Alemtuzumab as First-line Treatment for Progressive B-cell Chronic Lymphocytic Leukaemia

a report by
Claire Dearden

Royal Marsden NHS Foundation Trust and Institute of Cancer Research

DOI: 10.17925/EOH.2007.0.1.72

Chronic lymphocytic leukaemia (CLL) is the commonest of the adult leukaemias in the western world. The clinical course is highly variable with some patients surviving decades without requiring therapy while others have more aggressive disease requiring immediate treatment and associated with a shortened survival. Conventional treatment has relied on alkylating agents such as chlorambucil and, more recently, purine analogues such as a fludarabine. As single agents these therapies achieve good overall response (OR) rates of up to 80%, but complete remission (CR) rates of <10% for chlorambucil and 15–20% for single-agent fludarabine. Combinations of these drugs, such as fludarabine together with cyclophosphamide, have shown an increase in CR rates up to 40% with a prolongation of progression-free survival (PFS). However, none of the randomised studies has shown any survival advantage. This latter observation is largely due to the ability to successfully re-treat relapsed patients. However, patients who become refractory to alkylator- and fludarabine-based treatments have traditionally had a poor response (<20%) to salvage therapy and a greatly shortened survival (median 10 months).[1] Over the past decade this bleak situation for patients has been improved by the introduction of novel agents, including monoclonal antibodies. Alemtuzumab is a fully humanised monoclonal antibody directed against the CD52 antigen, which is widely expressed on B and T lymphocytes. It is licensed for the treatment of fludarabine refractory CLL and has been shown to induce remissions in 33–53% of patients in this setting.[2,3] The standard dosing schedule is 30mg given three times a week intravenously for 12 weeks.

Alemtuzumab Monotherapy

The first report of the use of alemtuzumab as front-line therapy was in 1996 by Osterborg et al.[4] Nine patients received the standard treatment, although in four patients the antibody was administered subcutaneously, and therapy was continued in all patients up to 18 weeks. The OR rate was 89% with three patients achieving CR. This group expanded the patient cohort and reported a further 41 patients treated with subcutaneous alemtuzumab as first-line therapy for a total of 18 weeks.[5]

Claire Dearden is Consultant Haematologist and Head of the Chronic Lymphocytic Leukaemia (CLL) Unit at the Royal Marsden Hospital and Institute of Cancer Research in London, UK. She trained in haematology at the Hammersmith, Royal Marsden and St George's Hospitals. Her research interests focus on mature B- and T-cell malignancies, including CLL, hairy cell leukaemia and T-cell leukaemias. She is a member of numerous societies, including the British and American Societies of Haematology, is a member of the UK Medical Research Council Adult Leukaemia Working Party and the National Cancer Research Institute CLL Trials Group, is on the Executive Board of the UK CLL Forum and chairs the regional Tumour Working Group for Haematological Cancers. She has also authored or co-authored many journal articles, meeting abstracts and book chapters in the field of haematological malignancy.

The OR rate was maintained at 81% in 38 evaluable patients. Nineteen per cent of patients achieved CR and 68% a partial remission (PR). At the time of publication in 2002 the time to treatment failure had not been reached at 18+ months. These results are comparable to those observed for single-agent fludarabine[6] and superior to those for single-agent rituximab[7] (see *Table 1*). Interestingly, complete responders required 18 weeks of therapy to achieve their best response, with significant improvement in bone marrow clearance between the 12- and 18-week evaluation points. Furthermore, patients with low-volume lymphadenopathy also achieved complete remissions in contrast to the observation in relapsed refractory patients that lymphadenopathy predicted a poor response to single-agent antibody treatment. Ten per cent of patients developed cytomegalovirus (CMV) reactivation that responded rapidly to treatment with intravenous ganciclovir. There was no increase in bacterial sepsis. Although transient injection site reactions were observed with the subcutaneous administration in the majority of patients, many of the initial reactions associated with intravenous administration such as rigours, nausea and hypertension were not seen. One in five patients had a transient grade 4 neutropaenia, but other side effects were rare.

> …some patients survive decades without requiring therapy while others have more aggressive disease requiring immediate treatment and associated with a shortened survival.

At the American Society of Hematology (ASH) meeting in December 2006 the results of an international prospective, randomised, controlled trial (CAM307) comparing chlorambucil with intravenous alemtuzumab as front-line therapy for CLL were reported.[8] Two hundred and ninety-seven patients were randomised to receive either alemtuzumab at the standard dose of 30mg three times per week for up to 12 weeks or chlorambucil 40mg/m^2 once every 28 days up to 12 cycles. Response rates assessed by an independent panel showed OR of 83% for alemtuzumab compared with 55% for chlorambucil with CR rates of 24% and 2%, respectively (see *Table 1*). This translated into improved PFS for the patients who received alemtuzumab, with a 43% lower risk of progression or death. Notably, in patients who had the cytogenetic deletion of 17p (p53), there was a three-fold increase in OR with alemtuzumab (64%) compared with chlorambucil (26%). Statistically significant superior responses were also seen for patients

with deletion 13q and deletion 11q treated with alemtuzumab compared with chlorambucil. Infections, including CMV, were reported in 76% of patients receiving alemtuzumab compared with 50% of chlorambucil patients while on study. Grade 3 and 4 lymphopaenia and neutropaenia were more common with alemtuzumab, but anaemia and thrombocytopenia were similar in the two treatment groups. Episodes of bacterial sepsis and febrile neutropaenia were comparable and the increase in infection in the alemtuzumab arm was almost entirely attributable to CMV reactivation. Although CMV reactivation occurred in half the patients, it was only symptomatic in 16%. This toxicity was therefore manageable by screening and pre-emptive treatment. Grade 3 or 4 infusion-related events were seen in 13% of patients receiving alemtuzumab and these were largely confined to the first few weeks of therapy. In contrast, adverse events increased over time in the chlorambucil arm where the median duration of treatment was twice as long. The toxicity profile of alemtuzumab in previously untreated patients appears to be much more acceptable with no increased treatment-related mortality compared with chlorambucil in the CAM307 randomised study. The Lundin study showed that efficacy for 18 weeks of subcutaneous alemtuzumab was equivalent to 12 weeks of intravenous therapy. Since subcutaneous administration results in fewer infusion-related side effects, this may be the preferable route.

Several studies, using a variety of treatment regimens, have confirmed the observation that those patients achieving minimal residual disease (MRD)-negativity have prolonged remissions compared with those patients who are MRD-positive at the end of therapy.

Alemtuzumab Consolidation Therapy

Studies of alemtuzumab treatment of CLL, particularly in the relapsed/refractory setting, have consistently shown that patients with bulky nodal disease are less likely to respond to treatment compared with those patients who have low volume or no lymph node enlargement. This is in contrast to the excellent clearance of disease from the blood and bone marrow. In addition, in the Moreton study[3] patients who achieved complete remissions and who were also negative for minimal residual disease (MRD) using a sensitive four-colour flow cytometry[9] had significantly prolonged PFS and overall survival (OS). Several studies, using a variety of treatment regimens, have confirmed the observation that those patients achieving MRD-negativity have prolonged remissions compared with those patients who are MRD-positive at the end of therapy.[10–12] These observations have provided a rationale for using alemtuzumab as consolidation of remissions achieved using fludarabine-based induction regimens. Four groups have published their results for this strategy using various treatment schedules, doses and routes of administration (see *Table 2*).[13–16] Although not comparable, all have demonstrated the efficacy of such an approach in improving responses in around 50% of patients receiving consolidation. There has only been one randomised study which was reported by the German study group in 2004[13] and updated at ASH in 2006.[17] Patients who had been treated to maximum response with fludarabine or fludarabine plus cyclophosphamide were randomised to receive alemtuzumab at the standard dose of 30mg three times per week for 12 weeks given intravenously at a median of two months following induction treatment or to have no further treatment. The trial was stopped prematurely having recruited 21 patients (11 to alemtuzumab and 10 to observation) because of a high infection rate in the alemtuzumab arm. However, despite the small numbers of patients, this trial did show a significant improvement in PFS for patients receiving alemtuzumab consolidation (median not reached) compared with 27.7 months for the observation arm. Factors contributing to the toxicity of alemtuzumab in this setting may be the dose and duration of therapy and, most importantly, the short interval between completing induction treatment and introduction of consolidation.

Consolidation after first induction treatment of CLL is therefore feasible and can deepen remission and increase PFS in a proportion of patients. However, there is a risk of toxicity and there are also financial implications. It may therefore be prudent to reserve this strategy for those patients with higher risk disease. Furthermore, a larger randomised study needs to be completed in such a group to confirm safety and efficacy as well as establishing the optimal timing, dose and delivery (intravenous or subcutaneous).

Alemtuzumab for High-risk Chronic Lymphocytic Leukaemia

It is well recognised that patients who have deletions of chromosome 17p resulting in dysfunction of the p53 pathway have resistance to conventional chemotherapy such as alkylating agents or purine

Table 1: Response Rates for Single Agent Front-line Therapy in Chronic Lymphocytic Leukaemia

Agent	OR (%)	CR (%)	Ref
Chlorambucil	55	2	7*
Alemtuzumab (IV)	83	24	7*
Alemtuzumab (SC)	87	19	5
Fludarabine	6%	20	6
Rituximab	51	4	8

** CAM307 phase III prospective randomised trial comparing chlorambucil and alemtuzumab. CR = complete response; IV = intravenous; OR = overall response; SC = subcutaneous.*

Table 2: Alemtuzumab Consolidation Therapy

Study	Median Interval from Chemo-therapy to Maintenance	Route	Dose	Improved Response
Wendtner (2004)[13]	67 days (45–90)	IV	30mg TIW	45%; improved PFS
O'Brien (2003)[14]	6 months (1–40)	IV IV	10mg TIW 30mg TIW	39% 56%
Rai (2002)[15]	~2 months	IV/SC	30mg TIW	92% OR: 42% CR: 44%
Montillo (2004)[16]	At least 8 weeks after F	SC	10mg TIW	51%

CR = complete response; F = fludarabine; IV = intravenous; OR = overall response; PFS = progression-free survival; SC = subcutaneous; TIW = three times a week.

analogues and also have significantly shortened survival compared with those patients without this abnormality.[18] Although p53 deletion in CLL is infrequent at initial presentation – occurring in 5–10% of patients – this abnormality becomes increasingly common as the CLL advances and becomes chemo-resistant. There has now been a number of reports showing that alemtuzumab has efficacy in this subgroup, probably by killing cells through a p53-independent mechanism.[19–21] The only other therapy shown to be effective in this way is high-dose steroids.[22] In CLL patients with p53 deletion who do not have bulky nodal disease, single-agent alemtuzumab may be an appropriate treatment choice either at first or subsequent line of therapy. However, in those patients with enlarged nodes it would seem logical to combine alemtuzumab with high-dose steroids, and this regimen does appear to be effective in a small number of patients who have been treated.[23] It is now critical that patients who are about to embark on treatment, whether this is first- or subsequent-line, should have analysis to detect the presence of the p53 deletion since this will affect selection of treatment. The knowledge of specific genetic abnormalities will allow the prospective selection of appropriate treatments in order to reduce the damage caused by ineffective chemotherapy and to maximise the opportunity for achieving a good remission.

> Alemtuzumab has been shown to be an effective monotherapy in both first-line and refractory chronic lymphocytic leukaemia.

Alemtuzumab Combination Regimens

To date, experience with alemtuzumab in combination regimens is somewhat limited, and has been explored only in the relapsed patient setting. Single-centre data of combinations with fludarabine (FluCam – fludarabine and alemtuzumab[24]; C-FAR – cyclophosphamide, fludarabine, alemtuzumab and rituximab[25]) have all shown improved efficacy compared with alemtuzumab as a single agent in an equivalent clinical setting. There are currently a number of trials examining fludarabine/alemtuzumab-based combinations in the first-line setting and the results of these are awaited. Studies of high-dose steroids and alemtuzumab in high-risk CLL are ongoing.

Conclusion

There have been major advances in the management of CLL over the past decade. This includes the ability to stratify patients according to biological risk parameters such as genetic abnormalities, the introduction of novel therapies such as monoclonal antibodies and the ability to achieve a high proportion of good remissions, including eradication of minimal residual disease. All these strategies have resulted in improved selection of patients for appropriate therapy and better PFS. Alemtuzumab has been shown to be an effective monotherapy in both first-line and refractory CLL and it is now clear from several studies that toxicity is much reduced and more manageable when alemtuzumab is used earlier in therapy. More data are now needed on the use of alemtuzumab in front-line combination regimens. The most compelling data for alemtuzumab efficacy are in the high-risk cytogenetic group exhibiting p53 deletion when used either as a single agent or in combination with high-dose steroids. In addition, this antibody therapy has been shown to be effective in eradicating residual disease after completion of induction therapy, although the optimal regimen (dose, schedule and route of administration) is still to be determined. ■

1. Keating MJ, O'Brien S, Kantarjian H, et al., Results of first salvage therapy for patients refractory to a fludarabine regimen in chronic lymphocytic leukaemia, *Leuk Lymphoma*, 2002;43: 1755–62.
2. Keating MJ, Flinn I, Jain V, et al., Therapeutic role of alemtuzumab (Campath-1H) in patients who have failed fludarabine: results of a large international study, *Blood*, 2002;99:3554–61.
3. Moreton P, Kennedy B, Lucas G, et al., Eradication of minimal residual disease in B-cell chronic lymphocytic leukaemia after alemtuzumab therapy is associated with prolonged survival, *J Clin Oncol*, 2005;23(13):2971–9.
4. Osterborg A, Fassas AS, Anagnostopoulos A, et al., Humanized CD52 monoclonal antibody Campath-1H as first-line treatment in chronic lymphocytic leukaemia, *Br J Haematol*, 1996;93: 151–3.
5. Lundin J, Kimby E, Bjorkholm M, et al., Phase II trial of subcutaneous anti-CD52 monoclonal antibody alemtuzumab (Campath-1H) as first-line treatment for patients with B-cell chronic lymphocytic leukemia (B-CLL), *Blood*, 2002;100: 768–73.
6. Rai KR, Peterson BL, Appelbaum FR, et al., Fludarabine compared with chlorambucil as primary therapy for chronic lymphocytic leukaemia, *N Engl J Med*, 2000;343:1750–57.
7. Hainsworth JD, Litchy S, Barton JH, et al., Single-agent rituximab as first-line and maintenance treatment for patients with chronic lymphocytic leukemia or small lymphocytic lymphoma: a phase II trial of the Minnie Pearl Cancer Research Network, *J Clin Oncol*, 2003;21:1746–51.
8. Hillmen P, Skotnicki A, Roback T, et al., Alemtuzumab (Campath, MabCampath) has superior progression free survival (PFS) vs chlorambucil as front-line therapy for patients with progressive B-cell chronic lymphocytic leukaemia (BCLL), *Blood*, 2006;11:p93a, a301.
9. Rawstron AC, Kennedy B, Evans PA, et al., Quantitation of minimal disease levels in chronic lymphocytic leukemia using a sensitive flow cytometric assay improves the prediction of outcome and can be used to optimize therapy, *Blood*, 2001;98: 29–35.
10. Esteve J, Villamor N, Colomer D, et al., Stem cell transplantation for chronic lymphocytic leukemia: different outcome after autologous and allogeneic transplantation and correlation with minimal residual disease status, *Leukemia*, 2001;15:445–51.
11. Bosch F, Ferrer A, Lopez-Guillermo A, et al., Fludarabine, cyclophosphomide and mitoxantrone in the treatment of resistant or relapsed chronic lymphocytic leukaemia, *Br J Haematol*, 2002;119:976–84.
12. Weirda W, O'Brien S, Wen Sijin, et al., Chemo-immunotherapy with fludarabine, cyclophosphamide, and rituximab for relapsed and refractory chronic lymphocytic leukaemia, *J Clin Oncol*, 2005;23:4070–78.
13. Wendtner CM, Ritgen M, Schweighofer CD, et al., Consolidation with alemtuzemab in patients with chronic lymphocytic leukemia (CLL) in first remission-experience on safety and efficacy within a randomized multicenter phase III trial of the German CLL Study Group (GCLLSG), *Leukemia*, 2004;18:1093–1101.
14. O'Brien, SM, et al., Alemtuzumab as treatment for residual disease after chemotherapy in patients with chronic lymphocytic leukaemia, *Cancer*, 2003;98:2657–63.
15. Rai KR, Byrd JC, Peterson B, et al., Alemtuzumab following fludarabine for previously untreated patients with chronic lymphocytic leukaemia (CLL). CALGB study 19901, *Blood*, 2003;102:676A, a2506.
16. Montillo M, Tedeschi A, Miqueleiz S, et al., Alemtuzumab as consolidation after a response to fludarabine is effective in purging residual disease in patients with chronic lymphocytic leukaemia, *J Clin Oncol,* 2006;24(15):2337–42.
17. Schweighofer M, Ritgen B, Eichorst R, et al., Consolidation with alemtuzumab improves progression-free survival in patients with chronic lymphocytic leukaemia (CLL) in first remission long-term follow-up of a randomized phase III trial of the German CLL study group (GCLLSG), *Blood*, 2006;108:p14, a33.
18. Dohner H, Fischer K, Bentz M, et al., p53 gene deletion predicts for poor survival and non-response to therapy with purine analogs in chronic B-cell leukemias, *Blood*, 1995;85:580–89.
19. Stilgenbauer S, Dohner H, Campath-1H-induced complete remission of chronic lymphocytic leukemia despite p53 gene mutation and resistance to chemotherapy, *N Engl J Med*, 2002;347:452–3.
20. Lozanski G, Heerema NA, Flinn IW, et al., Alemtuzumab is an effective therapy for chronic lymphocytic leukemia with p53 mutations and deletions, *Blood*, 2004;103:3278–81.
21. Osuji N, Del Giudice I, Matutes E, et al., The efficacy of alemtuzumab for refractory chronic lymphocytic leukemia in relation to cytogenetic abnormalities of p53, *Haematologica*, 2005;90:1435–36.
22. Thornton PD, Hamblin M, Treleaven JG, et al., High dose methyl prednisolone in refractory chronic lymphocytic leukaemia, *Leuk Lymphoma*, 1999;34:167–70.
23. Pettitt AR, Matutes E, Oscier D, Alemtuzumab in combination with high-dose methylprednisolone: a rational approach for CLL patients with p53 defects, *Leuk Lymphoma,* 2005;46 (Suppl. 1): S92.
24. Elter T, Borchmann P, Schulz H, et al., Fludarabine in combination with alemtuzumab is effective and feasible in patients with relapsed or refractory B-cell chronic lymphocytic leukemia: results of a phase II trial, *J Clin Oncol*, 2005;23: 7024–31.
25. Weirda WG, O'Brien S, Faderl S, et al., Combined cyclophosphomide, fludarabine, alemtuzumab and rituximab (CFAR), an active regimen for heavily treated patients with CLL, *Blood*, 2006;108:p14, a31.

Bayer HealthCare
Bayer Schering Pharma

- First drug with proven efficacy in Fludara® refractory patients[1]
- Clears both blood and bone marrow with no effect on stem cells[2]
- Median survival of 16 months (32 months in responders)[2]
- Use of MabCampath® can eliminate minimal residual disease (MRD), which may lead to an increase in survival[3]
- Beneficial overall safety profile in relation to disease severity and prognosis in patients with fludarabine-refractory B-cell CLL[4]

References:
1. Keating MJ et al. Blood 2002;99:3554-61
2. Rai KR et al. J Clin Oncol 2002;20:3891-7
3. Moreton P et al. J Clin Oncol 2005;23:2971-2979
4. Österborg A et al. Semin Oncol 2006;33(Suppl 5):S29-S35

MABCAMPATH® alemtuzumab

Target-specific treatment for CLL

Prescribing information: Name of the medicinal product: MabCampath® 30 mg/ml concentrate for solution for infusion. **Qualitative and quantitative composition:** Each vial contains 30 mg alemtuzumab. Alemtuzumab is a genetically engineered humanised IgG1 kappa monoclonal antibody specific for a 21-28 kD lymphocyte cell surface glycoprotein (CD52). The antibody is produced in mammalian cell (Chinese Hamster ovary) suspension culture in a nutrient medium. **Therapeutic indications:** MabCampath® is indicated for the treatment of patients with chronic lymphocytic leukaemia (CLL) who have been treated with alkylating agents and who have failed to achieve a complete or partial response or achieved only a short remission (less than 6 months) following fludarabine phosphate therapy. **Contraindications:** Hypersensitivity or anaphylactic reactions to alemtuzumab, to murine proteins or to any of the excipients; in patients with active systemic infections; in patients infected with HIV; in patients with active secondary malignancies; pregnancy and breast-feeding. **Undesirable effects:** More than 80% patients may be expected to experience adverse reactions; the most commonly reported reactions usually occur during the first week of therapy. The frequencies of the adverse reactions are based on clinical trial data in the B-CLL study population (n= 149). The frequencies are defined according to CIOMS III + V guidelines (very common ≥1/10, common ≥1/100 - < 1/10, uncommon ≥1/1,000 - < 1/100). No information is available for events that occur at lower frequency, due to the size of the population studied (n= 149). The most appropriate MedDRA term is used to describe a certain reaction. Synonyms or related conditions are not listed, but should be taken into account as well. *Infusion-related reactions:* very commonly reported reactions (due to release of cytokines) have been acute infusion-related reactions including fever, rigors, nausea, vomiting, hypotension, fatigue, rash, urticaria, dyspnoea, headache, pruritus and diarrhoea. The majority of these reactions are mild to moderate in severity. Serious reactions, including bronchospasm, hypoxia, syncope, pulmonary infiltrates, acute respiratory distress syndrome, respiratory arrest, myocardial infarction, arrhythmias, acute cardiac insufficiency and cardiac arrest, have occurred in association with cytokine release, with fatal outcome in rare cases. Acute infusion-related reactions usually occur during the first week of therapy and substantially decline thereafter. Grade 3 or 4 infusion-related reactions are uncommon after the first week of therapy. Severe anaphylactic and other hypersensitivity reaction, including anaphylactic shock and angioedema, have been reported rarely following MabCampath® administration. These symptoms can be ameliorated or avoided if premedication and dose escalation are utilised. *Infections and Infestations:* grade 3 or 4 infections have been reported very commonly including Herpes simplex and pneumonia of grade 3 or 4 severity. Opportunistic infections, including those due to reactivation (e.g. *Pneumocystis carinii* pneumonia (PCP), cytomegalovirus (CMV), *Aspergillus* pneumonia and herpes zoster) occur commonly. Rhinocerebral mucormycosis has been reported but is uncommon. Other serious and sometimes fatal viral (e.g. adenovirus, parainfluenza, hepatitis B, Progressive Multifocal Leukoencephalopathy (PML)), bacterial (including tuberculosis and atypical mycobacterioses, nocardiosis), protozoan (e.g. toxoplasma gondii), and fungal infections, including those due to reactivation of latent infections have occurred during post-marketing surveillance. The recommended anti-infective prophylaxis treatment appears to be effective in reducing the risk of PCP and Herpes zoster infections. The prolonged decrease in T-lymphocytes that can be associated with MabCampath® treatment may lead to an increased risk for latent viral reactivation of Epstein Barr Virus (EBV). Evolution of EBV infection/reactivation into EBV-associated lymphoproliferative disorder has been observed in immunocompromised patients in rare cases. *Blood and lymphatic system disorders:* severe bleeding reactions have been reported commonly. Pancytopenia has been reported commonly and may be grade 3 or 4 in severity or serious in nature. Common: neutropenic fever, purpura. *Immune system disorders:* autoimmune phenomena have been reported uncommonly during or after treatment with MabCampath® (e.g. autoimmune haemolytic anaemia, autoimmune thrombocytopenia, aplastic anemia, Guillain Barré syndrome and its chronic form, chronic inflammatory demyelinating polyradiculoneuropathy). In rare cases these can be life-threatening or fatal. A positive Coombs test is also a common event. *Metabolism and nutritional disorders:* very common: anorexia,; common: hyponatraemia, dehydration, weight decrease, hypocalcaemia, thirst; tumour lysis syndrome with fatal outcome has been rarely reported. *Nervous system disorders:* very common: headache; common: taste loss, tremor, hypoesthesia, paresthesia, hyperkinesias, dizziness, vertigo; intracranial haemorrhage has occurred in patients with thrombocytopenia with fatal outcome in rare cases. *Cardiac disorders:* common: tachycardia, palpitation; congestive heart failure, cardiomyopathy, and decreased ejection fraction have been reported uncommonly in patients previously treated with potentially cardiotoxic agents. *Psychiatric disorders:* common: confusion, anxiety, somnolence, depression, insomnia. *Eye disorders:* common: conjunctivitis. *Vascular disorders:* very common: hypotension; common: hypertension, vasospasm, flushing. *Respiratory, thoracic and mediastinal disorders:* very common: dyspnoea; common: bronchospasm, coughing, hypoxia, haemoptysis. *GI disorders:* very common: nausea, vomiting, diarrhoea; common: GI haemorrhage, stomatitis, constipation, dyspepsia, ulcerative stomatitis, flatulence, abdominal pain. *Hepatobiliary disorders:* common: hepatic function abnormal. *Skin and subcutaneous tissue disorders:* very common. pruritus, urticaria, rash; common: erythematous rash, bullous eruption. *Musculoskeletal and connective tissue:* common: arthralgia, skeletal pain, back pain, myalgia. *General disorders and administration site conditions:* very common: chest pain, asthenia, malaise, influenza-like symptoms, oedema, oedema mouth, temperature change sensation, injection site reaction. **Date of revision of the text:** July 2006 Please note! For current prescribing information refer to the package insert and/or contact your local Bayer Schering Pharma Organization. Bayer Schering Pharma AG, 13342 Berlin, Germany

EU2007.0936