravenous formulation.

Features and properties of oral fludarabine (Fludara® Oral)	
Indication	
Previously treated B-cell chronic lymphocytic leukaemia (CLL) [focus of this review]	
Mechanism of action	
Antimetabolite antineoplastic (purine nucleoside analogue)	Inhibition of DNA synthesis (primary mechanism) and RNA synthesis (secondary mechanism)
Dosage and administration	
Recommended dosage	40 mg/m^2
Route of administration	Oral
Frequency of administration	Once daily for 5 days of each 28-day cycle (usually for six cycles)
Pharmacokinetic profile (mean values after single-dose administration of 50–90mg in fasting state for patients with lymphoid malignancies including CLL)	
Bioavailability	≈55%
Peak plasma concentration (90mg dose)	485–488 ng/mL
Time to peak plasma concentration	1.1–1.3h
Elimination half-life	26.5h
Adverse events	
Most frequently reported	Myelosuppression (granulocytopenia, leucocytopenia, thrombocytopenia and anaemia)
Other frequently reported	Infection, nausea/vomiting, diarrhoea

Fludarabine is an antimetabolite cytotoxic agent used for the treatment of patients with various lymphoid malignancies, primarily B-cell chronic lymphocytic leukaemia (CLL).[1] B-cell CLL is a disease of immunologically incompetent (but morphologically mature) lymphocytes that is generally not curable and usually occurs in middle-aged and elderly individuals,[2] affecting twice as many men as women.[3] The overall 5-year survival rate in patients with CLL is approximately 60%, although this varies depending on disease stage (e.g. Rai stages 0-IV; Binet stages A-C).[2]

The intravenous formulation of fludarabine has been available for a number of years. It is well established as an effective first-line treatment option in B-cell CLL[2] and recently received European marketing approval as first-line treatment for B-cell CLL.[4] It has also emerged as the preferred or standard second-line therapy for patients with B-cell CLL initially treated with an alkylating agent-based regimen,[5-9] although some authorities suggest that patients with refractory B-cell CLL should be enrolled in a clinical trial (i.e. to evaluate new or existing treatment regimens).[2,5]

In recent years, an oral formulation of fludarabine (Fludara®[1] Oral) has become available, first in the UK, then in the majority of other European countries, for the treatment of patients with B-cell CLL after initial therapy with an alkylating agent-containing regimen has failed.[10,11] It is the first commercially available oral formulation of a purine analogue for clinical use in B-cell CLL. The UK National Institute for Clinical Excellence (NICE) has since recommended oral fludarabine as second-line therapy for patients with B-cell CLL who have either failed, or are intolerant of, first-line chemotherapy, and who would otherwise have received combination chemotherapy with cyclophosphamide-based regimens.[3] The NICE guidelines also indicate that oral fludarabine is more cost effective than intravenous fludarabine, and suggest that patients are more likely to find the oral formulation acceptable because of its much greater convenience (e.g. hospital visits may be reduced). The use of oral fludarabine as second-line therapy for patients with B-cell CLL is the focus of this profile.

1. Pharmacodynamic Profile

- Fludarabine is a purine (adenine) nucleoside analogue and a member of the antimetabolite class of cytotoxic drugs.[1,11,12] It is a synthetic prodrug that is rapidly dephosphorylated to F-ara-A (9-β-*D*-arabinofuranosyl-2-fluoroadenine) by serum phosphatases.[1,12] F-ara-A is the main plasma metabolite of fludarabine evaluated in pharmacokinetic analyses (see section 2). Unlike the parent compound, which is highly polar at physiological pH, F-ara-A is able to enter cells where it undergoes phosphorylation to form the active moiety, F-ara-A triphosphate (F-ara-ATP).[1,12] Because F-ara-A is taken into cells by nucleoside transport systems of varying affinities, it is thought that this may provide a partial explanation for the observed therapeutic index of fludarabine.[12]
- The dominant mechanism of action of F-ara-ATP is inhibition of DNA synthesis, although effects on RNA synthesis also contribute to inhibition of cell growth.[1,12] Apoptosis (programmed cell death) has also been demonstrated in human leukaemia cell lines and may occur in both replicating and quiescent CLL cells.[1,12] The relative importance and specific mechanisms by which F-ara-ATP induces apoptosis requires further investigation.
- DNA synthesis is inhibited by a number of actions of F-ara-ATP.[1,12] Incorporation of F-ara-ATP into elongating nucleic acid chains results in the termination of DNA synthesis. F-ara-ATP is both a poor substrate for elongation and resistant to removal by DNA polymerases involved in DNA replication and repair. Priming of DNA synthesis and the joining together of DNA pieces are processes disrupted by F-ara-ATP through inhibition of DNA primase and DNA ligase. In addition, by inhibiting ribonucleotide reductase, F-ara-ATP reduces the cellular level of substrates for DNA polymerase required for DNA replication and repair, an action known as 'self-potentiation' because F-ara-ATP de-

1 Use of tradenames is for identification purposes only and does not imply product endorsement.

pletes the natural metabolites with which it competes for incorporation into DNA.[1,12]

2. Pharmacokinetic Profile

The pharmacokinetic properties of oral fludarabine have been evaluated in several studies, some of which involved an aqueous solution of fludarabine,[13-15] while more recent studies evaluated the marketed tablet formulation.[16-18] Collectively, these studies showed that an oral fludarabine dose of 40 mg/m^2/day would provide similar systemic drug exposure to an intravenous dose of 25 mg/m^2/day. Indeed, these pharmacokinetic data were the basis of the oral dosage regimen of fludarabine selected for clinical investigation in the key phase II multicentre trial conducted with the drug (see section 3).[19]

As mentioned in section 1, fludarabine is a prodrug, and the primary plasma metabolite is F-ara-A. Thus, pharmacokinetic analyses of oral fludarabine measured plasma and urine concentrations of F-ara-A (by high-performance liquid chromatography techniques) rather than fludarabine itself. The focus of this section is on studies using the marketed (10mg tablet) formulation of oral fludarabine. These pharmacokinetic analyses[16-18] were multicentre, randomised crossover studies in patients with previously treated B-cell CLL or low-grade (indolent) B-cell non-Hodgkin's lymphoma (NHL) and, unless stated otherwise, oral fludarabine was administered under fasting conditions.

- Foran et al.[17] demonstrated a linear, dose-proportional increase in area under the plasma concentration-time curve (AUC_{0-24}) for F-ara-A following single-dose oral administration of fludarabine 50, 70 and 90mg. The study was designed to replace the first dose of a standard 5-day cycle of intravenous fludarabine 25 mg/m^2/day with the oral test doses (50, 70 and 90mg) in random order during cycles 1–3 (n = 18) and with an intravenous test dose (50mg) on day 1 of cycle 4 (n = 15). Data from 18 patients who received all three oral doses showed that mean AUC values for the 50 (1760 ng • h/mL), 70 (2367 ng • h/mL) and 90mg (3016 ng • h/mL) doses increased by factors of 1.36 and 1.72 (minor calculation discrepancies presumably due to rounding). These values were very similar to the increases in dose by factors of 1.4 (i.e. from 50 to 70mg) and 1.8 (i.e. from 50 to 90mg). Peak plasma concentrations (C_{max}) of F-ara-A also increased in proportion to fludarabine dose over the 50–90mg range (mean values 306–485 ng/mL); mean time to achieve C_{max} (t_{max}) was 1.1–1.2h, which was independent of the oral dose administered.

- In the same study,[17] systemic bioavailability of oral fludarabine (50, 70 and 90mg as single doses) was determined in 15 patients who also received a single intravenous dose of fludarabine 50mg. Mean bioavailability was approximately 55% (range 54–56%) and was not related to dose. Between patients, bioavailability ranged from 30–80%; however, intraindividual variation in bioavailability across the dosage range of 50–90mg was low.

- Similar results were briefly reported by other investigators.[18] Mean systemic bioavailability of oral fludarabine was approximately 51% at steady-state on the basis of comparisons of AUC values of F-ara-A after multiple doses of fludarabine 50 mg/day orally or intravenously in 16 patients. This study also provided mean values for elimination half-life ($t_{1/2}\beta$ = 22.5h), C_{max} (300 ng/mL) and t_{max} (1.6h) after multiple daily doses of fludarabine 50mg orally.

- In a further study, the relative bioavailability of oral fludarabine was not affected by a high-fat meal, although the rate of systemic absorption was somewhat delayed.[16] During their first two cycles of therapy, fludarabine 90mg orally was administered on day 1 (with or without food in a randomised fashion), followed by intravenous fludarabine 25 mg/m^2/day on days 3–6. Mean values for AUC_{0-24} (3280 vs 3050 ng • h/mL) and AUC_{0-48} (4230 vs 3910 ng • h/mL) were marginally higher and t_{max} was somewhat delayed (2.2 vs 1.3h) for the fed versus fasted state, although these differences were not statistically significant and were deemed to be clinically irrelevant. Mean values for C_{max} (442 vs 488 ng/mL) and $t_{1/2}\beta$ (26.9 vs 26.5h) were similar between groups.

3. Therapeutic Trials

• A prospective, multicentre phase II study evaluated the clinical efficacy of oral fludarabine 40 mg/m^2/day for 5 days every 4 weeks for six to eight cycles as second-line therapy in patients with B-cell CLL.[19] The intention-to-treat (ITT) population comprised 78 patients who received oral fludarabine for relapsed or refractory disease; all patients had been previously treated with one or more regimens including an alkylating agent, the most common regimen being chlorambucil with or without prednisolone. The primary efficacy endpoint was response to treatment (complete response [CR] plus partial response [PR]) evaluated 3–5 weeks after the final cycle of drug therapy. Response criteria were those of the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) or the US National Cancer Institute (NCI).

• According to IWCLL criteria, the overall response rate was 46.2% (95% CI 34.8–57.8%); 20.5% and 25.6% of patients achieved CR and PR, respectively.[19] Using NCI criteria, the overall response rate was slightly higher (51.3% [95% CI 39.7–62.8%]), with 17.9% and 33.3% of patients achieving CR and PR, respectively.[19] Results were deemed to be similar to those achieved with intravenous fludarabine in a similar historical control group, of whom 48% responded to second-line therapy with parenteral fludarabine (figure 1).[20]

• Results of the phase II study[19] also showed the following: patients with less advanced disease (e.g. Binet stage A or B) had higher overall response rates than those with more advanced disease (e.g. Binet stage C); the optimal duration of therapy was six cycles for most patients; and WHO performance status was either improved (15.4%) or remained unchanged (55.1%) in the majority of patients.

• A response rate of 66.7% (12 of 18 patients; all PRs) was reported in another study of oral fludarabine after two cycles of therapy.[16] However, this trial was designed as a pharmacokinetic analysis (see section 2), included a mixed patient population (previously treated B-cell CLL [n = 10] and NHL [n = 8]) and involved administration of both oral (90mg on day 1) and intravenous fludarabine (25 mg/m^2/day on days 3–6) in both study cycles.

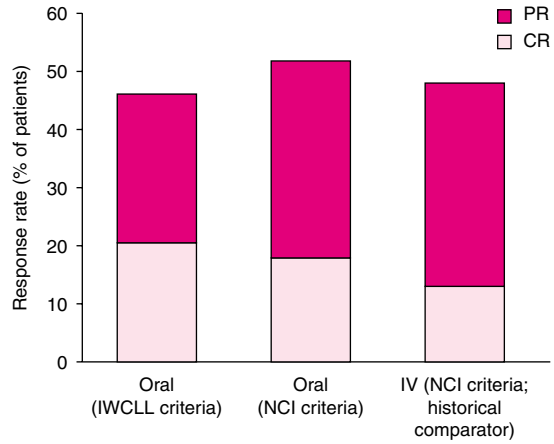

Fig. 1. Clinical response rates with oral fludarabine as second-line therapy in 78 patients with B-cell chronic lymphocytic leukaemia (CLL)[19] and with intravenous (IV) fludarabine in an historical control group of 48 similar patients.[20] In the multicentre phase II trial evaluating oral therapy, fludarabine 40 mg/m^2/day was administered for 5 days every 28 days for six cycles.[19] In the historical control group receiving IV therapy, fludarabine 25 mg/m^2/day was administered for 5 days every 28 days for six cycles.[20] In both studies there was provision for (up to two[19] or four[20]) additional cycles of therapy. All patients had been previously treated with one or more alkylating agent-containing regimens and had either failed to respond to or had relapsed during or after such treatment. Response (complete response [CR] plus partial response [PR]) was defined according to the International Workshop on Chronic Lymphocytic Leukemia (IWCLL) or US National Cancer Institute (NCI) criteria for the intent-to-treat population.

• Although not the focus of the current profile, oral fludarabine (as monotherapy[21] or in combination with cyclophosphamide[22]) has also been evaluated in previously untreated patients with B-cell CLL in multicentre, phase II trials (reported as abstracts/posters). As monotherapy, fludarabine 40 mg/m^2/day orally for 5 days every 4 weeks for six to eight cycles was associated with an overall response rate of 71.6% (95% CI 60.5–81.1%) according to IWCLL criteria for the ITT population of 81 patients.[21] CR was achieved in 37% of patients and PR in 34.6%.

• Oral fludarabine 30 mg/m^2/day plus oral cyclophosphamide 200 mg/m^2/day, both given for 5 days every 4 weeks for six cycles, was associated with an overall response rate of approximately 80% (ITT

analysis, NCI criteria) in 75 previously untreated patients with B-cell CLL.[22] CR was achieved in 49.3%, nodular PR in 5.3% and PR in 25.3%.

4. Tolerability

- The tolerability profile of intravenous fludarabine is well established, with the most common adverse effects being myelosuppression, fever/chills, infection, and nausea and vomiting.[23] Data from the phase II trials described in section 3 indicate that the oral formulation of fludarabine has a similar tolerability profile to that of the intravenous formulation.[19,21,22]
- WHO grade 3 or 4 adverse events reported in the multicentre phase II trial of oral fludarabine therapy in previously treated patients with B-cell CLL are presented in figure 2.[19] The most frequently reported adverse effect was myelosuppression; WHO grade 3 or 4 granulocytopenia (53.8%), leucocytopenia (28.2%), thrombocytopenia (25.6%) and anaemia (24.4%) occurred in a substantial proportion of patients.
- Other frequently reported adverse effects in the multicentre phase II trial in previously treated patients included infection (44.9%), nausea/vomiting (38.5%) and diarrhoea (38.4%); the vast majority of these were of mild to moderate severity (WHO grade 1 or 2).[19] Gastrointestinal adverse effects were more frequently reported with the oral formulation of fludarabine than previously reported with the intravenous formulation. However, most cases of nausea/vomiting associated with oral fludarabine were mild to moderate in severity (37.2% WHO grade 1 or 2 vs 1.3% WHO grade 3), and only 3.8% of patients reported WHO grade 3 diarrhoea. No patients withdrew from the study because of nausea/vomiting or diarrhoea.[19]
- A total of 30 severe adverse events were reported in 22 patients enrolled in the multicentre phase II trial of oral fludarabine in previously treated patients, including four cases of autoimmune haemorrhagic/haemolytic anaemia (AIHA).[19] AIHA has also been reported with oral fludarabine in previously untreated patients[21,22] and with intravenous fludarabine as second-line therapy.[20] Patients should be monitored for this relatively uncommon haematological toxicity during therapy with purine analogues such as fludarabine.[19]
- Preliminary data from multicentre phase II trials of oral fludarabine, with[22] or without cyclophosphamide,[21] in previously untreated patients with B-cell CLL showed that first-line treatment with the oral formulation was generally well tolerated.
- Additional tolerability data are provided from pharmacokinetic analyses in small groups of patients with previously treated B-cell CLL or low-grade B-cell NHL receiving varying dosages of oral fludarabine.[16,17] In general, the type, severity and frequency of haematological and other adverse events were broadly similar to those reported in the larger multicentre phase II study in previously treated patients with B-cell CLL.[19]
- A single case of progressive multifocal leucoencephalopathy (PML) has been reported in a 61-year-old man with B-cell CLL who developed the subacute demyelinating disorder 7 months after completing a course of oral fludarabine therapy.[24] PML results from infection of the oligodendrocytes by the JC virus and occurs almost exclusively in immunocompromised individuals. Although there have also been a small number of similar reports with intrave-

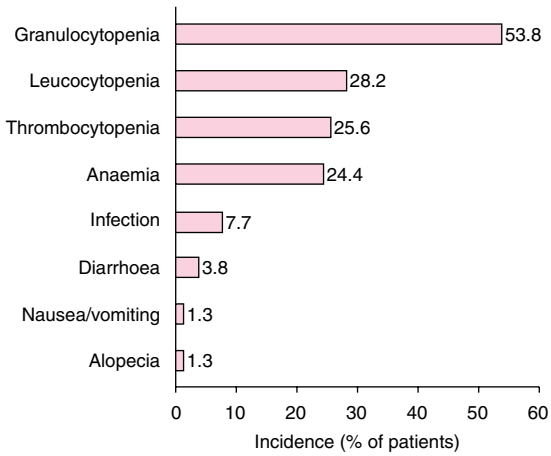

Fig. 2. Incidence of WHO grade 3 or 4 adverse effects with oral fludarabine as second-line therapy in 78 patients with B-cell chronic lymphocytic leukaemia in a multicentre phase II trial.[19] Patients received fludarabine 40 mg/m^2/day orally for 5 days every 28 days for six to eight cycles.

nous fludarabine,[25-27] a causal relationship between purine analogues and PML has not been established.[24]

5. Dosage and Administration

The recommended dosage of oral fludarabine is 40 mg/m^2/day for 5 days every 28 days for the treatment of patients with B-cell CLL who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating agent-containing regimen.[10,11] The usual duration of therapy is six 28-day cycles.[11] Oral fludarabine may be taken without regard to meals (see section 2).[16]

6. Oral Fludarabine: Current Status

Oral fludarabine tablets are available in the UK and most other European countries for second-line therapy in patients with B-cell CLL. Concentrations of the primary plasma metabolite of fludarabine achieved following administration of oral fludarabine at the recommended dosage are essentially equivalent to those achieved after a standard dosage regimen of intravenous fludarabine. Moreover, in patients with previously treated B-cell CLL, oral fludarabine achieved clinical response rates and had a tolerability profile similar to those associated with intravenous fludarabine in a similar historical group of patients. Guidelines from NICE in the UK recommend oral fludarabine as second-line therapy for patients with B-cell CLL who have either failed, or are intolerant of, first-line chemotherapy, and who would otherwise have received combination chemotherapy with cyclophosphamide-based regimens. The NICE guidelines found the oral formulation to be more cost effective than intravenous fludarabine, and suggested that oral fludarabine is more likely to be acceptable to patients (and caregivers) because it can be administered on an outpatient basis and may reduce the need for hospital visits. Phase II multicentre trials with oral fludarabine in previously untreated patients with B-cell CLL also indicate good response rates, suggesting a potential future role of oral fludarabine as first-line therapy.

References

1. Adkins JC, Peters DH, Markham A. Fludarabine: an update of its pharmacology and use in the treatment of haematological malignancies. Drugs 1997 Jun; 53 (6): 1005-37
2. National Cancer Institute. Chronic lymphocytic leukemia (PDQ®): treatment [online]. Available from URL: http://www.cancer.gov/cancer_information/ [Accessed 2003 Jul 15]
3. National Institute for Clinical Excellence. Technology Appraisal Guidance. No. 29. Guidance on the use of fludarabine for B-cell chronic lymphocytic leukaemia. London: National Institute for Clinical Excellence, 2001 Sep: 14
4. Schering AG. Fludara® (fludarabine phosphate) receives marketing approval in the UK as first-line treatment for B-cell chronic lymphocytic leukemia (media release 2003 Feb 11) [online]. Available from URL: www.schering.co.uk [Accessed 2003 Jun 12]
5. Kalil N, Cheson BD. Management of chronic lymphocytic leukaemia. Drugs Aging 2000 Jan; 16: 9-27
6. Kay NE, Hamblin TJ, Jelinek DF, et al. Chronic lymphocytic leukemia. Hematology (Am Soc Hematol Educ Program) 2002, 193-213
7. Montserrat E. Current and developing chemotherapy for CLL. Med Oncol 2002; 19 Suppl.: S11-9
8. Hamblin TJ. Achieving optimal outcomes in chronic lymphocytic leukaemia. Drugs 2001; 61 (5): 593-611
9. Keating MJ. Chronic lymphocytic leukemia. Semin Oncol 1999; 26 Suppl. 14 (5): 107-14
10. Schering AG. Schering launches oral formulation of Fludara® (media release 2003 Jan 22) [online]. Available from URL: www.schering.co.uk [Accessed 2003 Jun 9]
11. British National Formulary. 45th edition ed. London: British Medical Association and Royal Pharmaceutical Society of Great Britain, 2003
12. Gandhi V, Plunkett W. Cellular and clinical pharmacology of fludarabine. Clin Pharmacokinet 2002; 41 (2): 93-103
13. O'Rourke TJ, Burris HA, Rodriguez GI, et al. Phase I pharmacokinetic and bioavailability study of five daily intravenous and oral doses of fludarabine phosphate in patients with advanced cancer [abstract no. 736]. 33rd Annual Meeting of the American Society of Clinical Oncology; 1997 May 17-20; Denver, 210a
14. Kemena A, Keating M, Plunkett W. Plasma and cellular bioavailability of oral fludarabine [abstract no. 199]. Blood 1991 Nov 15; Suppl. 1 (10): 52a
15. Kemena A, Keating M, Plunkett W. Oral bioavailability of plasma fludarabine and fludarabine triphosphate (F-ara-ATP) in peripheral CLL cells [abstract no. 238]. Onkologie 1991 Oct; 14 (Suppl. 2): 83
16. Oscier D, Orchard JA, Culligan D, et al. The bioavailability of oral fludarabine phosphate is unaffected by food. Hematol J 2001; 2 (5): 316-21
17. Foran JM, Oscier D, Orchard J, et al. Pharmacokinetic study of single doses of oral fludarabine phosphate in patients with "low-grade" non-Hodgkin's lymphoma and B-cell chronic lymphocytic leukemia. J Clin Oncol 1999 May; 17 (5): 1574-9
18. Klein M, Ludwig W-D, Fülle HH, et al. 2F-ara-A pharmacokinetics including systemic availability during treatment with fludarabine phosphate given either perorally as an immediate release tablet formulation or intravenously as a solution [abstract no. 525]. Onkologie 1997 Oct; 20 Suppl. 1: 137

19. Boogaerts MA, Van Hoof A, Catovsky D, et al. Activity of oral fludarabine phosphate in previously treated chronic lymphocytic leukemia. J Clin Oncol 2001 Nov 15; 19 (22): 4252-8
20. Johnson S, Smith AG, Löffler H, et al. Multicentre prospective randomised trial of fludarabine versus cyclophosphamide, doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic leukaemia. The French Cooperative Group on CLL. Lancet 1996; 347: 1432-8
21. Rossi J-F, Van Hoof A, De Bock R, et al. Oral fludarabine phosphate as first-line treatment of chronic lymphocytic leukemia [abstract no. 1491 plus poster no. 657-I]. Blood 2002 Nov 16; 100 (11 Pt 1): 384-5
22. Cazin B, Maloum K, Divine M, et al. Oral fludarabine and cyclophosphamide in previously untreated CLL: preliminary data on 75 pts [abstract no. 773]. Blood 2002 Nov 16; 100 (11 Pt 1): 206a
23. Mosby's Drug Consult: Fludarabine phosphate [online]. Available from URL: http://www.mosbydrugs.com [Accessed 2003 Jul 7]
24. Cid J, Revilla M, Cervera A, et al. Progressive multifocal leukoencephalopathy following oral fludarabine treatment of chronic lymphocytic leukemia. Ann Hematol 2000 Jul; 79 (7): 392-5
25. Cohen RB, Abdallah JM, Gray JR, et al. Reversible neurologic toxicity in patients treated with standard-dose fludarabine phosphate for mycosis fungoides and chronic lymphocytic leukemia. Ann Intern Med 1993; 118: 114-6
26. Johnson PWM, Fearnley J, Domizio P, et al. Neurological illness following treatment with fludarabine. Br J Cancer 1994; 70: 966-8
27. Zabernigg A, Maier H, Thaler J, et al. Late-onset fatal neurological toxicity of fludarabine [letter]. Lancet 1994; 344: 1780

Correspondence: *Greg L. Plosker*, Adis International Limited, 41 Centorian Drive, Private Bag 65901, Mairangi Bay, Auckland 1311, New Zealand.
E-mail: demail@adis.co.nz