Nilotinib monohydrochloride (Tasigna®) is a selective tyrosine kinase inhibitor active against Bcr-Abl kinase. It is licensed for the treatment of adults with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib. The recommended dose for both the chronic and accelerated phase is 400mg twice daily, taken orally.

The British Committee for Standards in Haematology in their guidelines for the management of patients with Bcr-Abl-positive chronic myeloid leukaemia state that initial treatment should be with imatinib, and for patients progressing to advanced phase disease following treatment with imatinib, consideration should be given to the use of either dasatinib or nilotinib.

The London Cancer New Drugs Group has previously supported the use of dasatinib for CML (10).

The Scottish Medicines Consortium (SMC) has advised NHS Boards and Area Drug and Therapeutic Committees that nilotinib is accepted for restricted use within NHS Scotland for the treatment of chronic phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in adults resistant to or intolerant of at least one prior therapy including imatinib.

Clinical evidence for the use of nilotinib in patients with chronic and accelerated phase Philadelphia chromosome positive CML is limited to uncontrolled phase II studies. There have been no published randomised, controlled trials evaluating clinical outcomes for patients with nilotinib. The primary efficacy outcomes (in the phase II trials) of haematological response rate has ranged from 47% to 74%, while the rate of major cytogenetic response has ranged from 29% to 48%.

According to the Scottish Medicines Consortium, although cytogenetic response has previously been shown to be a good surrogate marker for survival in CML patients treated with imatinib, no data correlating cytogenetic response and survival have been demonstrated yet for nilotinib due to the relatively short follow-up period.

Estimated overall survival has ranged from 79% to 95% over 12 months follow-up, but data on progression-free survival are not available. Additionally, there are no data on quality of life of patients receiving nilotinib.

Nilotinib is associated with grade 3 to 4 thrombocytopenia, neutropenia and anaemia, and is more frequent in patients with accelerated-phase CML. Therefore, full blood counts should be performed at baseline, then every 2 weeks for the first 2 months, and monthly thereafter or as clinically indicated. A small proportion of patients in the trials required interventions with haematopoietic growth factors or platelet transfusions.

Grade 3 or 4 elevations in AST, ALT, bilirubin and lipase were also observed in the trials described above, and these were managed by dose interruption and/or dose reduction of nilotinib. Please refer to the Summary of Product Characteristics on detailed advice with respect to caution and contraindications for use of nilotinib.
Nilotinib (Tasigna®) is a selective tyrosine kinase inhibitor active against Bcr-Abl kinase. Bcr-Abl is the oncogenic tyrosine kinase expressed by Philadelphia chromosome-positive (Ph+) stem cells, directly involved in the pathogenesis of chronic myeloid leukaemia (CML). In vivo studies have shown that nilotinib inhibits the autophosphorylation of Bcr-Abl, PDGFR, and c-Kit, thereby reducing tumour size (1).

Nilotinib (Tasigna®) is licensed for the treatment of adults with chronic phase and accelerated phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) with resistance or intolerance to prior therapy including imatinib (1). The recommended dose for both the chronic and accelerated phase is 400mg twice daily, taken orally.

CML is a myeloproliferative disorder resulting from a chromosomal rearrangement leading to the formation of a novel fusion gene, Bcr-Abl, which encodes the Bcr-Abl protein that has constitutive protein tyrosine kinase activity. In the absence of treatment, CML progresses within several years from a chronic phase to an accelerated phase, and eventually culminates in blastic phase and death.

According to the National Institute for Health and Clinical Excellence (NICE) guidance on the use of imatinib for CML, the chronic phase of CML is usually relatively stable and benign, and typically lasts around 3–5 years following diagnosis, whilst the accelerated phase typically lasts for 2–15 months before progression to the blast-crisis phase occurs. The blast-crisis phase lasts 3–6 months. (3)

The British Committee for Standards in Haematology recently issued guidelines for the management of patients with Bcr-Abl-positive chronic myeloid leukaemia (CML) (4). The Committee states that for patients presenting in the chronic phase of disease, treatment should be initiated with imatinib, or in the context of a clinical trial, an imatinib containing regimen. The guidelines suggest that imatinib should be initiated at a dose of 400mg per day for adults, as lower doses may encourage the emergence of drug resistance. These guidelines also suggest imatinib dose escalation to 600–800mg/day when first line imatinib 400mg/day fails.

For patients presenting with advanced phase disease who will not have been exposed to imatinib previously, initial treatment should be with imatinib, and for patients progressing to advanced phase disease following treatment with imatinib, consideration should be given to the use of either dasatinib or nilotinib.

The Scottish Medicines Consortium (SMC) has advised NHS Boards and Area Drug and Therapeutic Committees that nilotinib is accepted for restricted use within NHS Scotland for the treatment of chronic phase Philadelphia chromosome positive chronic myelogenous leukaemia (CML) in adults resistant to or intolerant of at least one prior therapy including imatinib (5). It should be restricted to use in patients who are in the chronic phase of the disease. The Committee also added that the manufacturer did not make a submission for use in the accelerated phase, and therefore the drug could not be recommended for this phase.

The SMC had also recently issued guidance on the use of dasatinib (Sprycel®) in Scotland (6). They accepted dasatinib for restricted use within NHS Scotland for the treatment of adults with chronic phase CML and resistance or intolerance to prior therapy including imatinib. They rejected it for use in patients with accelerated or blast phase disease on the basis that they could not accept the manufacturer’s justification of treatment cost in relation to its health benefits.

According to a study published in Blood (7), in newly diagnosed patients with CML, imatinib is associated with a complete cytogenetic response rate of 87%, a progression rate to accelerated or blast phase of 7%, and an estimated 5-year survival rate of 89%. However, resistance to imatinib occurs annually in 3 to 4% of patients with CML in chronic phase.
Clinical evidence

Clinical evidence for the use of nilotinib in patients with chronic and accelerated phase Philadelphia chromosome positive CML is limited to uncontrolled phase II studies.

The most recent phase II study, published in Blood, investigated the efficacy and safety of nilotinib in patients with imatinib-resistant and/or intolerant CML in accelerated phase (7). The multi-centre, international, single-arm, open label trial involved 119 patients aged over 18 years, with accelerated phase CML. CML in accelerated phase was defined by one or more of the following characteristics present within 4 weeks of the start of treatment, and in the absence of previous transformation to blastic phase:

- Between 15% to 30% of blasts in blood or bone marrow
- 30% or more blasts plus promyelocytes in peripheral blood or bone marrow (provided that less than 30% of blasts were present in the bone marrow)
- Peripheral blood basophils of more than 20%, and/or
- Thrombocytopenia of less than $100 \times 10^9/L$ unrelated to the administration of therapy

Additionally, imatinib resistance was defined by one of the following criteria during treatment with at least 600mg imatinib per day:

- Disease progression from chronic phase to accelerated phase occurring during imatinib therapy
- Disease progression defined as at least a 50% increase in peripheral white blood cell count, blast count, basophils, or platelets during imatinib therapy for accelerated phase, or
- Lack of haematological response (HR) in the bone marrow following a minimum of 4 weeks of imatinib therapy for accelerated phase.

Imatinib intolerance was defined as the discontinuation of imatinib therapy due to any of the following grade 3 or 4 adverse events that persisted in spite of optimal supportive care measures, or grade 2 adverse events related to imatinib therapy in spite of optimal supportive care measures that persisted for at least 1 month or that recurred more than 3 times whether the dose was reduced or discontinued. Additionally, the protocol definition of imatinib intolerance required the lack of a major cytogenic response (MCyR) with imatinib.

Patients were excluded if they had evidence of abnormal cardiac function or conduction, including myocardial infarction within the previous 12 months, a left ventricular ejection fraction of $\leq 45\%$ by echocardiogram, and a history of congenital long QT syndrome or a corrected QT interval ($QTc$) of more than 450 milliseconds on screening ECG.

All patients initially received nilotinib 400mg orally twice daily. If the patient did not return to chronic phase within 1 month, or if there was a loss in haematological or cytogenetic response, or if the patient experienced disease progression, the dose of nilotinib was increased to 600mg twice daily provided the patient did not experience any toxicity. Treatment with nilotinib was continued until the patient experienced disease progression, developed unacceptable toxicity that precluded any further treatment, withdrew consent, and/or if the patient was felt by the investigator to be no longer benefiting.

The primary efficacy outcome was the rate of haematological response (HR) confirmed at 2 consecutive visits at least 4 weeks apart, defined as complete HR (CHR), bone marrow response (MR), otherwise termed as “no evidence of leukaemia”, or a return to chronic phase (RTC).

- A CHR was defined as: marrow blasts of less than 5%, no blasts in peripheral blood, a neutrophil count of $1.5 \times 10^9/L$ or more, a platelet count of $20 \times 10^9/L$ or more, basophils of less than 5% and no extramedullary disease.
- A RTC was defined as: less than 15% blasts in marrow and peripheral blood, less than 30% blasts plus promyelocytes in marrow and peripheral blood, less than 20% basophils, and no extramedullary disease (with the exception of liver or spleen enlargement).

Secondary efficacy outcomes included time to HR, duration of HR, time to and duration of MCyR, and overall survival. Safety outcomes included assessments of blood chemistry values, vital signs, physical examinations including weight and WHO performance status, and repeat cardiac assessments including ECGs and cardiac enzymes (cardiac troponin, creatinine phosphokinase [CK], and the MB isoenzyme of CK [CK-MB]).

The sample size was estimated based on the Fleming single-stage design to test the null hypothesis that $p$ is less than or equal to 0.10, where $p$ is the HR. If however the true response rate is a p value of 0.25 or greater, then 64 patients are needed to reject the null hypothesis with a power of 90% and a one-sided alpha level of significance of 2.5%. However, enrolment of additional patients was allowed, and all patients were assessed for the safety outcomes.

The study involved 119 patients, and the median duration of time since first diagnosis of CML was almost 6 years, and the median duration of prior imatinib therapy was 976 days (2 to 2163 days). Additionally, most patients had also received other therapies such as hydroxyurea (92%), and interferon-alpha (58%). Eighty-one percent of patients enrolled had previously experienced imatinib resistance, with 49% of these patients having received at
least 800mg imatinib. The median dose intensity of therapy with nilotinib in the 119 patients was 790mg/day (range 180 to 1149mg/day). Ninety patients did not go through a dose escalation, and for these patients, the median dose intensity was 727mg/day (range 180 to 800mg/day), whilst for the 29 patients who went through a dose escalation the dose intensity was 919mg/day (684 to 1149mg/day).

The following results were reported:

- 56 patients (47%) achieved an overall haematological response (HR) (95% CI 38% - 56%)
- The median time to first HR in these 56 patients was 1 month (range 0.8 to 5.5 months).
- Of those who achieved a HR, 39 patients who were assessed again at 12 months remained in response at the time, 70% (57% - 83%); 17 patients were not assessed for response at 12 months
- A CHR was achieved by 31 patients (26%), an MR was achieved by 11 patients and a RTC was achieved by 14 patients.
- A MCyR was achieved in 35 patients (29%; 21%-39%)
- The estimated overall survival in all 119 patients at 12 months was 79% (70% - 87%)
- The most commonly reported non-haematological side-effects considered possibly related to nilotinib, and of any grade severity were rash (22%), pruritus (20%), constipation (11%), headache (10%), fatigue (10%), nausea (10%), diarrhoea, and muscle spasm (9%). The most commonly reported haematological adverse events of grade 3 or higher severity were thrombocytopenia (35%) and neutropenia (21%), and these were generally managed by dose reductions and/or interruptions of nilotinib.
- A total of 28% of patients required support with haematopoietic growth factors or platelet transfusions.
- Grade 3 or 4 elevations in AST and ALT occurred in 1% and 2% of patients respectively, which were managed by dose reductions or interruptions
- Grade 3 or 4 elevations of bilirubin occurred in 9% of patients, and grade 3 or 4 lipase elevations occurred in 18% of patients
- One patient discontinued treatment with nilotinib due to pancreatitis
- There were 10 deaths occurring either on study or within 28 days of discontinuation of nilotinib; Of these 10 patients, 5 patients died of progressive CML, 1 of sepsis, 1 due to intracranial haemorrhage, 1 due to pulmonary infection, 1 due to metastatic melanoma, and 1 due to cardiac failure (this patient had a normal left ventricular function at baseline, but a past medical history of COPD).

The authors concluded that nilotinib produced a significant haematological and cytogenetic response in imatinib-resistant and –intolerant patients with CML in accelerated phase. Additionally, the authors suggest that similar rates of HRs were observed in patients with and without Bcr-Abl tyrosine kinase mutations.

The second phase II study published in Blood investigated the rate of major cytogenetic response in patients with chronic phase CML, following resistance or intolerance to imatinib (8). The results of this study are an interim analysis of the first 280 consecutively enrolled patients with at least 6 months of follow-up.

The study involved patients with Philadelphia chromosome positive CML who were in chronic phase and had imatinib resistance or intolerance, and a World Health Organisation (WHO) performance score of <= 2, a normal hepatic, renal and cardiac function. Patients with imatinib resistance had to have been treated with a minimum imatinib dose of 600mg daily for at least 3 months with no response. Patients in accelerated or blastic phase were excluded, as were patients who had received treatment with imatinib for 7 days and hydroxyurea for 2 days prior to the initiation of nilotinib. Imatinib resistance was defined as failure to achieve either:

- CHR after 3 months,
- cytogenetic response after 6 months
- MCyR after 12 months
- or a loss of haematological or cytogenetic response at any time during treatment with imatinib.

Entry criteria for imatinib intolerance included patients with intolerant symptoms defined as any non-haematological toxicity of Grade 3 or higher in severity, or of grade 2 and higher lasting for more than 1 month or recurring more than 3 times despite dose reduction and maximal supportive care. The definition of intolerance also included haematological toxicity of grade 4 severity persisting for more than 7 days.

Nilotinib was initiated at a dose of 400mg twice daily, and patients were instructed to take it on an empty stomach (i.e. fast for 2 hours before and 1 hour after taking the drug). The dose of nilotinib was escalated to 600mg twice daily if:

- a haematological response (HR) had not yet been achieved at 3 months
- a cytogenetic response had not yet been observed at 6 months
- a McyR had not been observed at 12 months, or if
- there was loss in haematological or cytogenetic response or disease progression at any time.
The primary efficacy outcome was overall major cytogenetic response, and secondary outcome measures included time to major cytogenetic response, duration of major cytogenetic response, complete haematological response (CHR), time to and duration of CHR, and overall survival. Assuming a one sided p value of 0.025, and a power of 0.90, a minimum of 132 patients were required, and a response in at least 21 patients out of the 132 patients would be sufficient to reject the null hypothesis. A total of 318 patients were enrolled, but results in this publication were presented for the initial cohort of 280 patients with at least 6 months of follow-up, or those who prematurely discontinued study treatment. Patients had previously received treatment with interferon alfa (184 patients, 66%), cytarabine (71 patients, 25%), hydroxyurea (233 patients, 83%), imatinib less than 600mg/day (77 patients, 28%), imatinib 600 to 800mg per day (91 patients, 33%), and imatinib more than 800mg per day (111 patients, 40%). Previous imatinib resistance had been observed in 194 patients (69%), and 86 patients (31%) had reported previous intolerance to imatinib.

Over the study period, patients discontinued treatment with nilotinib for the following reasons: adverse events (42 patients, 15%), disease progression (32, 11%), withdrawal of consent (10, 4%), other reasons including abnormal laboratory tests, administrative problems, loss to follow-up and protocol violation (14 patients).

Additionally, the following results were reported:

- Major cytogenetic response (MCyR) was characterised as either complete (0% Philadelphia-chromosome positive cells in metaphase in bone marrow), partial (1 to 35% Philadelphia-chromosome positive cells in metaphase in bone marrow), minor (36 to 65% Philadelphia-chromosome positive cells in metaphase in bone marrow), minimal response (66 to 95%), and no response (>95%).

- The median time to major cytogenetic response was 2.8 months.
- Among the patients achieving a major cytogenetic response, 96% continued on nilotinib without progression or death for at least 6 months from the date the of achieving response, whilst the remaining 4% of patients discontinued treatment due to disease progression or death.
- The estimated 12-month overall survival was 95%.
- A CHR, assessable in 185 patients without a CHR at baseline was achieved in 137 patients (74%; 67.1% to 80.2%).
- 11 patients who had achieved a CHR discontinued treatment with nilotinib due to progression or death.
- The most commonly reported non-haematological adverse effects of any severity were rash (28%), nausea (24%), pruritus (24%), headache (19%), and fatigue (19%).
- Clinically notable adverse events reported with other second-line Bcr-Abl inhibitors such as pleural effusions, pericardial effusions, pulmonary oedema and left ventricular dysfunction (all grades 1 to 2) were observed in 3 patients (1.1%).
- Grade 3 or 4 toxicities were noted in less than 3% of patients; the most commonly noted grade 3 or 4 haematological toxicities were neutropenia (29%) and thrombocytopenia (29%), with median durations of 15 and 22 days respectively. Both these adverse effects were manageable by dose reductions or interruptions; however, 5% of patients required interventions with haematopoietic growth factors or platelet transfusions (10%).
- Grade 3 or 4 elevations in ALT occurred in 4% of patients, elevations in AST occurred in 4% of patients, elevations in bilirubin occurred in 9% of patients and elevations in lipase occurred in 14% of patients. These were all self-limiting and resolved spontaneously, with continuation of nilotinib at the same dose, within 1 to 2 weeks.
- Pancreatitits occurred in 3 patients (1%).
- Almost all imatinib intolerant patients were able to tolerate nilotinib (2 of the 86 patients intolerant to imatinib were also intolerant to nilotinib).
- A total of 4 deaths occurred during the study or within 28 days of discontinuing nilotinib: 1 patient had a myocardial infarction, 1 patients died of coronary artery disease, and 2 patients died of sepsis.
The authors concluded that nilotinib provides an alternative effective treatment for patients whose disease becomes intolerant to, or resistant to imatinib.

Finally, research presented in Cancer describes the outcome of 420 patients with CML post-imatinib failure (resistance-recurrence in 374 patients and toxicity in 46 patients) (9). The study involved 574 patients identified since 1999, who were taken off imatinib, and the reasons for imatinib discontinuation were analysed. These included 321 patients in chronic phase, 161 in the accelerated phase, and 92 patients in the blastic phase. Imatinib therapy had been discontinued for the following reasons:

Table 1: Reasons for discontinuation of imatinib (6)

<table>
<thead>
<tr>
<th>Reason for discontinuation of imatinib</th>
<th>Number of patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Haematological resistance or recurrence</td>
<td>66</td>
</tr>
<tr>
<td>Cytogenetic resistance or recurrence</td>
<td>63</td>
</tr>
<tr>
<td>Progression of disease</td>
<td>245</td>
</tr>
<tr>
<td>Imatinib toxicity</td>
<td>46</td>
</tr>
<tr>
<td>Choice of stem cell transplant as the next best option</td>
<td>13</td>
</tr>
<tr>
<td>Death during imatinib therapy</td>
<td>14</td>
</tr>
<tr>
<td>Other (no follow-up available or non-compliance)</td>
<td>127</td>
</tr>
</tbody>
</table>

This analysis therefore only included data from patients in whom imatinib therapy was discontinued for either resistance/recurrence (n=374), or for imatinib toxicities (n=46). These 420 patients were also categorised by whether they received imatinib for:

- Chronic phase and progressed while in chronic phase (chronic to chronic), accelerated phase (chronic to accelerated), or in blastic phase (chronic to blastic phase)
- Accelerated phase and progressed in accelerated phase (accelerated to accelerated), or in blastic phase (accelerated to blastic phase)
- Blastic phase

The following results were reported:

- The estimated 3-year survival rate was 72% in 88 patients who progressed in chronic phase, 30% in 130 patients who remained or progressed in accelerated phase, and 7% in 156 patients who remained or progressed in blastic phase
- Survival in chronic phase was better when subsequent therapy was nilotinib or dasatinib vs. allogeneic stem cell transplant vs. others (estimated 2-year survival rates 100% vs. 72% vs. 67%; p=0.01)

Adverse effects/safety issues

According to the manufacturer of nilotinib, and as reported by the phase II trials described above, nilotinib is associated with grade 3 to 4 thrombocytopenia, neutropenia and anaemia, and is more frequent in patients with accelerated-phase CML. Therefore, full blood counts should be performed at baseline, then every 2 weeks for the first 2 months, and monthly thereafter or as clinically indicated (1). A small proportion of patients in the trials required interventions with haematopoietic growth factors or platelet transfusions.

Grade 3 or 4 elevations in AST, ALT, bilirubin and lipase were also observed in the trials described above, and these were managed by dose interruption and/or dose reduction of nilotinib. The trials excluded patients with hepatic impairment, and the manufacturers advise caution when used in patients with hepatic impairment as metabolism of nilotinib is mainly hepatic.

The most frequent non-haematological drug-related adverse events were rash, pruritus, nausea, constipation, diarrhoea, fatigue, muscle spasm and headache.

Cost

The basic NHS price (excluding VAT) for 112 x 200mg capsules (1 month) is £2,432.85, the same as a 1 month supply of dasatinib (Sprycel®). The manufacturer recommends that nilotinib should be continued as long as the patient continues to benefit. Both phase II studies described above reported outcome data for 12 months. Therefore, the cost for one patient receiving nilotinib at the licensed dose of 400mg twice daily for 12 months would equate to approximately £31,627. Please see table 2 below for basic drug costs for imatinib, nilotinib and dasatinib for CML.

<p>| Table 2. Costs for 12 month imatinib, nilotinib and dasatinib treatment |</p>
<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>Cost of one year’s treatment (NHS list price + VAT)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nilotinib</td>
<td>400mg bd</td>
<td>£31,627</td>
</tr>
<tr>
<td>Dasatinib</td>
<td>70mg to 100mg twice daily</td>
<td>£31,627 to £63,254</td>
</tr>
<tr>
<td>Imatinib</td>
<td>400mg once daily to 400mg twice daily (chronic phase)</td>
<td>£19,463 to £38,926</td>
</tr>
<tr>
<td>Imatinib</td>
<td>600mg once daily to 400mg twice daily (accelerated phase)</td>
<td>£29,199 to £38,926</td>
</tr>
</tbody>
</table>
NICE estimate that there are around 5 cases of CML per 100,000 population. If we assume that 80% receive treatment with imatinib and that 5% stop treatment each year and are considered suitable for a second-line agent then we might expect around 0.2 new cases per 100,000 population once steady state has been reached. Assuming a majority of patients in the chronic phase stay on treatment we would therefore expect an incremental increase in use each year. Given these assumptions, if nilotinib and/or dasatinib is accepted for use in the NHS for patients with CML who have failed treatment with imatinib we might expect an average of 1 case per 100,000 population to be eligible for treatment at this moment and for this to increase incrementally over the next few years to perhaps reach a steady state level of 2 patients per 100,000 population. At this level of use, the drug cost would increase by between £31,627 to £63,254 per 100,000 population. If treatment is restricted to patients with chronic phase disease as per the SMC recommendation this would reduce uptake – the SMC state that 26% of patients that are resistant to imatinib have chronic phase disease and therefore the cost impact would decrease by about 60%.

Points for consideration

- Current NICE advice does not provide definitive advice on the management of patients that are intolerant or unresponsive to conventional dose imatinib, except to state that the use of imatinib in patients that progress to accelerated or blast phase disease whilst taking imatinib should be done within the context of further clinical study.

- Although the British Committee for Standards in Haematology guidelines recommends either dasatinib or nilotinib for patients with imatinib intolerance or resistance, there are no data to support an informed decision between the choice of dasatinib and nilotinib.

- Evidence for the use of nilotinib is limited to 2 phase II uncontrolled trials. There are no phase III randomised studies available which allow a direct comparison of nilotinib with current standard treatment and no data which allow quantification of its impact on clinical outcomes.

- The surrogate marker, rate of cytogenetic response, has been used as the primary efficacy outcome. Although cytogenetic response has previously been shown to be a surrogate marker for survival in CML patients treated with imatinib, no data are available yet to demonstrate correlation between cytogenetic response and survival for nilotinib-treated patients.

- There are no data on quality of life for patients receiving nilotinib.

- All efficacy data for patients who were intolerant or resistant to imatinib have been grouped together and therefore it is not possible to determine eligibility with respect to imatinib-intolerance or imatinib-resistance.

References

2. Nilotinib monohydrochloride monograph. DRUGDEX via MICROMEDEX [accessed 16 June 2008]


The document reflects the views of LCNDG and may not reflect those of the reviewers.

Please direct any comments to Hina Radia, London & South East Medicines Information Service, Guy’s Hospital, Great Maze Pond, London SE1 9RT
Tel: 020 7188 3853, Fax: 020 7188 3857, email: hina.radia@gstt.nhs.uk