Fludarabine phosphate
for the first-line treatment of
Chronic Lymphocytic Leukaemia

Appendices to NICE STA Submission

1. Appendices

Appendix 1: Other sources searched

1.   The American Society of Hematology Annual Meeting Abstracts (where there are searchable abstracts that can be accessed via the internet at http://www.hematology.org/meetings/. These were abstracts for the years 2003 – 2005. Initial selection of abstracts was done by using the term 'CLL'. Resulting abstracts were then handpicked by title to obtain abstracts in CLL, previously untreated patients only, and then handpicked by abstract using the inclusion and exclusion criteria.

   - 47th ASH Annual Meeting, December 10-13 2005
     http://www.abstracts2view.com/hem_ash05atlanta/

   - 46th ASH Annual Meeting, December 4-7 2004
     http://www.abstracts2view.com/hem_sandiego2004/

   - 45th ASH Annual Meeting, December 6-9 2003
     http://www.abstracts2view.com/hem/

2.   British Society for Haematology, http://www.b-s-h.org.uk/

3.   Bandolier, http://www.jr2.ox.ac.uk/bandolier/

4.   eGuidelines, http://www.eguidelines.co.uk/

5.   MRC website, http://www.mrc.ac.uk

6.   Scottish Intercollegiate Guidelines Network (SIGN), http://www.sign.ac.uk/

Appendix 2: Search strategies used

1.1.1. Studies in First line treatment of Chronic Lymphocytic Leukaemia

PUBMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi)

This was accessed via the internet and provides bibliographic information including MEDLINE (1966 – January 2006), OLDMEDLINE (1950 through 1965) and MEDLINE In Process citations. Search undertaken January 2006.

#1.   Search "Leukemia, B-Cell" [MeSH]

#2.   Search cll[Title/Abstract] OR b-cll[Title/Abstract]

#3.   Search chronic AND lymphocytic AND leukemia[Title/Abstract]

#4.   Search chronic AND lymphocytic AND leukaemia[Title/Abstract]

#5.   Search #1 OR #2 OR #3 OR #4

#6.   Search "Study Characteristics"[Publication Type]

#7.   Search "Single-Blind Method"[MeSH]

#8.   Search "Double-Blind Method"[MeSH]

#9.   Search "Cross-Over Studies"[MeSH]

#10.   Search "Follow-Up Studies"[MeSH]

#11.   Search "Evaluation Studies"[MeSH]

#12.   Search "Epidemiologic Study Characteristics"[MeSH]

#13.   Search "Prospective Studies"[MeSH]

#14.   Search #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13

#15.   Search Study[Title/Abstract] OR Trial[Title/Abstract]

#16.   Search #14 OR #15

#17.   Search #5 AND #16 Limits: Humans

#18.   Search naive Field: Title/Abstract, Limits: Humans

#19.   Search untreated Field: Title/Abstract, Limits: Humans

#20.   Search first AND line Field: Title/Abstract, Limits: Humans

#21.   Search first-line Field: Title/Abstract, Limits: Humans

#22.   Search initial Field: Title/Abstract, Limits: Humans

#23.   Search #18 OR #19 OR #20 OR #21 OR #22 Field: Title/Abstract, Limits: Humans

#24.   Search #23 AND #17 Field: Title/Abstract, Limits: Humans (692 hits)

#25.   Search fludarabine OR cyclophosphamide OR chlorambucil Field: Title/Abstract, Limits: Humans

#26.   Search #24 AND #25 (214 hits)

#27.   Search "Randomized Controlled Trials"[MeSH] Limits: Humans

#28.   Search "Randomized Controlled Trial"[Publication Type] Limits: Humans

#29.   Search "Controlled Clinical Trials"[MeSH] Limits: Humans

#30.   Search randomized OR randomised Field: Title/Abstract, Limits: Humans

#31.   Search #27 OR #28 OR #29 OR #30

#32.   Search #26 AND #31 Field: Title/Abstract, Limits: Humans (52 hits)

EMBASE via DataStar
EMZZ which contains material from 1974 to January 2006. Search undertaken January 2006.

1. cll.TI,AB.

2. cll

3. b-cll.TI,AB.

4. CHRONIC-LYMPHATIC-LEUKEMIA#.DE. OR B-CELL-LEUKEMIA#.DE.

5. (chronic ADJ lymphocytic ADJ leukaemia).TI,AB.

6. (chronic ADJ lymphocytic ADJ leukemia).TI,AB.

7. (1 OR 2 OR 3 OR 4 OR 5 OR 6).TI,AB.

8. study

9. controlled ADJ trial

10. randomised ADJ controlled

11. randomis$

12. clinical ADJ (trial OR study)

13. prospective study/

14. double blind

15. trial$.TI,AB.

16. (8 OR 9 OR 10 OR 11 OR 12 OR 13 OR 14 OR 15).TI,AB. Restricted to human

17. 7 AND 16

18. naïve.TI,AB.

19. untreated.TI,AB.

20. first ADJ line

21. (18 OR 19 OR 20).TI,AB.

22. 17 AND 21

23. (fludarabine OR cyclophosphamide OR chlorambucil).TI,AB.

24. 22 AND 23

Cochrane Library 2005 Issue 4

This search allowed for collection of references for the Clinical and Cost Effectiveness sections.

ID	Search	Hits
#1	**chronic** in **All Fields** and **lymphocytic** in **All Fields** and **leukemia** in **All Fields** in **all products**	303
#2	**chronic** in **All Fields** and **lymphocytic** in **All Fields** and **leukaemia** in **All Fields** in **all products**	79
#3	**untreated** in **All Fields** or **naive** in **All Fields** in **all products**	7173
#4	**first** in **All Fields** and **line** in **All Fields** in **all products**	3237
#5	(**#3** OR **#4**)	10147
#6	(**#1** OR **#2**)	320
#7	(**#5** AND **#6**)	76
#8	MeSH descriptor **Randomized Controlled Trials** explode all trees in **MeSH products**	8416
#9	(**#7** AND **#8**)	5

1.1.2. Cost and quality of life studies in first line CLL

PUBMed (http://www.ncbi.nlm.nih.gov/entrez/query.fcgi)

This was accessed via the internet and provides bibliographic information including MEDLINE (1966 – January 2006), OLDMEDLINE (1950 through 1965) and MEDLINE In Process citations. Search undertaken January 2006.

#1.   Search "Leukemia, B-Cell" [MeSH]

#2.   Search cll[Title/Abstract] OR b-cll[Title/Abstract]

#3.   Search chronic AND lymphocytic AND leukemia[Title/Abstract]

#4.   Search chronic AND lymphocytic AND leukaemia[Title/Abstract]

#5.   Search #1 OR #2 OR #3 OR #4

#6.   Search naive Field: Title/Abstract, Limits: Humans

#7.   Search untreated Field: Title/Abstract, Limits: Humans

#8.   Search first AND line Field: Title/Abstract, Limits: Humans

#9.   Search #6 OR #7 OR #8 Field: Title/Abstract, Limits: Humans

#10.   Search #5 AND #9

#11.   Search "Health Care Economics and Organizations"[MeSH] Field: Title/Abstract

#12.   Search "Economics"[MeSH] Field: Title/Abstract

#13.   Search "Costs and Cost analysis"[MeSH]

#14.   Search "Health Care Costs"[MeSH]

#15.   Search"Quality of Life"[MeSH]

#16.   Search (costs OR cost OR costed OR costly OR costing).tw.

#17.   Search (economic$ OR pharmacoeconomic$ OR price$ OR pricing).tw.

#18.   Search (#10 OR #11 OR #12 OR#13 OR #14 OR #15 OR #16 or #17)

#19.   Search #10 and #18

EMBASE via DataStar

EMZZ which contains material from 1974 to January 2006. Search undertaken for cost and quality of life studies in January 2006.

1. cll.TI,AB.

2. cll

   Cost and quality of life studies in first line CLL

3. b-cll.TI,AB.

4. CHRONIC-LYMPHATIC-LEUKEMIA#.DE. OR B-CELL-LEUKEMIA#.DE.

5. (chronic ADJ lymphocytic ADJ leukaemia).TI,AB.

6. (chronic ADJ lymphocytic ADJ leukemia).TI,AB.

7. (1 OR 2 OR 3 OR 4 OR 5 OR 6).TI,AB.

8. naïve.TI,AB.

9. untreated.TI,AB.

10. first ADJ line

11. (8 OR 9 OR 10).TI,AB.

12. 11 AND 7

13. Economic-Aspect#.DE. OR Economic-Evaluation#.DE. OR Health-Economics#.DE.

14. Cost#.W.DE.

15. Cost-Benefit-Analysis.DE.

16. Cost-Utility-Analysis.DE.

17. Cost-Effectiveness-Analysis.DE.

18. (cost or costs or costed or costly or costing).TI,AB.

19. Economics.DE.

20. Quality-of-life#.DE.

21. Treatment-outcome#.DE.

22. outcome-assessment#.DE.

23. (13 OR 14 OR 15 OR 16 OR 17 OR 18 OR 19 OR 20 OR 21 OR 22)

24. 12 AND 24

Appendix 3: Studies excluded from the review of clinical effectiveness

Reference	Reason for exclusion
Adkins JC, Peters DH, Markham A. (1997) Fludarabine. An update of its pharmacology and use in the treatment of haematological malignancies. *Drugs* 53(6): 1005-1037.	*Review – relevant RCTs included as individual study.*
Andritsos L, Khoury H. (2002) Chronic lymphocytic leukemia. *Curr Treat Options Oncol* 3(3): 225-231.	*Review – relevant RCTs included as individual study.*
Binet JL, Dighiero G. (1994) Comparison of fludarabine (FDB), CAP and CHOP in previously untreated stage B and C chronic lymphocytic leukemia (CLL). First interim results of a randomized clinical trial in 247 patients. *Blood* 84: 461a Abstract 1831.	*Fludarabine not compared with either FC or chlorambucil*
Binet JL, Chastang C, Chevret S, Dighiero G, Maloum K, Travade P, et al. (1993) Comparison of fludarabine (FDB), CAP and CHOP in advanced previously untreated chronic lymphocytic leukemia (CLL). Preliminary results of a randomized clinical trial. *Blood* 82: 140a Abstract 546.	*Fludarabine not compared with either FC or chlorambucil*
Cheson BD, Vena DA, Sorenson JM, Fallavollita. (1991) Current status of U.S. clinical trials in chronic lymphocytic leukemia. *Leukemia and Lymphoma* 5 (SUPPL): 119-122.	*Review – relevant RCTs included as individual study.*
Cheze S, Leporrier M. Chronic lymphocytic leukemia: Strategies for optimizing therapy. (2002) *American Journal of Cancer* 1(2): 127−143.	*Review – relevant RCTs included as individual study.*
CLL Trialists' Collaborative Group. (1999) Chemotherapeutic options in chronic lymphocytic leukemia: a meta-analysis of the randomized trials. *J Natl Cancer Inst.* 91(10): 861-868.	*Does not include the intervention fludarabine.*
Else M, Smith AG, Hawkins K, Crofts S, Course M, Richards S et al (2005) Quality of Life in the LRF CLL4 Trial. *Blood* 106 (11): Abstract 2111.	*Does not contain clinical efficacy data.*

Reference	Reason for exclusion
Flinn IW, Grever MR, Hussein MA (2003) Phase III randomised study of fludarabine with or without cyclophosphamide in patients with previously untreated Chronic Lymphocytic Leukaemia. National Institute of Health, ClinicalTrials Gov [http://www.clinicaltrials.gov]	*Brief protocol details only. More info in Flinn 2004.*
Flinn I, Byrd C, Morrison C, Jamison J, Diehl L, Murphy T, et al. (2002) Fludarabine and cyclophosphamide with filgrastim support in patients with previously untreated indolent lymphoid malignancies. *Blood* 96(1): 71-75.	*Not an RCT*
Grever MR, Lucas DM, Dewald GW, Neuberg DS, Flinn IW, Appelbaum FR et al. (2004) Outcome of Treatment with Fludarabine Versus Fludarabine and Cyclophosphamide in Chronic Lymphocytic Leukemia (CLL) Is Adversely Impacted by High Risk Genetic Features: Results from ECOG 2997. *Blood* 104 (11): Abstract 3487.	*Clinical outcomes reported elsewhere (Flinn 2004).*
Hancock S, Wake B, Hyde C. West Midlands Health Technology Assessment Collaboration. (2002) Fludarabine as first line therapy for chronic lymphocytic leukaemia.	*Review – relevant RCTs included as individual study.*
Hyde C, Wake B, Bryan S, Barton P, Fry-Smith A, Davenport C, et al. (2002) Fludarabine as second-line therapy for B cell chronic lymphocytic leukaemia: a technology assessment.	*Not discussing first line studies.*
Jaksic B, Brugiatelli M, Suciu S, Baumelou E, Wijermans P, Delmer A et al. (2000) Fludarabine versus high-dose continuous chlorambucil in untreated patients with B-CLL: results of CLL1 EORTC randomized trial. *Hematology and Cell Therapy* 42(1): 97.	*Does not use NCI response assessment criteria.*
Jaksic B, Brugiatelli M, Suciu S, Baumelou E, Wijermans PW, Delmer A et al. (1998) Randomized phase II study in untreated B-cell chronic lymphocytic leukaemia (B-CLL) comparing fludarabine (FAMP) vs high dose continuous chlorambucil (HD-CLB). *Blood* 92(10) Suppl 1 (Pt 1): 103a, Abstract 421.	*Does not use NCI response assessment criteria.*

Reference	Reason for exclusion
Jaksic B, Delmer A, Brugiatelli M, Suciu S, Baumelou E, Roozendaal KJ, et al. (1996) Fludarabine vs. high dose continuous chlorambucil: interim analysis of a randomized phase II study in untreated B-cell chronic lymphocytic leukemia (B-CLL). *Blood* 88(10): 588a.	*Does not use NCI response assessment criteria.*
Johnson S, Smith AG, Loffler H, Osby E, Juliusson G, Emmerich B et al. (1996) Multicentre prospective randomised trial of fludarabine versus cyclophosphamide, doxorubicin, and prednisone (CAP) for treatment of advanced-stage chronic lymphocytic leukaemia. *Lancet*. 347(9013): 1432-1438.	*Fludarabine not being compared with chlorambucil or FC*
Kalil N, Cheson BD. (2000) Management of chronic lymphocytic leukaemia. *Drugs & Aging* 16(1): 9-27	*Review – relevant RCTs included as individual study.*
Keating MJ, O'Brien S, Lerner S, Koller C, Beran M et al. (1998) Long-term follow-up of patients with chronic lymphocytic leukemia (CLL) receiving fludarabine regimens as initial therapy. *Blood* 92(4): 1165-1171.	*Not an RCT. Pooled data from 3 non-comparative studies.*
Keating MJ, O'Brien S, McLaughlin P, Dimopoulos M, Gandhi V, Plunkett W, et al. (1996) Clinical experience with fludarabine in hemato−oncology. *Hematology and Cell Therapy* 38 (SUPPL. 2): S83−S91.	*Review – relevant RCTs included as individual study.*
Keating MJ, McLaughlin P, Plunkett W, Robertson LE, O'Brien S, Gandhi V, et al. (1994a) Fludarabine--present status and future developments in chronic lymphocytic leukemia and lymphoma. *Ann Oncol* 5 (Suppl 2): 79-83.	*Review – relevant RCTs included as individual study.*
Keating MJ, Estey E, O'Brien S, Kantarjian H, Robert-son LE, Plunkett W. (1994b) Clinical experience with fludarabine in leukaemia. *Drugs*. 47 (Suppl 6): 39-49	*Review – relevant RCTs included as individual study.*
Keating MJ, O'Brien S, Plunkett W, Robertson LE, Gandhi V, Estey E, et al. (1994c) Fludarabine phosphate: A new active agent in hematologic malignancies. *Seminars in Hematology* 31/1: 28−39.	*Review – relevant RCTs included as individual study.*

Reference	Reason for exclusion
Keating MJ, O'Brien S, Kantarjian H, Plunkett W, Estey E, Koller C, et al. (1993a) Long-term follow-up of patients with chronic lymphocytic leukemia treated with fludarabine as a single agent. *Blood*. 81(11): 2878-2884.	*Not an RCT*
Keating MJ, O'Brien S, Robertson LE, Kantarjian H, Dimopoulos M, McLaughlin P, et al. (1993b) New initiatives with fludarabine monophosphate in hematologic malignancies. *Seminars in Oncology* 20(SUPPL. 7): 13–20.	*Not an RCT*
Kimby E, Brandt L, Nygren P, Glimelius B. (2001) A systematic overview of chemotherapy effects in B-cell chronic lymphocytic leukaemia. *Acta Oncol*. 40(2-3): 224-230.	*Review – relevant RCTs included as individual study.*
Lamanna N. (2005) Advances in the treatment of chronic lymphocytic leukemia. *Curr Oncol Rep*. 7(5): 333-338.	*Review – relevant RCTs included as individual study.*
Leporrier M. (2004) Role of fludarabine as monotherapy in the treatment of chronic lymphocytic leukaemia. *The Hematology Journal* 5 (suppl 1): S10-S19.	*Review – relevant RCTs included as individual study*
Leporrier M, Chevret S, Cazin B, Boudjerra N, Feugier P, Desablens B et al. (2001) Randomized comparison of fludarabine, CAP, and ChOP in 938 previously untreated stage B and C chronic lymphocytic leukemia patients. *Blood* 98(8): 2319-2325.	*Fludarabine not compared with either FC or chlorambucil*
Leporrier M, Chevret S, Cazin B, Feugier P, Rapp MJ, Boudjerra N et al. (1997) Randomized comparison of fludarabine, CAP and ChOP in 695 previously untreated stage B and C chronic lymphocytic leukemia (CLL). Early stopping of the CAP accrual. *Blood* 90(10) Suppl 1 (Pt 1): 529a, Abstract 2357.	*Fludarabine not compared with either FC or chlorambucil*
Montserrat E. (2002) Current and developing chemotherapy for CLL. *Med Oncol*. 19 Suppl: S11-S19.	*Review – relevant RCTs included as individual study.*

Reference	Reason for exclusion
O'Brien SM, Kantarjian HM, Cortes J, Beran M, Koller CA, Giles FJ, et al. (2001) Results of the fludarabine and cyclophosphamide combination regimen in chronic lymphocytic leukemia. *J Clin Oncol*. 19(5): 1414-1420.	*Not an RCT. Non-compar-ative study. Less than 50 patients receiving fludara-bine & cyclophospham-ide as first-line therapy.*
Plosker GL, Figgitt DP. (2003) Oral fludarabine. *Drugs* 63(21): 2317-2323.	*Review – relevant RCTs included as individual study.*
Richards S. (2005) Fludarabine increases complete response but not survival compared with conventional alkylator-based regimens for previously untreated chronic lymphocytic leukaemia. *Cancer Treat Rev*. 31(4): 332-335.	*Review – relevant RCTs included as individual study. – included in meta-analysis section.*
Richards S, Clarke M, Wheatley K, Peto R. (1999) Chemotherapeutic options in chronic lymphocytic leukaemia: A meta-analysis of the randomised trials. *Journal of the National Cancer Institute* 91(10): 861-868.	*Review – relevant RCTs included as individual study.*
Robak T. (2002) The role of nucleoside analogues in the treatment of chronic lymphocytic leukemia-lessons learned from prospective randomized trials. *Leuk Lymphoma* 43(3): 537-548	*Review – relevant RCTs included as individual study.*
Rossi JF, van Hoof A, de Boeck K, Johnson SA, Bron D, Foussard C, et al. (2004) Efficacy and safety of oral fludarabine phosphate in previously untreated patients with Chronic Lymphocytic Leukemia. *J Clin Oncol*. 22(7): 1260-1267	*Not an RCT.*
Schiavone EM, De Simone M, Palmieri S, Annunziata M, Pocali B, Copia C, et al. (2003) Fludarabine plus cyclophoshamide for the treatment of advanced chronic lymphocytic leukaemia. *Eur J Haematol*. 71(10; 23-28.	*Not an RCT*

Reference	Reason for exclusion
Schmitt B, Wendtner CM, Bergmann M, Busch R, Franke A, Pasold R, et al. (2002) Fludarabine combination therapy for the treatment of chronic lymphocytic leukemia. *Clin Lymphoma* 3(1): 26-35.	*More recent information on this abstract is included in the review. See Eichhorst 2006.*
Spriano M, Clavio M, Carrara P, Canepa L, Miglino M, Pierri I, et al. (1994) Fludarabine in untreated and previously treated B-CLL patients: a report on efficacy and toxicity. Haematologica 79(3): 218-224.	*Not an RCT.*
Stephens JM, Gramegna P, Laskin B, Botteman MF, Pashos CL. (2005) Chronic lymphocytic leukemia: economic burden and quality of life: literature review. *Am J Ther*. 12(5): 460-466.	*Focuses on quality of life and economics of CLL treatment rather than clinical effectiveness parameters.*
Stelitano C, Morabito F, Kropp M, Callea V, Iuliano F, Oriana V, et al. (1999) Fludarabine treatment in B-cell chronic lymphocytic leukaemia: Response, toxicity and survival analysis in 47 cases. *Haematologica* 84(4): 317-323.	*Not an RCT*
Steurer M, Pall G, Bohlius J, Schwarzer G, Greil R. Purine. (2003) Antagonists for Chronic Lymphocytic Leukaemia. *The Cochrane Database of Systematic Reviews*: Protocols 2003 Issue 3.	*Protocol only available. Not an RCT.*
Tothova E, Kafkova A, Fricova M, Guman T, Stecova N. (2003) Fludarabine combined with cyclophosphamid is highly effective in the treatment of chronic lymphocytic leukemia. *Neoplasma* 50(6): 433-437.	*Non-comparative study.*
Wilhelm M, Tony HP, Rueckle-Lanz H, Wilms K. (1997) First-line therapy of advanced chronic lymphocytic leukemia. *Leukemia* 11 Suppl 2: S14-S18.	*Review – relevant RCTs included as individual study.*

Reference	Reason for exclusion
Yee IC, Browman G, Wong S, Esmail R, Abu-Zahra H, Crump M, et al. (1999) The role of fludarabine in intermediate – and high – risk chronic lymph-ocytic leukaemia. *Current Oncology* 6(2): 90-102.	*Review – relevant RCTs included as individual study. Review – relevant RCTs included as individual study.*
[No authors listed] (2005) Fludarabine: new indication. First-line treatment of CLL: unconvincing evidence. *Prescrire Int*. 14(75): 3-5.	*Review – relevant RCTs included as individual study.*

Appendix 4: Data Extraction Form

First Author, year	
Study Location & Population	
Trial design Any cross-over?	
Primary Endpoints	
Number entered into study / Number randomised / Number of patients evaluated for response etc / Evaluated as intention-to-treat?	
Mean no of cycles	
Drop-outs or exclusions before assessments / Losses to follow-up	
Inclusion criteria	
Exclusion criteria	
Baseline characteristics incl age / Baseline comparability	
Length of study / follow-up	
Intervention & dose	

Comparator(s) & dose	
Concomitant therapy	
Response rates & duration	
Median progression-free survival & overall survival	
Pts evaluated for adverse events	
Deaths during Rx	
Thrombocytopenia	
Anaemia	
Neutropenia	
Infections	
Other adverse events	
Quality of life info	
Statistical Analysis incl study power	

Other notes:

Appendix 5: CONSORT flowcharts for RCTs

Catovsky 2005

Assessed for eligibility ($n = 783$)

Enrollment

Is it Randomised ? YES

Excluded ($n = 6$)

Not meeting inclusion criteria ($n = na$)

Refused to participate ($n = na$)

Other reasons ($n = na$)

Allocation

Chlorambucil

Allocated to intervention ($n = 387$)

Received allocated intervention ($n = na$)

Did not receive allocated intervention ($n = na$)

Give reasons:

Fludarabine

Allocated to intervention ($n = 194$)

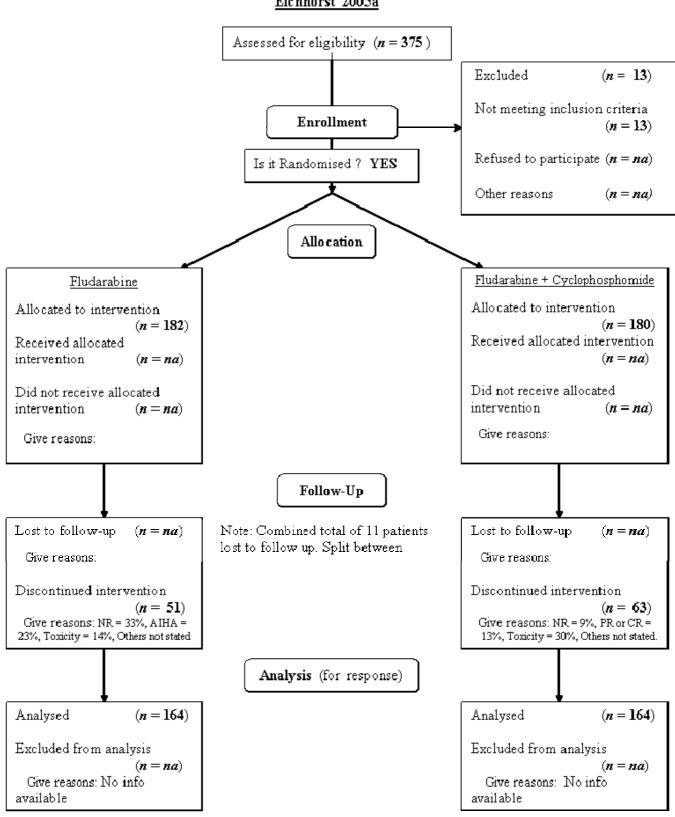Received allocated intervention ($n = na$)

Did not receive allocated intervention ($n = na$)

Give reasons:

Fludarabine + Cyclophosphomide

Allocated to intervention ($n = 196$)

Received allocated intervention ($n = na$)

Did not receive allocated intervention ($n = na$)

Give reasons:

Follow-Up

Lost to follow-up ($n = na$)

Give reasons:

Discontinued intervention ($n = na$)

Give reasons:

Lost to follow-up ($n = na$)

Give reasons:

Discontinued intervention ($n = na$)

Give reasons:

Lost to follow-up ($n = na$)

Give reasons:

Discontinued intervention ($n = na$)

Give reasons:

Analysis

Analysed ($n = na$)

Excluded from analysis ($n = na$)

Give reasons:

Analysed ($n = na$)

Excluded from analysis ($n = na$)

Give reasons:

Analysed ($n = na$)

Excluded from analysis ($n = na$)

Give reasons:

Eichhorst 2005a

Assessed for eligibility ($n = 375$)

Enrollment

Is it Randomised ? **YES**

Excluded   ($n = 13$)

Not meeting inclusion criteria
($n = 13$)

Refused to participate ($n = na$)

Other reasons   ($n = na$)

Allocation

Fludarabine

Allocated to intervention
($n = 182$)
Received allocated
intervention   ($n = na$)

Did not receive allocated
intervention   ($n = na$)

  Give reasons:

Fludarabine + Cyclophosphomide

Allocated to intervention
($n = 180$)
Received allocated intervention
($n = na$)

Did not receive allocated
intervention   ($n = na$)

  Give reasons:

Follow-Up

Lost to follow-up   ($n = na$)

  Give reasons:

Discontinued intervention
($n = 51$)
Give reasons: NR = 33%, AIHA =
23%, Toxicity = 14%, Others not stated

Note: Combined total of 11 patients
lost to follow up. Split between

Lost to follow-up   ($n = na$)

  Give reasons:

Discontinued intervention
($n = 63$)
Give reasons: NR = 9%, PR or CR =
13%, Toxicity = 30%, Others not stated.

Analysis (for response)

Analysed   ($n = 164$)

Excluded from analysis
($n = na$)
  Give reasons: No info
available

Analysed   ($n = 164$)

Excluded from analysis
($n = na$)
  Give reasons: No info
available

Eichhorst 2005B

Assessed for eligibility ($n = 191$)

Enrollment

Is it Randomised ? **YES**

Excluded   ($n = na$)

Not meeting inclusion criteria
                                    ($n = na$)

Refused to participate ($n = na$)

Other reasons   ($n = na$)

Allocation

Fludarabine

Allocated to intervention
                                ($n =$ 92)
Received allocated
intervention   ($n = na$)

Did not receive allocated
intervention   ($n = na$)

 Give reasons:

Chlorambucil

Allocated to intervention
                                ($n =$ 99)
Received allocated intervention
                                ($n = na$)

Did not receive allocated
intervention   ($n = na$)

 Give reasons:

Follow-Up

Lost to follow-up   ($n = na$)

 Give reasons:

Discontinued intervention
                                ($n = na$)
 Give reasons:

Lost to follow-up   ($n = na$)

 Give reasons:

Discontinued intervention
                                ($n = na$)
 Give reasons:

Analysis

Analysed   ($n = na$)

Excluded from analysis
                                ($n = na$)
 Give reasons:

Analysed   ($n = na$)

Excluded from analysis
                                ($n = na$)
 Give reasons:

Flinn 2004

Assessed for eligibility ($n = 278$)

Enrollment

Is it Randomised ? **YES**

Excluded   ($n = 9$)

Not meeting inclusion criteria
                    ($n = 5$)

Refused to participate ($n = 4$)

Other reasons   ($n = na$)

Allocation

Fludarabine

Allocated to intervention
                    ($n = 137$)
Received allocated
intervention   ($n = na$)

Did not receive allocated
intervention   ($n = na$)

  Give reasons:

Fludarabine + Cyclophosphomide

Allocated to intervention
                    ($n = 141$)
Received allocated intervention
                    ($n = na$)

Did not receive allocated
intervention   ($n = na$)

  Give reasons:

Follow-Up

Lost to follow-up   ($n = na$)

  Give reasons:

Discontinued intervention
                    ($n = na$)
  Give reasons:

Lost to follow-up   ($n = na$)

  Give reasons:

Discontinued intervention
                    ($n = na$)
  Give reasons:

Analysis (for response)

Analysed   ($n = 121$)

Excluded from analysis
                    ($n = na$)
  Give reasons:

Analysed   ($n = 125$)

Excluded from analysis
                    ($n = na$)
  Give reasons:

Rai 2000

Assessed for eligibility ($n = 544$)

Enrollment

Is it Randomised ? YES

Excluded   ($n = 35$)

Not meeting inclusion criteria
                                      ($n = 32$)

Refused to participate ($n = na$)

Other reasons   ($n = 3$)

Allocation

Fludarabine

Allocated to intervention
                              ($n = 195$)
Received allocated
intervention   ($n = 179$)

Did not receive allocated
intervention   ($n = 16$)

Give reasons: 15 x ineligible,
1 x drop-out before

Fludarabine + Chlorambucil

Allocated to intervention
                              ($n = 149$)
Received allocated
intervention   ($n = 137$)

Did not receive allocated
intervention   ($n = 12$)

Give reasons: 10 x ineligible,
2 x drop-out before

Chlorambucil

Allocated to intervention
                              ($n = 200$)
Received allocated intervention
                              ($n = 193$)

Did not receive allocated
intervention   ($n = 7$)

Give reasons: 7 x ineligible

Follow-Up

Lost to follow-up   ($n = 9$)

  Give reasons:

Discontinued intervention
                              ($n = na$)
  Give reasons:

Lost to follow-up   ($n = 13$)

  Give reasons:

Discontinued intervention
                              ($n = na$)
  Give reasons:

Lost to follow-up   ($n = 7$)

  Give reasons:

Discontinued intervention
                              ($n = na$)
  Give reasons:

Analysis

Analysed   ($n = na$)

Excluded from analysis
                              ($n = na$)
  Give reasons:

Analysed   ($n = na$)

Excluded from analysis
                              ($n = na$)
  Give reasons:

Analysed   ($n = na$)

Excluded from analysis
                              ($n = na$)
  Give reasons:

Spriano 2000

Assessed for eligibility $(n = 150)$

Enrollment

Is it Randomised ? **YES**

| Excluded | $(n = na)$ |

Not meeting inclusion criteria
$(n = na)$

Refused to participate $(n = na)$

Other reasons $(n = na)$

Allocation

Fludarabine

Allocated to intervention
$(n = 75)$
Received allocated
intervention $(n = na)$

Did not receive allocated
intervention $(n = na)$

Give reasons:

Chlorambucil + Prednisone

Allocated to intervention
$(n = 75)$
Received allocated intervention
$(n = na)$

Did not receive allocated
intervention $(n = na)$

Give reasons:

Follow-Up

Lost to follow-up $(n = na)$

Give reasons:

Discontinued intervention
$(n = na)$
Give reasons:

Lost to follow-up $(n = na)$

Give reasons:

Discontinued intervention
$(n = na)$
Give reasons:

Analysis (for response)

Analysed $(n = 69)$

Excluded from analysis
$(n = na)$
Give reasons:

Analysed $(n = 73)$

Excluded from analysis
$(n = na)$
Give reasons:

Appendix 6: Glossary of terms

Adenopathy
Swelling or enlargement of the lymph nodes, also known as lymphadenopathy.

Allogeneic Transplantation
A transplant using a human donor who has bone marrow that is a genetic match to the recipient.

Alkylating Agent
A chemotherapeutic agent such as chlorambucil or cyclophosphamide, which blocks cell division by adding alkyl groups to molecules.

Autoimmune Haemolytic Anaemia
Anaemia resulting from reduced red blood cell survival time and haemolysis, due to production of autoantibody directed to cells of red blood cell lineage.

Autologous Transplants
Transplant whereby the patient's own cells or tissues are collected and reinfused or transplanted.

B-cell CLL
CLL variant involving a particular type of lymphocyte known as B-lymphocytes. These develop in the bone marrow and are capable of producing antibodies.

CD4
A protein molecule found on helper T lymphocytes and other cells.

CD4 counts
One of the most commonly used markers for assessing the state of the immune system. Also called T4 cell count. As CD4 cell count declines, the risk of developing opportunistic infections increases.

Chronic Lymphocytic Leukaemia
A slowly progressing form of leukaemia characterised by an increased number of the type of white blood cells known as lymphocytes.

Complete Response
The disappearance of all signs and symptoms of disease according to a standardised definition. This may vary making it necessary to check which set of criteria is being used within each study.

Cytogenetic Abnormalities
Chromosomal abnormalities associated with the disease.

First Line treatment
Therapy administered when patient first becomes symptomatic, often after a period of 'watch & wait'.

Hepatosplenomegaly
Enlargement of the liver and spleen.

High-Risk Disease
Generally synonymous with Rai stages III-IV and Binet stage C.

Hodgkin Disease
A malignant disease of the lymph nodes characterised by the presence of the Reed-Sternberg cell.

Immunosuppression
Suppression of the immune response as a result of drugs (chemotherapy) or radiation.

Intermediate-Risk Disease
Generally synonymous with Rai stages I-II and Binet stage B.

Low-Risk Disease
Generally synonymous with Rai stage 0 and Binet stage A.

Lymphadenopathy
Swelling or enlargement of the lymph nodes, also known as adenopathy.

Lymphocytosis
An increase in the number of lymphocytes in the blood.

Monoclonal Antibodies
Antibodies specific for a single antigen. They can be produced in large quantities in the laboratory.

Myelosuppression
Decreased platelets and red and white blood cells, caused by disease or drug therapies.

Neutropenia
A below-normal number of neutrophils, ($<2 \times 10^9$l).

Non-Hodgkin Lymphoma
A malignant disease of the lymphatic system (lymph vessels and lymph nodes) without the presence of Reed-Sternberg cells.

Opportunistic Infections
An organism capable of causing disease only in a host whose resistance is lowered--usually by other diseases or by drugs.

Overall Response

The total number of patients who have responded to therapy according to the response criteria of the study. This is the sum of the Complete Responses and the Partial Responses.

Overall Survival

The percentage of subjects in a study who have survived for a defined period of time. Usually reported as time since diagnosis or treatment. Also called the survival rate.

Partial Response

The reduction, but not complete disappearance, of cancer in response to therapy according to a standardised definition. This may vary making it necessary to check which set of criteria is being used within each study.

Progression-Free Survival

Interval between diagnosis of metastatic disease, or the initiation of therapy and diagnosis of progression. The exact definition may vary making it necessary to check which definition is being used within a particular study.

Prolymphocytes

An early lymphocyte precursor. Not commonly seen in the blood but in prolymphocytic leukaemia they may be present in large numbers.

Purine Analogues

A drug, which is an analogue of one of the purine bases, adenine or guanine, found in DNA and RNA. Some examples are fludarabine, cladribine and pentostatin.

Relapse

Resurgence of CLL following a 'Response' to treatment, usually marked by onset of new symptoms or return of previously experienced symptoms.

Refractory Disease

Patient has not responded to therapy or *Relapsed* from therapy within 6 months.

Response

Improvement in disease to meet relevant specified criteria (clinical factors and symptoms). See also 'Complete Response', 'Overall Response' and 'Partial Response'.

Salvage Therapy (Third Line Treatment)

Treatment options applied when patients have relapsed following, or proved refractory to second-line treatment. (NB: This is the definition within the cotext of this submission; it is acknowledged that in clinical practice the term 'salvage' is frequently applied to patients who have failed all standarad treatments)

Second Line Treatment
Therapy administered when patients have become *Refractory* to or progrerssed follwing first-line treatment.

Splenomegaly
Enlargement of the spleen.

Thrombocytopenia
A below-normal number of platelets, $<100,000 \times 10^9$l.

1.   TRADE NAME OF THE MEDICINAL PRODUCT

Fludara® oral 10 mg film-coated tablet

2.   QUALITATIVE AND QUANTITATIVE COMPOSITION

Each film-coated tablet contains fludarabine phosphate 10mg.

For excipients, see 6.1

3.   PHARMACEUTICAL FORM

Film-coated tablet.

Salmon-pink, capsule-shaped tablet marked with 'LN' in a regular hexagon on one side

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 Fludara oral 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.

Fludara oral is indicated for the treatment of patients with B-cell chronic lymphocytic leukaemia (CLL) with sufficient bone marrow reserve and who have not responded to or whose disease has progressed during or after treatment with at least one standard alkylating- agent containing regimen.

4.2 Posology and method of administration

Fludara oral should be prescribed by a qualified physician experienced in the use of antineoplastic therapy.

- Adults

The recommended dose is 40 mg fludarabine phosphate/m² body surface given daily for 5 consecutive days every 28 days by the oral route. This dose corresponds to 1.6 times the recommended intravenous dose of fludarabine phosphate (25 mg/m² body surface per day).

The following table provides guidance for determining the number of tablets of Fludara oral to be administered:

Body Surface Area (BSA) [m²]	Calculated total daily dose based on BSA (rounded up or down to whole number) [mg/day]	Number of tablets per day (total daily dose)
0.75 - 0.88	30 – 35	3 (30 mg)
0.89 - 1.13	36 – 45	4 (40 mg)
1.14 - 1.38	46 – 55	5 (50 mg)
1.39 - 1.63	56 – 65	6 (60 mg)
1.64 - 1.88	66 – 75	7 (70 mg)
1.89 - 2.13	76 – 85	8 (80 mg)
2.14 - 2.38	86 – 95	9 (90 mg)
2.39 - 2.50	96 – 100	10 (100 mg)

Fludara oral can be taken either on an empty stomach or together with food. The tablets have to be swallowed whole with water, they should not be chewed or broken.

The duration of treatment depends on the success of treatment and the tolerability of the drug. Fludara oral should be administered until best response is achieved (complete or partial remission, usually 6 cycles) and then the drug should be discontinued.

Patients undergoing treatment with Fludara should be closely monitored for response and toxicity. Individual dosing should be carefully adjusted according to the observed haematological toxicity.

Dose adjustments for the first treatment cycle (start of therapy with Fludara) are not recommended (except in patients with impairment of renal function – see 4.2).

If at the start of a subsequent cycle cell numbers are too low to administer the recommended dosage and there is evidence of treatment associated myelosuppression, the planned treatment cycle should be postponed until granulocyte count is above 1.0×10^9/l and platelet count is above 100×10^9/l. Treatment should only be postponed up to a maximum of two weeks. If granulocyte and platelet counts have not recovered after two weeks of postponement, the dose should be reduced according to the suggested dose adjustments in the table below.

Granulocytes and / or Platelets $[10^9$/l]		Fludarabine phosphate dose
0.5 - 1.0	50 - 100	**30** mg/m^2/day
<0.5	<50	**20** mg/m^2/day

Dose should not be reduced if thrombocytopenia is disease related.

If a patient does not respond to treatment after two cycles and shows no or little haematological toxicity a careful dose adjustment towards higher fludarabine phosphate doses in subsequent treatment cycles could be considered

- Patients with reduced kidney or liver function

Doses should be adjusted for patients with reduced kidney function. 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. For further information see section 4.4. Fludara oral treatment is contraindicated if creatinine clearance is < 30 ml/min (see 4.3).

No data are available concerning the use of Fludara in patients with hepatic impairment. In this group of patients, Fludara should be used with caution and administered if the perceived benefit outweighs any potential risk (see 4.4).

- Children

The safety and effectiveness of Fludara oral in children has not been established.

- Elderly patients

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

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 (see 4.4).

4.3 Contraindications

Hypersensitivity to fludarabine phosphate or to any of the excipients

enal impairment with creatinine clearance < 30 ml/min

Decompensated haemolytic anaemia

Pregnancy and lactation

4.4 Special warnings and special precautions for use

When used at high doses in dose-ranging studies in patients with acute leukaemia, intravenous Fludara was associated with severe neurological effects, including blindness, coma and death. This severe central nervous system toxicity occurred in 36 % of patients treated intravenously 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 has occurred rarely (coma, seizures and agitation) or uncommonly (confusion) (see section 4.8). Patients should be closely observed for signs of neurological side effects.

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

In patients with impaired state of health, Fludara oral 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 Fludara. In a Phase I intravenous 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.

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

Cumulative myelosuppression may be seen. While chemotherapy-induced myelosuppression is often reversible, administration of fludarabine phosphate requires careful haematological monitoring.

Fludara 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 intravenous Fludara. 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 Fludara 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 intravenous Fludara therapy.

Tumour lysis syndrome associated with intravenous Fludara treatment has been reported in patients with large tumour burdens. Since Fludara 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, and hospitalisation may be recommended for these patients during the first course of treatment.

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 intravenous Fludara. The majority of patients experiencing haemolytic anaemia developed a recurrence in the haemolytic process after rechallenge with Fludara.

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

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 (see 4.2).

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

No data are available concerning the use of Fludara in children. Therefore, treatment with Fludara 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 Fludara, vaccination with live vaccines should be avoided.

The reported incidence of nausea/vomiting was higher with the oral than the i.v. formulation. If this presents a persistent clinical problem it is recommended to switch to the i.v. formulation.

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

4.5 Interaction with other medicinal products and other forms of interaction

In a clinical investigation using intravenous Fludara 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 Fludara in combination with pentostatin is not recommended.

The therapeutic efficacy of Fludara 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 with of Fludara and subsequent Ara-C treatment. Plasma concentrations of Ara-C and the elimination rate of Ara-CTP were not affected.

In a clinical investigation, pharmacokinetic parameters after peroral administration were not significantly affected by concomitant food intake (see 5.2).

4.6 Pregnancy and lactation

- Pregnancy

Fludara should not be used 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 feto-placental barrier.

- Lactation

Breast-feeding should be discontinued for the duration of Fludara 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.

However, Fludara treatment may be associated with fatigue or visual disturbances. Patients experiencing such adverse events should avoid driving and using machines.

4.8 Undesirable effects

Based on the experience with the intravenous use of Fludara, 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 Fludara. Fatalities as a consequence of serious adverse events have been reported.

The most frequently reported adverse events and those reactions which are more clearly related to the drug are arranged below according to body system regardless of their seriousness. Their frequencies (common $\geq 1\%$, uncommon $\geq 0.1\%$ and $< 1\%$) are based on clinical trial data regardless of the causal relationship with intravenous Fludara. The rare events ($< 0.1\%$) were mainly identified from the post-marketing experience.

- Body as a whole

Infection, fever, fatigue, weakness, malaise, and chills have been commonly reported.

- Haemic and lymphatic system

Haematological events (neutropenia, thrombocytopenia, and anaemia) have been reported in the majority of patients treated with Fludara. Myelosuppression may be severe and cumulative. Fludara's prolonged effect on the decrease in the number of T-lymphocytes may lead to 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 4.4. "Special

warnings and special precautions for use"). Evolution of EBV-infection/reactivation into EBV-associated lymphoproliferative disorders has been observed in immunocompromised patients.

In rare cases, the occurrence of myelodysplastic syndrome (MDS) has been described in patients treated with Fludara. The majority of these patients also received prior, concomitant or subsequent treatment with alkylating agents or irradiation. Monotherapy with Fludara has not been associated with an increased risk for the development of MDS.

Clinically significant autoimmune phenomena have been reported to occur uncommonly in patients receiving Fludara (see section 4.4).

- Metabolic and nutritional disorders

Tumour lysis syndrome has been reported uncommonly in patients treated with Fludara. 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.

Oedema has been commonly reported.

Changes in hepatic and pancreatic enzyme levels are uncommon .

- Nervous system

Peripheral neuropathy has been commonly observed.

Confusion is uncommon. Coma, and agitation and seizures occur rarely.

- Special senses

Visual disturbances are commonly reported events in patients treated with Fludara. In rare cases, optic neuritis, optic neuropathy and blindness have occurred.

- Cardiovascular system

In rare cases, heart failure and arrhythmia have been reported in patients treated with Fludara.

- Respiratory system

Pneumonia commonly occurs in association with Fludara treatment. Pulmonary hypersensitivity reactions to Fludara (pulmonary infiltrates/pneumonitis/fibrosis) associated with dyspnoea and cough have been uncommonly observed.

- Digestive system

Gastrointestinal disturbances such as nausea and vomiting, diarrhoea, stomatitis and anorexia, are common events. Gastrointestinal bleeding, mainly related to thrombocytopenia has been uncommonly reported in patients treated with Fludara.

- Skin and appendages

Skin rashes have been commonly reported in patients treated with Fludara.

In rare cases a Stevens-Johnson syndrome or a toxic epidermal necrolysis (Lyell's syndrome) may develop.

- Urogenital system

Rare cases of haemorrhagic cystitis have been reported in patients treated with Fludara.

4.9   Overdose

High doses of Fludara given intravenously 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 Fludara overdosage. Treatment consists of drug discontinuation and supportive therapy.

5.   PHARMACOLOGICAL PROPERTIES

5.1   Pharmacodynamic properties

Pharmacotherapeutic group: Antineoplastic and immunomodulating agents

ATC Code: L01B B05

Fludara contains fludarabine phosphate, a water-soluble fluorinated nucleotide 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 is a potent inhibitor of DNA synthesis and also reduces RNA and protein synthesis.

Inhibition of DNA synthesis leads to a reduction in cell division and induction of apoptosis. This is believed to be the dominant mechanism of action of the compound.

A randomised trial of intravenous Fludara 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 Fludara compared to CAP (45% vs. 26% and 13% vs. 6%, respectively); response duration and overall survival were similar with Fludara and CAP. Within the stipulated treatment period of 6 months the number of deaths was 9 (Fludara) 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 Fludara 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 and after peroral dosing of fludarabine phosphate (Fludara, 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. After intravenous and peroral administration of fludarabine phosphate, 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.

After peroral fludarabine phosphate doses, maximum 2F-ara-A plasma levels reached approximately 20 - 30 % of corresponding intravenous levels at the end of infusion and occurred 1 – 2 hours postdose. The systemic 2F-ara-A availability was 50 - 65 % following single and repeated doses and was similar after ingestion of a solution or immediate release tablet formulation. After oral dose of 2F-ara-AMP with concomitant food intake a slight increase (<10 %) of systemic availability (AUC), a slight decrease of maximum plasma levels (C_{max}) of 2F-ara-A and a delayed time of occurrence of C_{max} was observed; terminal half-lives were unaffected.

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 intravenous dose was excreted in the urine. Mass balance studies in laboratory animals with ³H-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. In patients, severe side effects were observed closer to the recommended therapeutic dose (factor 3 to 4) and included severe neurotoxicity partly with lethal outcome (cf. section 4.9).

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 Fludara points to a comparable toxicological profile in humans, although additional undesirable effects such as neurotoxicity were observed in patients (cf. 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 Fludara is associated with a relevant risk of teratogenic effects in humans (cf. 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 Fludara 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 is 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. The similarity in nature of the observed lesions in the gastrointestinal tract after intravenous or intragastric dosing in animal experiments supports the assumption that the fludarabine phosphate induced enteritis is a systemic effect.

6.   PHARMACEUTICAL PARTICULARS

6.1   List of excipient(s)

Tablet core: Cellulose, microcrystalline
Lactose, monohydrate
Silica, colloidal anhydrous
Croscarmellose sodium
Magnesium stearate

Film-coat: Hypromellose
Talc
Titanium dioxide (E171)
Ferric oxide pigment, yellow (E172)
Ferric oxide pigment, red (E172)

6.2   Incompatibilities

Not Applicable

6.3   Shelf-life

2 years.

6.4   Special precautions for storage

Store in the original package

6.5   Nature and contents of container

Blisters of 5 tablets each, comprising polyamide/aluminium/polypropylene thermoformable foil with a lidding foil of aluminium. The blisters are packed in a polyethylene tablet container with a child-resistant polypropylene screw cap.

Pack sizes: 15 or 20 film-coated tablets per tablet container

6.6   Instructions for use/handling

Fludara should not be handled by pregnant staff.

Procedures for proper handling and disposal should be observed. Consideration should be given to handling and disposal according to guidelines used for cytotoxic drugs. Waste material may be disposed of by incineration.

7.   MARKETING AUTHORISATION HOLDER

Schering Health Care Limited
The Brow
Burgess Hill
West Sussex RH15 9NE
United Kingdom

8.   MARKETING AUTHORISATION NUMBER

PL 00053/0290

9.   DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

24 October 2000

10.   DATE OF (PARTIAL) REVISION OF THE TEXT

27 November 2001October 2004

LEGAL CATEGORY

POM

1. NAME OF THE MEDICINAL PRODUCT

Fludara® 50mg powder for solution for injection or infusion

2. QUALITATIVE AND QUANTITATIVE COMPOSITION

Each vial contains 50mg fludarabine phosphate

1ml of reconstituted solution contains 25mg fludarabine phosphate.

For excipients, see section 6.1.

3. PHARMACEUTICAL FORM

Powder for solution for injection or infusion.

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 Fludara 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

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

It is strongly recommended that Fludara should be only administered intravenously. No cases have been reported in which paravenously administered Fludara 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 in10 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 Fludara 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 Fludara in patients with hepatic impairment. In this group of patients, Fludara 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. Fludara treatment is contraindicated, if creatinine clearance is < 30 ml/min.

- Children

The safety and effectiveness of Fludara in children has not been established.

4.3. Contraindications

Fludara 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 special precautions for use

When used at high doses in dose-ranging studies in patients with acute leukaemia, Fludara 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 Fludara 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, Fludara 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 Fludara. 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.

Fludara 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 Fludara-treated patients. 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 Fludara 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 Fludara therapy.

Tumour lysis syndrome associated with Fludara treatment has been reported in CLL patients with large tumour burdens. Since Fludara 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 Fludara. The majority of patients experiencing haemolytic anaemia developed a recurrence in the haemolytic process after rechallenge with Fludara. Patients treated with Fludara should be closely monitored for haemolysis.

Patients undergoing treatment with Fludara should be closely monitored for signs of autoimmune haemolytic anaemia (decline in haemoglobin linked with haemolysis and positive Coombs test). Discontinuation of therapy with Fludara 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 Fludara in elderly persons (> 75 years), caution should be exercised with the administration of Fludara in these patients.

No data are available concerning the use of Fludara in children. Therefore, treatment with Fludara 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 Fludara vaccination with live vaccines should be avoided.

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

4.5. Interaction with other medicinal products and other forms of interaction

In a clinical investigation using Fludara 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 Fludara in combination with pentostatin is not recommended.

The therapeutic efficacy of Fludara 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

Fludara and subsequent Ara-C treatment. Plasma concentrations of Ara-C and the elimination rate of Ara-CTP were not affected.

4.6. Use during pregnancy and lactation

- Pregnancy

Fludara should not be used 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 should be discontinued for the duration of Fludara 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

The effect of treatment with Fludara on the patient's ability to drive or operate machinery has not been evaluated.

4.8. Undesirable effects

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 Fludara. Fatalities as a consequence of serious adverse events have been reported.

The most frequently reported adverse events and those reactions which are more clearly related to the drug are arranged below according to body system regardless of their seriousness. Their frequencies (common $\geq 1\%$, uncommon $\geq 0.1\%$ and $< 1\%$) are based on clinical trial data regardless of the causal relationship with Fludara. The rare events ($< 0.1\%$) were mainly identified from the post-marketing experience.

- Body as a whole

Infection, fever, fatigue, weakness, malaise, and chills have been commonly reported.

- Haemic and lymphatic system

Haematological events (neutropenia, thrombocytopenia, and anaemia) have been reported in the majority of patients treated with Fludara. Myelosuppression may be severe and cumulative. Fludara´s prolonged effect on the decrease in the number of T-lymphocytes may lead to 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 4.4. "Special warnings and special precautions for use"). Evolution of EBV-infection/reactivation into EBV-associated lymphoproliferative disorders has been observed in immunocompromised patients.

In rare cases, the occurrence of myelodysplastic syndrome (MDS) has been described in patients treated with Fludara. The majority of these patients also received prior, concomitant or subsequent treatment with alkylating agents or irradiation. Monotherapy with Fludara has not been associated with an increased risk for the development of MDS.

Clinically significant autoimmune phenomena have been reported to occur uncommonly in patients receiving Fludara (see section 4.4).

- Metabolic and nutritional disorders

Tumour lysis syndrome has been reported uncommonly in patients treated with Fludara. 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.

Oedema has been commonly reported.

Changes in hepatic and pancreatic enzyme levels are uncommon .

- Nervous system

Peripheral neuropathy has been commonly observed. Confusion is uncommon. Coma, agitation and seizures occur rarely.

- Special senses

Visual disturbances are commonly reported events in patients treated with Fludara. In rare cases, optic neuritis, optic neuropathy and blindness have occurred.

- Respiratory system

Pneumonia commonly occurs in association with Fludara treatment. Pulmonary hypersensitivity reactions to Fludara (pulmonary infiltrates/pneumonitis/fibrosis) associated with dyspnoea and cough have been uncommonly observed.

- Digestive system

Gastrointestinal disturbances such as nausea and vomiting, diarrhoea, stomatitis, and anorexia are common events. Gastrointestinal bleeding, mainly related to thrombocytopenia has been uncommonly reported in patients treated with Fludara.

- Cardiovascular system

In rare cases, heart failure and arrhythmia have been reported in patients treated with Fludara.

- Urogenital system

Rare cases of haemorrhagic cystitis have been reported in patients treated with Fludara.

- Skin and appendages

Skin rashes have been commonly reported in patients treated with Fludara.

In rare cases a Stevens-Johnson syndrome or a toxic epidermal necrolysis (Lyell's syndrome) may develop.

4.9.   Overdose

High doses of Fludara 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 Fludara overdosage. Treatment consists of drug discontinuation and supportive therapy.

5.   PHARMACOLOGICAL PROPERTIES

5.1.   Pharmacodynamic properties

- Pharmacotherapeutic group: Antineoplastic agents

ATC-code L01B B05

Fludara 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 Fludara 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 Fludara 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 Fludara group. The median survival of the two patient groups was 56.1 months for Fludara 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 Fludara 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 Fludara 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 Fludara 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 Fludara group than in the chlorambucil group.

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

A randomised trial of Fludara 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 Fludara compared to CAP (45% vs. 26% and 13% vs. 6%, respectively); response duration and overall survival were similar with Fludara and CAP. Within the stipulated treatment period of 6 months the number of deaths was 9 (Fludara) 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 Fludara 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 (Fludara, 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 ³H-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. In patients, severe side effects were observed closer to the recommended therapeutic dose (factor 3 to 4) and included severe neurotoxicity partly with lethal outcome (see section 4.9).

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 Fludara 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 Fludara 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 Fludara 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 (to adjust the pH to 7.7).

6.2.   Incompatibilities

Must not be mixed with other drugs.

6.3. Shelf life

As packaged for sale: 3 years.

Chemical and physical in-use stability after reconstitution has been demonstrated for 7 days at 4 °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 and should not be longer than 24 hours at 2 to 8 °C or 8 hours at room temperature.

6.4. Special precautions for storage

This medicinal product does not require any special storage conditions.

For storage after reconstitution or dilution, see Section 6.3

6.5. Nature and content of container

10 ml colourless type I glass vials containing 50 mg fludarabine phosphate.

Each package contains 5 vials.

6.6. Instructions for use and handling and disposal

- Reconstitution

Fludara 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 and infused over approximately 30 minutes.

In clinical studies, the product has been diluted in 100 ml or 125 ml of 5 % dextrose injection or 0.9 % sodium chloride.

- 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. Fludara should not be used in case of a defective container.

- Handling and disposal

Fludara 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 Fludara 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.

7. MARKETING AUTHORISATION HOLDER
Schering Health Care Limited

The Brow

Burgess Hill

West Sussex RH15 9NE

8.   MARKETING AUTHORISATION NUMBER
PL/0053/0239

9.   DATE OF FIRST AUTHORISATION/RENEWAL OF THE
AUTHORISATION
11 August 2004

10.   DATE OF REVISION OF THE TEXT
August 2005

LEGAL CATEGORY

POM

1.   **NAME OF THE MEDICINAL PRODUCT**
Cyclophosphamide Tablets.

2.   **QUALITATIVE AND QUANTITATIVE COMPOSITION**
Cyclophosphamide monohydrate BP 53.50 mg equivalent to 50 mg anhydrous cyclophosphamide.

3.   **PHARMACEUTICAL FORM**
Sugar-coated tablets

4.   **CLINICAL PARTICULARS**

4.1.   **Therapeutic indications**

Alkylating, antineoplastic agent. Cyclophosphamide has been used successfully to induce and maintain regressions in a wide range of neoplastic conditions, including leukaemias, lymphomas, soft tissue and osteogenic sarcomas, paediatric malignancies and adult solid tumours; in particular, breast and lung carcinomas.

Cyclophosphamide is frequently used in combination chemotherapy regimens involving other cytotoxic drugs.

4.2.   **Posology and method of administration**

Route of administration: Oral.

Adults and children:

The recommended dose for cyclophosphamide tablets is 50-250 mg/m^2 daily (doses towards the upper end of this range should be used only for short courses).

The dose may be amended at the discretion of the physician.

It is recommended that the calculated dose of cyclophosphamide be reduced when it is given in combination with other antineoplastic agents or radiotherapy, and in patients with bone marrow depression.

Cyclophosphamide tablets should be swallowed whole, preferably on an empty stomach, but if gastric irritation is severe, they may be taken with meals.

A minimum output of 100 ml/hour should be maintained during therapy with conventional doses to avoid cystitis. If the larger doses are used, an output of at least this level should be maintained for 24 hours following administration, if necessary by forced diuresis. Alkalinisation of the urine is not recommended.

Cyclophosphamide should be given early in the day and the bladder voided frequently. The patient should be well hydrated and maintained in fluid balance.

Mesna (Uromitexan) can be used concurrently with cyclophosphamide to reduce urotoxic effects (for dosage see Uromitexan data sheet). If Mesna (Uromitexan) is used to reduce uroethelial toxicity, frequent emptying of the bladder should be avoided.

If the leucocyte count is below 4,000/mm^3 or the platelet count is below 100,000/mm^3, treatment with cyclophosphamide should be temporarily withheld until the blood count returns to normal levels.

4.3. Contraindications

Hypersensitivity and haemorrhagic cystitis.

4.4. Special warnings and precautions for use

Cyclophosphamide should be withheld in the presence of severe bone marrow depression and reduced doses should be used in the presence of lesser degrees of bone marrow depression. Regular blood counts should be performed in patients receiving cyclophosphamide.

It should not normally be given to patients with severe infections and should be withdrawn if such infections become life threatening.

Cyclophosphamide should be used with caution in debilitated patients and those with renal and/or hepatic failure. Cyclophosphamide is not recommended in patients with a plasma creatinine greater than 120 µmol/l (1.5 mg/100 ml) bilirubin greater than 17 µmol/l (1 mg/100 ml); or serum transaminases or alkaline phosphatase more than 2-3 times the upper limit of normal. In all such cases, dosage should be reduced.

Cyclophosphamide should be used only under the directions of physicians experienced in cytotoxic or immunosuppressant therapy.

Further Information:

The dosage regimen for mesna (Uromitexan) varies according to the dose of cyclophosphamide administered. In general i.v. Uromitexan is given as 60% w/w of the dose of i.v. Cyclophosphamide in three equal doses of 20% at 0, 4 and 8 hours. With the higher doses of cyclophosphamide, the dose and frequency of administration may need to be increased. Uromitexan Tablets are also available; full prescribing information for both presentation is available on the appropriate data sheet.

4.5. Interaction with other medicinal products and other forms of interaction

Oral hypoglycaemic agents may be potentiated by cyclophosphamide.

4.6. Pregnancy and lactation

This product should not normally be administered to patients who are pregnant or to mothers who are breast feeding. Alkylating agents, including cyclophosphamide, have been shown to possess mutagenic, teratogenic and carcinogenic potential. Pregnancy should therefore be avoided during cyclophosphamide therapy and for three months thereafter.

4.7. Effects on ability to drive and use machines

None known.

4.8. Undesirable effects

Single doses will produce a leucopenia which may be severe but usually returns to normal within 21 days.

Amenorrhoea and azoospermia often occur during treatment with cyclophosphamide but in most cases are reversible.

Haematuria may occur during or after therapy with Cyclophosphamide. Cyclophosphamide is excreted mainly in the urine, largely in the form of active metabolites which may give rise to a chemical cystitis which may be haemorrhagic. Acute sterile haemorrhagic cystitis may occur in up to 10% of patients not given mesna (Uromitexan) in conjunction with Cyclophosphamide. Late sequelae of this cystitis are bladder contracture and fibrosis.

Because of this, a high fluid intake should be maintained with frequent emptying of the bladder. Cyclophosphamide therapy may lead to inappropriate secretion of anti-diuretic hormone, fluid retention and hyponatremia, with subsequent water intoxication. Should this arise, a diuretic may be given. Cyclophosphamide may cause myocardial toxicity, especially at high dosage.

Cyclophosphamide may induce permanent sterility in children.

In addition to those noted above, the following may accompany cyclophosphamide therapy: hair loss, which may be total, although generally reversible; mucosal ulcertation; anorexia, nausea and vomiting; pigmentation, typically affecting the palms and nails of the hands and the soles of the feet, and interstitial pulmonary fibrosis.

Hepatic toxicity has rarely been reported.

Cyclophosphamide has been shown to be mutagenic, teratogenic, and carcinogenic in certain laboratory tests and as with other cytotoxic agents, there have been reports of possible drug-induced neoplasia. There is an excessive risk of acute leukaemia and bladder cancer following cyclophosphamide therapy.

An alteration in carbohydrate metabolism may be seen in patients on cyclophosphamide. Other side effects, such as pancreatitis, macrocytosis, and induction of hyperglycaemia or hypoglycaemia have been reported.

There are certain complications such as veno-occlusive disease, thromboembolism, disseminated intravascular coagulation or haemolytic uraemic syndrome, that may also be induced by the underlying disease, but which might occur with an increased frequency during chemotherapy that includes cyclophosphamide.

Side effects have occasionally occurred after cessation of therapy.

4.9.   Overdose

Myelosuppression (particularly granulocytopenia) and haemorrhagic cystitis are the most serious consequences of overdosage. Recovery from myelosuppression will occur by the 21st day after the overdosage in the great majority of patients (at doses up to 200 mg/kg i.v.) while granulocytopenia is usually seen by day 6 and lasts for a mean period of 12 days (up to 18 days). A broad spectrum antibiotic may be administered until recovery occurs. Transfusion of whole-blood, platelets or white cells and reverse barrier nursing may be necessary.

If the drug has been taken in the form of tablets, early gastric lavage may reduce the amount of drug absorbed.

During the first 24 hours and possibly up to 48 hours after overdosage, i.v. mensa may be beneficial in ameliorating damage to the urinary system. Normal supportive measures such as analgesics and maintenance of fluid balance should be instituted. If the cystitis does not resolve more intensive treatment may be necessary.

No further courses should be given until the patient has fully recovered.

5. PHARMACOLOGICAL PROPERTIES

5.1. Pharmacodynamic properties

Cyclophosphamide is an antineoplastic agent which is converted in the body to an active alkylating metabolite. It also possesses marked immunosuppressant properties. The principal site of cyclophosphamide activation is the liver. The chemotherapeutic and immunosuppressant activity of cyclophosphamide is thought to be mediated by the cytotoxic intermediates produced by activation by mixed function oxidases in hepatic microsomes. Non-enzymatic cleavage, possibly taking place in the tumour cells, results in the formulation of highly cytotoxic forms of the drug.

5.2. Pharmacokinetic properties

Cyclophosphamide may be incompletely absorbed from the gastro-intestinal tract. It rapidly disappears from the plasma and peak concentrations occur about 1 hour after an oral dose.

The metabolites of cyclophosphamide are excreted in the urine and these have an irritant effect on the bladder mucosa. Unchanged drug is also excreted in the urine and accounts for only 5-25% of the administered dose.

Metabolites have been found to be more protein bound than the parent compound.

5.3. Preclinical safety data

No further preclinical data are available.

6.   PHARMACEUTICAL PARTICULARS

6.1.   List of excipients

Maize starch
Pregelatinised starch
Lactose monohydrate
Gelatin
Microcrystalline cellulose
Sodium stearyl fumarate
Magnesium stearate
Coating
Polyethylene glycol
Sucrose
Maize starch
Calcium carbonate
Povidone
Opalux AS-9486 consisting of
- titanium dioxide
- red iron oxide
- yellow iron oxide
- sucrose
- purified water
- polyvinylpyrrolidone
- sodium benzoate
Carnauba wax

6.2.   Incompatibilities

None stated.

6.3.   Shelf life

60 months.

6.4. Special precautions for storage

Do not store above 25°C. Store in the original container in order to protect from moisture.

6.5. Nature and contents of container

White polyethylene containers with polyethylene snap-caps, containing a white capsule of desiccant.

6.6. Instructions for use, handling and disposal

None stated.

7. MARKETING AUTHORISATION HOLDER

Pharmacia Limited
Davy Avenue
Milton Keynes
MK5 8PH
UK

8. MARKETING AUTHORISATION NUMBER(S)

PL 00032/0335

9. DATE OF FIRST AUTHORISATION/RENEWAL OF THE AUTHORISATION

16 August 2002

10. DATE OF REVISION OF THE TEXT

23 June 2005

Ref: CP1_0 SPC

1.   TRADE NAME OF THE MEDICINAL PRODUCT

Endoxana Injection 500 mg.

2.   QUALITATIVE AND QUANTITATIVE COMPOISITION

Each vial contains cyclophosphamide monohydiate equivalent to 500 mg anhydrous cyclophosphamide.

When reconstituted for intravenous use, the solution for administration contains 20 mg cyclophosphamide per ml.

3.   PHARMACEUTICAL FORM

Powder for solution for injection.

A white crystalline powder contained in clear glass injection vials.

4.   CLINICAL PARTICULARS

4.1.   Therapeutic Indications

Endoxana is a cytotoxic drug for the treatment of malignant disease in adults and children. As a single agent, it has successfully produced an objective remission in a wide range of malignant conditions. Endoxana is also frequently used in combination with other cytotoxic drugs, radiotherapy or surgery.

4.2.   Posology and Method of Administration

Endoxana Injection is for intravenous or oral administration.

Endoxana should only be used by clinicians experienced in the use of cancer chemotherapy. Endoxana should only be administered where there are facilities for regular monitoring of clinical, biochemical and haematological parameters

before, during, and after administration and under the direction of a specialist oncology service.

Dosage
The dose, route of administration and frequency of administration should be determined by the tumour type, tumour stage, general condition of the patient and whether other chemotherapy or radiotherapy is to be administered concurrently. A guide to the dosage regimens used for most indications is given below.
This treatment should be continued until a clear remission or improvement is seen or be interrupted when the extent of leucopenia becomes unacceptable.

Conventional: 80-300 mg/m^2 daily as a single i.v.dose or daily divided oral doses.
300-600 mg/ m^2 as a single i.v. dose weekly.

High dose: 600 - 1500 mg/ m^2 as a single i.v. dose or short infusion given at 10-20 day intervals.

Elderly: No specific information on the use of this product in the elderly is available. Clinical trials have included patients over 65 years and no adverse reactions specific to this age group have been reported.

Children: No specific information. Children have received Endoxana. No adverse reactions specific to this group have been reported.

Administration
Endoxana is inert until activated by enzymes in the liver. However, as with all cytotoxics, it is suggested that reconstitution should be performed by trained personnel, in a designated area.

Those handling the preparation should wear gloves. Care should be taken to avoid splashing material into the eyes. The material should not he handled by women who are pregnant or who are breast-feeding.

For intravenous use, the contents of the vial should be dissolved in physiological saline (0.9% w/v sodium chloride) prior to administration. The pH of an aqueous solution is between 4 and 6. Endoxana is usually given directly into the tubing of a fast running i,v. infusion with the patient, supine. Care should he taken that extravasation does not take place, however, should it occur, no specific measures need he taken.

For oral use, an elixir may he prepared by dissolving the dry powder in Aromatic Elixir USP.

A minimum urine output of 100 ml/hour should be maintained during therapy with conventional doses to avoid cystitis. If the larger doses are used, an output of at least this level should he maintained for 24 hours following administration, if necessary by a forced diuresis.

Alkalisation of the urine is not recommended. Endoxana should be given early in the day and the bladder voided frequently. The patient should be well hydrated and maintained in fluid balance.

Mesna (Uromitexan) can be used concurrently to reduce urotoxic effects (see Uromitexan data sheet). If mesna (Uromitexan) is used to reduce urothelial toxicity, frequent emptying of the bladder should he avoided. Anti-emetics given before and during therapy may reduce nausea and vomiting.

Urine should be sent for laboratory analysis before and at the end of each course of treatment and the patient should be monitored for evidence of haematuria at regular intervals throughout the treatment period. The patient should be instructed to report any signs or symptoms of cystitis.

Endoxana Injection houId be avoided in patients with cystitis from any cause until it has been treated.

If the leukocyte count is below 4×10^9/L and/or the platelet count is below 100×10^9/L, treatment with Endoxana should be temporarily withheld until the blood count returns to normal levels.

4.3. Contra-indications

Endoxana is contra-indicated in patients with known hypersensitivity to cyclophosphamide, with acute infections, with bone-marrow aplasia, urinary tract infection or with acute urothelial toxicity from cytotoxic chemotherapy or radiation therapy.

Endoxana should not be used in the management of non-malignant disease, except for immunosuppression in life-threatening situations.

Endoxana is contra-indicated during pregnancy.

4.4. Special Warnings and Precautions for Use

Care should be exercised in patients who are elderly, debilitated, have diabetics mellitus or evidence of myelosuppression, or who have recently received, or are receiving, concurrent treatment with radiotherapy or cytotoxic agents.

Cardiotoxicity may be induced in patients who have had, or are receiving, rnediastinal irradiation, doxorubicin or pentostatin. It has also heen reported with high doses of cyclophosphamide. In such instances cyclophosphamide therapy should he stopped and appropriate treatment instituted.

Endoxana is not recommended in patients with plasma creatinine greater than 120 micromol/L (1.5 mg/ 100 ml), bilirubin greater than 17 micrormol/L (1 mg/ 100 ml), or with transaminases or alkaline phosphatase more than 2-3 times the normal value.

Endoxana may have an adverse effect on the gonads and amenorrhoea and azoospermia often occur which may he irreversible. Appropriate counselling should be given.

4.5. Interactions with other Medicaments and other forms of Interaction

Increased myelosuppression may be seen following concurrent administration of other marrow depressant drugs.

Endoxana potentiates the hypoglycaemic effects of the sulphonylurea compounds. Other clinically significant interactions are of cyclophosphamide with allopurinol (increased incidence of bone marrow depression) and suxamethonium (prolonged apnoea).

4.6. Pregnancy and Lactation

Endoxana should not be used in pregnancy, especially the first trimester, unless the expected benefit is thought to outweigh the substantial risk to the foetus. Endoxana has been shown to be teratogcnic Mothers should not breast-feed while being treated with Endoxana, or for 36 hours after stopping treatment.

Contraception in both sexes is advised during and for at least 3 months after Endoxana therapy. Patients should receive counselling with respect to subsequent pregnancies.

4.7. Effects on Ability to Drive and Use Machines

A patient's ability to drive or operate machinery may be aflfected by the possible side effects of cyclophosphamide administration, cg. nausea, vomiting

4.8. Undesirable Effects

Anorexia, nausea and vomiting and mucusal ulceration can occur. This may be reduced by the prior administration of an anti-emetic agent. Rarely renal and hepatic dysfunction (including jaundice and increased liver enzymes) have been reported.

Alopccia occurs to some degree in about 20% of patient's receiving over 100 mg daily and is inevitable following high doses. Epilation commences usually after the first three weeks of treatment, but regrowth is evident after three months in most patients even though they remain on treatment.

The reticulo-endotheial system is depressed, granulopoiesis and lymphopoiesis being more affected than thrombopoiesis and erythropoiesis, hut this depression is reversible. When a single dose is given, the fall in the peripheral white cell count reaches its nadir within 5-10 days. Recovery is seen at 10-14 days following administration, with full recovery in most cases by 21-28 days. The fall in the peripheral count and the time taken to recover may increase with increasing doses of Endoxana.

An alteration in carbohydrate metabolism may be seen in patients on Endoxana. Hyperglycaemia has been reported

Azoosperinia often occurs in men and is dose dependent. Spontaneous recovery of fertility may occur, and is also dependent on dose. Menstruation in women commonly ceases during therapy, and may he permanent, particularly in older women. Endoxana may have an adverse effect on prepubertal gonads.

Cardiotoxicity may be induced in patients who have had or are receiving mediastinal irradiation or doxorubicin. It has also been reported with high doses of cyclophosphamide. This mainly occurs as a tachyarrythmia and may progress

in severe cases to intractable heart failure. Following large doses, ECO changes and elevation of LDH, AST and CPK have been reported in some patients.

Haematuria may occur during or after therapy with Endoxana. Where mesna (Uromitexan) is not given in conjunctuion with Endoxana, acute sterile haemorrhagic cystitis may occur in up to 10% of patients. Late sequalae of this cystitis are bladder contracture and fibrosis.

Endoxana has been shown to be mutagenic, teratogenic, and carcinogenic in certain laboratory tests and, as with other cytotoxic agents, there have been reports of possible drug- induced neoplasia. There is an excessive risk of acute leukaemia and bladder cancer following cyclophosphamide therapy.

Cyclophosphamide therapy may lead to inappropriate secretion of anti-diuretic hormone with fluid retention and hyponatraemia, and subsequent water intoxication.

Other side-effects, such as pancretitis, pigmentation, macrocytosis, and induction of hyperglyeacmia or hypoglycaemia have bean reported. Pneumonitis and pulmonary fibrosis have also occasionally been associated with Endoxana therapy.

Note:
There are certain complications, such as veno-occlusive disease, thromboembolism, DIC (disseminated intravascular coagulation) or haemolytic uraemic syndrome, that may also he induced by the underlying disease, but which might occur with an increased frequency during chemotherapy that includes Endoxana.

Side-effects have occasionally occurred after cessation of treatment.

4.9.   Overdose

The most serious consequences of overdosage are myelosuppression, haemorrhagic cystitis and cardiotoxicity in the form of arrhythmias and severe heart failure. Myelosuppression usually recovers spontaneously, but until it does, administration of a broad-spectrum antibiotic may be advisable, Transfusion of whole-blood, platelets or white cell is rarely necessary.

If the overdose is recognised within the first 24 hours, and possibly up to 48 hours, i.v. Mesna may be beneficial in ameliorating damage to the urinary system. Normal supportive measures, such as analgesics and maintnance of fluid balance,

should he instituted. If, despite these measures, the cystitis does not resolve, more intensive treatment may he necessary and a urological opinion should he sought. No further courses should be given until the patient has fully recovered.

Endoxana is dialysable.

5.   PHARMACOLOGICAL PROPERTIES

5.1.   Pharmacodymimic Properties

Cyclophosphamide has been demonstrated to have a cytostatic effect in many tumour types. The active metabolites of cyclophosphamide are alkylating agents which transfer alkyl groups to DNA during the process of cell division, thus preventing normal synthesis of DNA.

5.2.   Pharmacokinetic Properties

Cyclophosphamide is well absorbed following an oral dose with a mean half-life of 4-8 hours for both oral and parenteral administration.

It is an inactive pro drug with alkylating metabolites produced hy hepatic metabolisin, reaching peak levels 4-6 hours after an i.v. injection. Hepatic enzymes may he induced. The parent compound binds poorly to plasma protein but the active metabolites are significantly protein-bound. The drug is widely distributed and crosses the blood-brain barrier, the placental barrier and is found in ascites. The metabolites are excreted renally.

5.3.   Preclinical Safety Data

There are no pre-clinical data of relevance to the prescriber which are additional to the information already stated in other sections of the Summary of Product Characteristics.

6.   PHARMACEUTICAL PARTICULARS

6.1.   List of Excipients

None.

6.2.   Incompatibilities

Benzyl alcohol increases the degradation rate of cyclophosphamide.

Shelf-Life

Unopened
36 months.

After reconstitutin for intravenous administration
Chemical and physical in-use stability has been demonstrated (in aqueous, sodium chloride, and glucose solutions) for 48 hours at $2 – 8^{\circ}$C.

From a microbiological point of view, the product should be used immediately. If not used inmediat:c1y, in-use storage times and conditions prior to use are the responsibility of the user and would normally not be longer than 24 hours at $2 – 8^{\circ}$C unless reconstitution has taken place in controlled and validated aseptic conditions.

After reconstitution in Aromatic Elixir USP for oral administration
At a concentration of 2 mg cyclophosphamide per ml in Aromatic Fliir USP, chemical and physical stability has been demonstrated for 14 days at $2 – 8^{\circ}$C.

6.3. Special Precautions for Storage

Do not store above 25°C.

Store in original container.

After reconstitution (for either intravenous or oral admmstmation), store at 2 – 8$^{°}$C and protect from light.

6.4. Nature and Contents of Container

50 ml type I or type III glass vials with butyl rubber closures and plastic and aluminium caps. Pack size: 1 vial.

6.5. Instructions for Use/Handl ing

For intro venous administration
Prior to administration the contents of a vial should he dissolved in 25 ml physiological saline (0.9% w/v sodium chloride) by introducing the saline into the vial and shaking vigorously until the powder is completely dissolved. Reconsi.ituiion results in a clear solution with a pH of between 4 and 6.

Endoxana Injection is compatible with the following infusion solutions: sodium chloride solution, glucose solution, sodium chloride and glucose solution, sodium chloride and potassium chloride solution, and potassium chloride and glucose solution.

For oral administration
Endoxana Injection may be dissolved in Aromatic Elixir USP.

General instructions
If vials are stored above the recommended temperature this can cause degradation of the active ingredient, identifiable by a yellow melted appearance to the vial contents. \/ials containing melted material should not be used.

Cyclophosphamide is a cytotoxic agent and should be treated accordingly. The material should not he handled by women who are pregnant or who are breast-feeding.

Adequate care and precautions should he taken in the disposal of empty vials and

items (syringes, needles, etc) ised in reconstitution and administration.

Administrative Data

7.   MARKETING AUTHORISATION H&CLER

Baxter Healthcare Ltd.,
Caxton Way,
Thetford,
Norfolk,
IP24 3SE
UK

8.   MARKETING AUTHORISATION NUMBER

PL 00116/0387

9.   DATE OF FIRST AUTHORISTION/REEWAL OF
AUTHORISATION

1st May 2003

10.   DATE OF (PARTIAL) REVISION OF THE TEXT

1st May 2003

Appendix 9   CLL4 Audit of resource use in CLL4 (attached as separate file)

Appendix 10 Studies included in the review of salvage treatments

Estimated values for "salvage" therapy consider a weighted average of all studies of HDMP
and alemtuzamab in pre-treated patients reported in the BCSH guidelines on the diagnosis
and management of chronic lymphocytic leukaemia.

Study name	Treatment	N	ORR (%)	OR (N)	DOR (months, median)
Osterborg 1997	Alemtuzumab	29	42%	12	NR
Kennedy 2001	Alemtuzumab	77	44%	34	NR
Rai 2001	Alemtuzumab	136	40%	54	NR
Keating 2002 c	Alemtuzumab	93	33%	31	NR
Kennedy 2002	Alemtuzumab + Fludarabine	6	66%	4	NR
Nabhan 2001	Alemtuzumab + Rituximab	9	0%	0	NR
Faderl 2001	Alemtuzumab + Rituximab	22	45%	10	NR
Thornton 2003	HDMP	25	77%	19	12
Rai 2002	Alemtuzumab	8	38%	3	NR
Mccune 2002	Alemtuzumab	13	46%	6	NR
Moreton 2004, 2005 (JCO) (Hillmen 2004 ASCO)	Alemtuzumab	91	54%	49	NR
Fiegl 2005	Alemtuzumab	106	22%	23	NR
Stilgenbauer 2004	Alemtuzumab	50	36%	18	NR
Osuji 2004	alemtuzumab	26	52%	14	4.1
Hazem 2005	Alemtuzumab (SC) + Fludarabine	36	44%	16	NR
Faderl 2005	Alemtuzumab (SC) + Rituximab	20	55%	11	NR
Mauro 2003	Alemtuzumab + FAND	4	100%	4	NR
Tedeschi 2005	Alemtuzumab + FC	3	100%	3	NR
Wierda 2005	Alemtuzumab + FCR	44	65%	29	NR
Faderl 2003	Alemtuzumab + Rituximab	32	63%	20	
Ciolli (2003)	Alemtuzumab sc	10	70%	7	NR
Faderl 2004	bortezomib	19	0%	0	NR
Eichhorst 2005 (3)	CHOP + rituximab	13	69%	9	NR
Byrd 2002	cladribine	28	32%	9	NR
Mauro 2002	FAND (fludarabine, Ara-C, mitoxantrone, dexamethasone)	14	50%	7	NR
O'Brien 2001	FC	28	39%	11	NR
Hendry 2004	FCM	24	79%	19	NR
Byrd 2004	flavopiridol	22	41%	9	NR
Mavromatis 2005	Fludarabine + rituximab + genasense	19	53%	10	NR
Tsimberidou 2004	FM	53	55%	29	NR
Call 2004	gemcitabine	19	5%	1	NR
Channan-Khan 2005	Lenalidomide	26	42%	11	NR
Friedenberg 1993	modified VAD	33	21%	7	6.5
O Brien 2001	rituximab (high dose)	40	36%	14	NR
Itala 2002	rituximab (weekly)	10	20%	2	NR
Coelho 2005	Rituximab + CVP	5	40%	2	NR
Ferrajoli 2005	Rituximab + GMCSF	26	54%	14	NR
Average		**1219**	**43%**	**521**	8.3

Notes:

Osterborg 1996 and Lundin 2002 report findings only for previously untreated patients and are excluded.

"NR" = not reported