Summary

The drug and the review

- Imatinib is a protein-tyrosine inhibitor with specific activity against the BCR-ABL tyrosine kinase.
- It has been licensed for the treatment of Philadelphia chromosome positive Ph+ CML and GIST for a number of years and both these indications have been addressed by NICE. More recently it has received a license for the treatment of adult patients with newly diagnosed Ph+ ALL integrated with chemotherapy and as a monotherapy for the treatment of adult patients with relapsed or refractory Ph+ ALL.
- The purpose of this review is to evaluate the evidence to support use in this indication in adults with newly diagnosed and relapsed disease.

Background

- Ph+ALL constitutes about 20% of all cases of ALL in adults which itself only occurs in an estimated 1.3 adults per 100,000 population per year. Therefore it is estimated that Ph+ALL occurs in about 3 adults per 1,000,000 population per year. This makes it a very rare disease and thus makes it difficult to carry out randomised studies powered to look at patient orientated outcomes.
- Ph+ALL has a very poor prognosis – in one series of 175 Ph+ ALL patients treated with chemotherapy it is reported that although initial CR was attained in 68.4% the probability of disease free survival was 13% at 3 years and only 6% if patients who went to receive allogenic HSCT are excluded from the analysis.
- Treatment usually consists of a remission-induction phase, followed by intensification (or consolidation) and then continuation treatment to eliminate residual leukaemia.
- Remission/induction treatment may consist of a combination of alkylating agent, alkaloid, anthracycline or antimetabolites and corticosteroids. Intrathecally administered methotrexate may also be administered if there is evidence of CNS leukaemia. Intensification or consolidation consists of further chemotherapy and allogenic or autologous transplantation where that is deemed appropriate and feasible. Prolonged consolidation treatment is given to non-transplant patients and may consist of systemic and intrathecal chemotherapy given for up to 2.5 years after the start of treatment intensification.

Literature

- Embase and Medline databases were searched for studies assessing the safety and efficacy of imatinib in adults with PH+ ALL. This was supplemented by a search of selected Internet sites (including ASCO, EMEA and NeLM). The bibliographies of any studies identified were used to identify additional studies and the review was widely circulated to clinical experts in the London networks and the manufacturers (Novartis) to ensure it was accurate and comprehensive.
- Only very limited published data were identified including one small (n=55) controlled study assessing imatinib in adults with newly diagnosed disease. The other data available are derived from small uncontrolled studies and some have not been fully published.

Summary continued on next page
Summary continued:

Efficacy studies

Newly diagnosed Ph+ALL

- One controlled study (n=55) which compared outcomes in patients not suitable for allogenic stem cell transplant and randomised to imatinib-based or chemotherapy-based induction therapy showed that 85.2% of patients treated with imatinib and 23.1% of patients randomised to chemotherapy achieved complete haematological response. However high levels of patient crossover make it difficult to interpret subsequent findings reported in this study.

- Four uncontrolled studies (combined n= 211) assessed the effect of adding imatinib to chemotherapy as part of induction or consolidation (the licensed indication) and collectively these studies showed that a complete haematological response was achieved in 93%, a major cytogenetic response in 90% and a complete molecular response in 48%. Similarly two studies (combined n= 48) assessed the effect of adding imatinib to corticosteroids and reported a complete haematological response rate of 89% and a complete molecular response rate of 26%.

Relapsed or refractory patients

- In a pooled analysis of two uncontrolled studies assessing imatinib monotherapy in this population (n= 68) it is reported that 30% achieved a complete haematological response –median time to progression was 5.4 months in patients that achieved CHR. Overall survival was 33.2% at 12 months and 22.6% at 18 months.

- The results of an expanded access programme (n=353) indicate that 87.6% of patients progressed within 12 months and the median time to progression was 3.2 months. The estimated probability of being alive at 12 months was 40.8%.

- Subgroup analyses of patients receiving imatinib as salvage therapy prior to SCT (n=30) and as a treatment for relapse after allogenic SCT (n=20) have been presented at conference.

Safety

- It is difficult to provide any meaningful insight into the specific toxicity profile of imatinib in patients with Ph+ ALL as the trials reported are very small, there are two different populations reported, there are only limited control data available and it is used both as a monotherapy and in combination with steroids and as a component in a variety of chemotherapy regimens.

- In newly diagnosed patients the EMEA state that infections occurred in 23 out of 91 (25%) of post-induction courses, fatigue in 8 (9%) and peripheral neuropathy in 7 (8%). Fluid retention was reported in 6 patients (7%) and increases in hepatic enzymes and creatinine in 5 patients (6%). In relapsed or refractory patients it is stated that 20% of patients on the expanded access programme discontinued treatment because of adverse effects and that 68% of patients in this programme experienced serious adverse events (progressive disease – 36%, infections - 27%). 43% of patients in the programme developed anaemia, 30% thrombocytopenia and 18% neutropenia. Grade 3 to 4 haematological adverse events usually lasted for between 1 and 4 weeks.

- In a recently published analysis of data from the international expanded access programme of imatinib in adults with Philadelphia chromosome positive leukaemias it is reported that of the 353 patients recruited with Ph+ ALL 17.3% had a serious adverse event, these included febrile neutropenia (2.5%), pyrexia (2.3%), and sepsis (1.4%)

Critical evaluation

- Evaluation is restricted by the lack of controlled data available and the complexity of the disease treatment. This prevents us from quantifying any potential incremental benefits or harms of imatinib over existing treatments, except to say that there is probably sufficient evidence to suggest that imatinib would appear to offer a satisfactory alternative approach to treatment in terms of comparative efficacy and safety.

Potential benefits of imatinib over existing technologies

- As an oral therapy imatinib would appear to offer distinct patient and service advantages in terms of need reduced need for IV access and daycare visits when used as a monotherapy. However when used as part of a multi-treatment regimen this advantage would appear to be no longer relevant.

Potential disadvantages of imatinib over existing technologies

- The potential disadvantages of imatinib are dictated by the nature of the evidence available to support its use in this condition – at present there is not sufficient evidence to rule out the possibility that its use could be associated with worse clinical outcomes than standard treatment and similarly it is not possible to assess its tolerability relative to standard therapy.

Health economics

- As far as we could ascertain there are no fully published health economic analyses available for this technology.

- One unpublished analysis presented at conference suggests that in adding imatinib to conventional chemotherapy in first-line treatment increases overall survival by 3.27 years (4.37 years vs 1.1 years) at an additional treatment cost of £52,600 per patient treated. This equates to an incremental cost utility ratio of £21,299 per QALY gained (range £15,249 to £27,557). It is not possible to independently assess the validity of these estimates.
Imatinib for acute lymphoblastic leukaemia (ALL) in adults

**Background**

Acute lymphoblastic leukaemia (ALL) is a heterogeneous disease with distinct biologic and prognostic groups in which lymphoid precursors with arrested maturation proliferate (1). This typically leads to a clinical presentation of sudden onset of symptoms of bone marrow failure including infection, bruising, tiredness and dyspnoea. Survival rates of between 40 and 50% at 5 years can be attained in young adults but results are not as good for those aged more than 60 years (2). Important prognostic factors include age at presentation, response to initial treatment, cytogenetic abnormalities (especially the presence of the Philadelphia chromosome), the initial white blood cell count and gender (3).

The annual incidence of ALL in adults is about 1.3 cases per 100,000 population. ALL has a bimodal distribution – the incidence is between 4 and 5 cases per 100,000 population aged between 2 and 4, this decreases during later childhood and young adulthood before a second, smaller peak occurs in adults aged over 50 years (incidence 1.0 per 100,000 population) (4).

The approach to treatment is adjusted according to phenotype, genotype and prognostic risk. However for all patients, except those with mature B-cell ALL, treatment consists of a remission-induction phase, followed by intensification (or consolidation) and then continuation treatment to eliminate residual leukaemia (3).

The goal of remission-induction therapy is to eradicate more than 99% of the initial burden of leukaemia cells and restore normal haematopoiesis and performance status (3). Treatment may consist of a combination of alkylating agent, alkaloid, anthracycline or antimetabolites and corticosteroids. Intrathecally administered methotrexate may also be administered if there is evidence of CNS leukaemia. In clinical trials involving adults complete remission rates of 78-93% have been reported during this phase (3). Intensification or consolidation consists of further chemotherapy and allogeneic or autologous transplantation where that is deemed appropriate and feasible. Prolonged consolidation treatment is given to non-transplant patients and may consist of systemic and intrathecal chemotherapy given for up to 2.5 years after the start of treatment intensification. (5)

Philadelphia chromosome positive ALL (Ph+ ALL) results from a reciprocal translocation involving a segment of the Abelson (ABL) oncogene on chromosome 9 being transferred to the breakdown cluster region (BCR) on chromosome 22. This results in the production of an abnormal protein tyrosine kinase called BCR-ABL. The production of BCR-ABL alters the signalling pathways that control the proliferation, survival and self-renewal of haematopoietic stem cells transforming normal haematopoietic cells into leukaemic cells. Ph+ ALL accounts for 20% of ALL seen in adults and for over 50% of ALL seen in adults aged over 50 years. Adults with Ph+ ALL treated with chemotherapy alone have a poor prognosis and in one series of 175 Ph+ ALL patients it is reported that although initial CR was attained in 68.4% the probability of disease free survival was 13% at 3 years (6% if patients who went to receive allogenic HSCT are excluded from the analysis) (6). The difference in prognosis is also reflected in an international trial in which 1521 adults aged under 60 years were treated with an identical induction regimen irrespective of risk assessment. Overall a complete response rate of 91% was achieved but when analysed in terms of Ph status complete response rates of 83% and 93% were seen for the Ph+ and Ph- populations respectively. This difference is also seen in the reported 5 year survival rates – 25% and 41% in the Ph+ population and Ph- populations respectively (7).

Allogenic stem cell transplantation is potentially curative and is considered to be the treatment of choice with 27-65% achieving long-term survival in patients undergoing such transplant in first complete remission. However this is not a viable option for many patients due to the lack of suitable donors, transplant-related toxicities and patient’s co-morbidities. Therefore there is a need both for effective treatments which maximise the opportunity for patients to be eligible for transplant and for treatments that offer better tolerated options for patients that relapse or are refractory to remission-induction treatment.

Imatinib is a protein-tyrosine inhibitor with specific activity against the BCR-ABL tyrosine kinase (1). It has been licensed for the treatment of Ph+ CML and GIST for a number of years and both these indications have been addressed by NICE. More recently it has received a license for the treatment of adult pa-

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**Summary continued**

**Estimated cost per 100,000 population**

- A 30-day supply of imatinib at a dose of 600mg/day costs £2406 (excluding VAT) – therefore it costs just under £29,000 per year to treat a patient with this drug at this dose.
- Assuming that the estimate of an incidence rate of 0.3 cases per 100,000 population is reasonable and that this also equates to the incidence of relapse then very crudely the model above suggests that when used in the first line setting it would increase costs by £52,600 per patient treated – therefore if all newly diagnosed patients were treated with imatinib it would ultimately increase costs by almost £16,000 per 100,000 population per year.
- If used in the relapse setting, it would appear that the median time to progression is around 3 months – therefore use would increase costs by about £2,175 per 100,000 population. It is unlikely that a patient would receive imatinib as both a first-line treatment and at relapse.

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*London New Drugs Group—APC/DTC Briefing*
patients with newly diagnosed Ph+ ALL integrated with chemotherapy and as a monotherapy for the treatment of adult patients with relapsed or refractory Ph+ ALL (8). The use in adults with Ph+ ALL is the focus of this review.

Clinical evidence

Newly diagnosed Ph+ ALL patients

There is one small, open-label, controlled study assessing the efficacy of imatinib in 55 patients aged over 54 years with newly diagnosed Ph+ ALL (9, 10). In this trial patients were randomised if they were not suitable for allogeneic stem cell transplantation and had received no prior chemotherapy except for a 5-day pre-phase treatment with dexamethasone, cyclophosphamide and intrathecal methotrexate (except for 3 patients who went on to receive imatinib). Patients were randomised to receive remission induction treatment with a 4-week cycle of imatinib (600mg daily) (n=28) or multiagent chemotherapy (dexamethasone, vincristine, idarubicin, cyclophosphamide, cytarabine and GCSF) (n=27). Crossover to the other induction arm was allowed if there was no reduction in blasts seen after 2 weeks. All patients who completed remission-induction therapy, and irrespective of response to that therapy, then went on to receive imatinib (600mg/day) in combination with chemotherapy as part of the chemotherapy consolidation (up to 5 cycles) and re-induction chemotherapy. The primary end-point of this trial was rate of haematological response after induction therapy. Secondary end-points included rates of complete molecular response, recurrence, death, discontinuation and frequency of severe (Grade 3/4 adverse events) during the induction phase. Randomisation produced two well-balanced groups at baseline, although there were relatively more patients with complex karyotype in the imatinib group (42% vs. 25%).

In the 27 evaluable patients randomised to imatinib it was shown that 23 (85.2%) achieved complete remission with neutrophil and platelet recovery and 3 incomplete remission to produce an overall remission rate of 96.3%. The one un evaluable patient and the one patient that only achieved a partial remission went on to achieve complete remission after the first cycle of consolidation treatment. Conversely in the 26 evaluable patients randomised to chemotherapy 6 (23.1%) achieved a complete remission with neutrophil and platelet recovery and 7 an incomplete remission to produce an overall remission rate of 50% (p = 0.0001). Two patients died during chemotherapy induction and of the 11 patients that switched over to imatinib (9 patients refractory to chemotherapy and 2 that only achieved a partial response) – 9 achieved complete remission.

Molecular response rates of 34.6% in patients randomised to receive imatinib induction (9 out of 26 evaluable) and 36.4% in patients randomised to receive chemotherapy (8 out of 22 evaluable) were seen after treatment consolidation.

This level of patient crossover and the fact that all patients subsequently received imatinib and chemotherapy makes it difficult to interpret the follow-up data presented below

After a median follow-up period of 11.2 months the following data are available (10)

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Imatinib (n=28) (%)</th>
<th>Chemotherapy (n=27) (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ongoing complete remission</td>
<td>7 (25%)</td>
<td>8 (29.6%)</td>
</tr>
<tr>
<td>Deaths</td>
<td>6 (21.4%)</td>
<td>8 (29.6%)</td>
</tr>
<tr>
<td>Recurrence</td>
<td>15 (53.6%)</td>
<td>11 (40.7%)</td>
</tr>
<tr>
<td>Estimated median remission duration</td>
<td>16.8 months</td>
<td>19.9 months</td>
</tr>
<tr>
<td>Estimated rate of overall survival at 18 months</td>
<td>57.2% (+/- 10%)</td>
<td>41% (+/- 10.6%)</td>
</tr>
<tr>
<td>Median overall survival</td>
<td>23.5 months</td>
<td>12.3 months</td>
</tr>
</tbody>
</table>

The EMEA also describe the results of six non-controlled studies that included patients with newly diagnosed Ph+ ALL (4). Four of these trials (Appendix 1) involving a total of 211 patients tested the effect of adding imatinib to induction or consolidation chemotherapy and it is stated that a complete haematological response was achieved in 93% (147 out of 158 evaluable patients) and a major cytogenetic response in 90% (19 out of 21 evaluable patients). A complete molecular response rate was achieved in 48% (49 out of 102 evaluable responses).

The other two trials (Appendix 2) tested the effect of the combination of imatinib and corticosteroids as induction and consolidation therapy in elderly patients. The overall complete haematological response rate was 89% (n=49) and a complete molecular response rate was 26% in the evaluable population (n=39).

The data from the AUS01 trial (see Appendix 1) which evaluated the efficacy of concurrent treatment with imatinib and hyper-CVAD (cyclophosphamide, vincristine, Adriamycin, and dexamethasone) have been updated several times since publication, most recently at ASCO 2008 (11). The authors report that over the period April 2001 to September 2006 fifty four patients with imatinib-naive de novo or minimally treated Ph-ALL (6 were refractory after one induction course). The regimen evolved over the course of the
study but the final regimen assessed was imatinib 600mg daily for days 1-14 of induction, imatinib 600mg daily during induction/consolidation courses 2-8, imatinib 800mg daily during a 2-year maintenance course and then continued indefinitely. Allogeneic stem cell transplant was performed during first complete response as feasible. Nine of the 54 patients were in complete remission at the start of treatment and 42 out of the remaining 45 patients (93%) achieved complete remission. 16 patients (33%) underwent SCT at first CR a median 5 months after start of treatment (range 1 to 13). With a median follow up of 4 years (range 13-74 months) 22% of patients had relapsed within a median of 15 months (range 8 to 42 months). Overall 3-year disease free survival and overall survival rates (irrespective of SCT) were 62% and 52% respectively.

The data from the JALSG study (referred to as AJP01 study by EMEA - see Appendix 1) which evaluated the efficacy of an induction regimen of cyclophosphamide, daunorubicin, vincristine, prednisolone, imatinib (600mg daily) and methotrexate/cytarabine/dexamethasone followed by 8 alternating cycles of chemotherapy (methotrexate, cytarabine and prednisolone) or imatinib and then two years of maintenance therapy of vincristine, imatinib and prednisolone have been updated (12). It is reported that event free survival and overall survival at 2 years were 51.1% and 57.9% respectively.

Similar results are also reported by Labarthe et al from the GRAAPH-2003 study (13). In this study 45 patients with newly diagnosed Ph+ ALL were treated either using imatinib with HAM (mitoxantrone with cytarabine) as their consolidation regimen if they were considered early responders to standard induction treatment. Imatinib was continued at a dose of 600mg daily until allogeneic stem cell transplantation. Patients considered to be poor early responders to standard induction treatment were switched between days 8 and 15 to the DIV regimen (vincristine, dexamethasone and imatinib). Imatinib was continued at a dose of 800mg daily until allogeneic stem cell transplantation. The overall complete response rate was 96% (43 out of 45 patients). 22 of these 45 patients were aged 55 years or less and had an identified donor and went on to receive a stem cell transplant in first CR. Overall of the 45 patients treated, 10 patients died and at 18 months the overall survival was estimated to be 65%. Of the 43 patients that achieved CR, 8 relapsed – two whilst receiving imatinib consolidation, 4 after allogeneic stem cell transplant and 2 after autologous stem cell transplant despite imatinib maintenance.

**Efficacy in relapsed or refractory patients**

There are no controlled studies assessing the efficacy of imatinib in this population. There are however a number of uncontrolled studies which have assessed imatinib as both a monotherapy and in combination with chemotherapy. The EMEA state that from the data that are available it would appear that treatment was associated with a haematological response rate of 33% of which 12% were complete responders and a major cytogenetic response rate of 23%. The median time to progression ranged from 1.9 to 3.1 months and the median overall survival from 5 to 9 months (4).

**Imatinib monotherapy**

There are at least 3 uncontrolled studies assessing the efficacy of imatinib in adults with relapsed or refractory Ph+ ALL.

In a Phase 1 dose-escalating study imatinib (300-1000mg daily) was given to 20 patients with PH+ ALL (n=10) or with CML and in lymphoid blast crisis (n=10) it is reported that 20% (n=4) had a complete haematological response and 50% (n=10) had a bone marrow response. The median duration of therapy was 74 days (range 1 to 349). 12 of the 14 responders relapsed within a median of 58 days after treatment initiation and the median duration of response amongst these 12 responders was 58 days (range 42 to 123), one patient underwent allogeneic stem cell transplant and one remained in remission after 243 days of imatinib treatment (14).

In a Phase II study 56 patients with either Ph+ ALL (n=48) or CML and in blast crisis (n=8) were treated with imatinib (600mg daily for all but 5 patients who received 400mg daily). Patients were eligible for the study of they had a morphologically confirmed diagnosis of relapsed Ph+ ALL [first (n= 19) or subsequent (n=12) after standard chemotherapy, autologous or allogeneic bone marrow or peripheral blood SCT) or refractory Ph+ ALL (n=17, failure of conventional induction therapy to induce complete remission after 2 courses). Co administration of other anti-cancer drugs or steroids was not permitted. The primary end-point was sustained haematological response lasting 4 weeks or longer. Treatment with 600mg imatinib was shown to induce a sustained haematological responses in 12 out of 46 (26%) of patients with Ph+ ALL, 4 achieved a complete CHR, in addition unconfirmed haematological responses were seen in 27 (59%). However the median duration of haematological response was only 3.4 months. The median time to progression and median survival in patients started on imatinib 600mg daily was 2.6 months (95% CI: 1.9 to 3.0 months) and 5 months (4.2 to 7.2 months) respectively (4, 15).
A pooled population analysis of results seen in 68 patients with relapsed or refractory Ph+ ALL recruited to one of these two studies has also been published (4). In this analysis it is stated that the overall haematological response rate was close to 70%, 30% showed a complete haematological response, 29% a complete marrow response and 11% a partial marrow response. Median time to progression (TTP) was 5.4 months in patients that achieved a CHR and 1.7 months in patients that achieved a partial response. Overall survival was 33.2% at 12 months and 22.6% at 18 months. Prognostic factors associated with inferior remission rates and response durations included >5% bone marrow blasts on day 14, prior remission of < 6 months, WBC count of > 10x10^9/L, circulating peripheral blood blasts at diagnosis, additional PH chromosomes or >/=2 BCR-ABL fusion signals.

**Imatinib monotherapy as salvage therapy prior to SCT**

A subgroup analysis of 30 patients from the above studies has been published (16). 22 out of the 30 eligible patients were transplanted a median of 67 days (range 34 to 246) after starting imatinib. Of the 30 patients eligible for SCT, 8 (27%) achieved a CHR and 10 (33%) a marrow CR. The responses lasted a median 70 days (range 13 to 184) and consequently 12 patients were transplanted with overt leukemia, and 10 were transplanted during a CHR or marrow CR. 6 of the 12 transplanted with overt leukemia and 2 of the 10 in remission died as a result of transplantation. 6 of the 10 patients transplanted during a haematological or marrow response achieved ongoing remission (median 12.8 months, range 1.7 to 23.8 months), however only 1 of the patients transplanted with over remission remained in remission 7 months after transplantation.

**Imatinib monotherapy for treatment of relapse after allogenic SCT**

A subgroup analysis of 20 patients from the above studies has been presented at conference (17). It was shown that CHR and complete cytogenetic response was achieved in 11 patients (55%) and marrow response with incomplete peripheral blood recovery in 4 (20%). Sustained HR lasting 5 to 21 months which were ongoing at the time of analysis were reported in 4 patients (20%).

**Imatinib prophylaxis after allogenic SCT**

The results of a small case series assessing the role of imatinib (aiming for 400mg daily) in preventing the recurrence of leukaemia in high-risk Ph-ALL patients has been published (18). In this series 15 patients were given imatinib from time of engraftment for one year. The authors report that 13 patients completed the course as described and at a median follow up of 1.3 years, 12 were alive.

**Imatinib in combination with chemotherapy for relapsed/ refractory Ph+ ALL**

The EMEA describe two very small uncontrolled studies involving a total of 12 patients with Ph+ ALL (4). In one study that involved 7 patients with relapsed Ph+ ALL, patients were treated with 1 week pre-phase course of imatinib (600mg od) and then continued with an induction regimen of standard-dose idarubicin/ cytarabine, with vincristine/ prednisolone added for lymphoid leukaemia) for an additional week. Imatinib was then stopped but re-started as a single agent once the blood-count had recovered. There was 7 (68%) CHRs seen among 9 evaluable patients with CML-LBC or relapsed Ph+ ALL and major cytogenetic responses in all 8 evaluable patients.

In the other study 5 patients with refractory Ph+ ALL were treated with intensive hyper-CVAD in combination with imatinib. Complete molecular remission was achieved in 2 of 4 refractory patients tested.

<table>
<thead>
<tr>
<th>Outcome assessed</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Estimated % of patients without disease progression at 12 months</td>
<td>12.4%</td>
</tr>
<tr>
<td>Median time to progression</td>
<td>3.2 months (3 to4)</td>
</tr>
<tr>
<td>Estimated probability of being alive at 12 months</td>
<td>40.8% (28 to 54)</td>
</tr>
<tr>
<td>Median survival</td>
<td>In patients aged &gt;/= 55 years - 8.9 months (7 to NA) In patients aged &lt; 55 years – 11.4 months (6 to NA)</td>
</tr>
</tbody>
</table>
### Adverse events/Safety issues

It is difficult to provide any meaningful insight into the specific toxicity profile of imatinib in patients with Ph+ ALL. As described above the trials reported are very small, there are two different populations reported, there is only limited control data available and it is used both as a monotherapy and in combination with steroids and as a component in a variety of chemotherapy regimens.

In newly diagnosed patients the EMEA state that infections occurred in 23 out of 91 (25%) of post-induction courses, fatigue in 8 (9%) and peripheral neuropathy in 7 (8%). Fluid retention was reported in 6 patients (7%) and increases in hepatic enzymes and creatinine in 5 patients (6%) (4).

In relapsed or refractory patients it is stated that 20% of patients on the expanded access programme discontinued treatment because of adverse effects and that 68% of patients in this programme experienced serious adverse events (progressive disease – 36%, infections - 27%). 43% of patients in the programme developed anaemia, 30% thrombocytopenia and 18% neutropenia. Grade 3 to 4 haematological adverse events usually lasted for between 1 and 4 weeks.

In a recently published analysis of data from the international expanded access programme of imatinib in adults with Philadelphia chromosome positive leukaemias it is reported that of the 353 patients recruited with Ph+ ALL 17.3% had a serious adverse event, these included febrile neutropenia (2.5%), pyrexia (2.3%), and sepsis (1.4%) (19). Overall the EMEA state that the safety profile of imatinib is consistent with that expected in ALL populations and seems not different from that seen previously with imatinib in other disease populations. The main adverse effects associated with imatinib in patients with CML are as follows (20):

- Nausea and vomiting – about 50% experience nausea and 25% experience vomiting
- Oedema and fluid retention – about 3% develop severe oedema and 10% have fluid retention
- Cutaneous disorders – about 25% develop a rash
- Heart failure – occurs in between 0.1 and 1% of patients treated with imatinib and may be more likely to occur in elderly patients and in those with a history of heart disease.

### Economic/Cost implications

A 30-day supply of imatinib at a dose of 600mg daily costs £2406.12 (excluding VAT) – therefore it costs just under £29,000 per year to treat a patient with this agent. Given the variety of dosage regimen and durations used it is difficult to provide a more accurate estimate of treatment cost.

One unpublished health economic assessment of the cost-effectiveness of imatinib added to conventional chemotherapy regimens (compared to chemotherapy alone) was identified (21). The model assessed direct medical costs and was based on a Markov model developed to follow a hypothetical cohort of 1000 Ph+ ALL patients. Estimates of disease free survival were derived from historical data published in 1998 and the JALSG study (discussed above). Within this model it is estimated that adding imatinib increases overall survival by 3.27 years (from 1.1 year to 4.37 years) and that this equates to an incremental gain of 2.47 QALYs. It is estimated that the additional costs associated with using imatinib are £52,600 per patient treated and therefore the cost per QALY gained is £21,299 (range £15,249 to £27,557). Unfortunately it is not possible to provide any assessment of whether these estimates are robust and the Scottish Medicines Consortium were unable to approve the use of imatinib for this indication as the manufacturer did not make a submission (22).

Assuming that the estimate of an incidence rate of 0.3 cases per 100,000 population is reasonable and that this also equates to the incidence of relapse then very crudely the model above suggests that when used in the first line setting it would increase costs by £52,600 per patient treated – therefore if all newly diagnosed patients were treated with imatinib it would increase costs by almost £16,000 per 100,000 population.

If used in the relapse setting, it would appear that the median time to progression is around 3 months – therefore use would increase costs by about £2,175 per 100,000 population. It is unlikely that a patient would receive imatinib as both a first-line treatment and at relapse.
Discussion points/Issues for consideration

- There are only very limited controlled data available to support the use of this agent and no controlled data available to support the licensed indications of treating adults with newly diagnosed Ph+ ALL integrated with chemotherapy and as a monotherapy for the treatment of adult patients with relapsed or refractory Ph+ ALL. Therefore it is not possible to adequately quantify the impact of this treatment on outcomes like overall survival, progression free survival or quality of life in either newly diagnosed patients or in those with relapsed/ refractory disease. However the data that are available suggest that imatinib has a positive impact on cytogenetic and molecular responses and that survival and relapse rates seen with imatinib-containing regimens are superior to historical cohort data.

- There are limited data available to suggest that when used in combination with chemotherapy in newly diagnosed patients it may enable a higher percentage of patients to get a bone marrow transplant. The data are currently not available to make a reliable assessment of the role of imatinib in conditioning regimens or as a post-transplant treatment.

- Given the range of uncontrolled data available it is not possible to determine the optimal dose or duration of imatinib treatment when used in either newly diagnosed or relapsed/ refractory patients.

- There are no published health economic analyses available to enable an assessment of cost-effectiveness and the SMC were unable to provide guidance to the NHS in Scotland because the manufacturer did not provide a submission to the group. The unpublished data that are available suggest that imatinib may be cost effective when used with chemotherapy in patients with newly diagnosed disease – but this estimate is dependent on a model which suggests that such treatment is associated with a 3-year prolongation of overall survival compared to traditional management.

- If imatinib is used as a primary treatment in newly diagnosed patients it is likely that patients will be refractory to it should they relapse.

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## Imatinib for acute lymphoblastic leukaemia (ALL) in adults

### Appendix 1

<table>
<thead>
<tr>
<th>Study Code</th>
<th>Study Design</th>
<th>Study Details</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADE04</td>
<td>Open label non-randomised study assessing imatinib after induction therapy</td>
<td>In one arm of this study 47 patients (43 with Ph+ ALL) received imatinib (400-600mg daily) for a median of 28 days after completing induction. 26 patients went on to receive a second treatment. In the other arm 46 patients received imatinib as part of induction treatment.</td>
<td>Co-administration of imatinib with induction therapy resulted in complete remission in 43 out of 45 patients (95%) and induced PCR negativity in 52%. 19% of the patients that received imatinib after completing induction therapy achieved PCR negativity – the result for complete remission is not provided.</td>
</tr>
<tr>
<td>AAU02</td>
<td>Open label non-randomised study assessing a 7-day course imatinib (600mg/day) in combination with chemotherapy as pre-induction therapy</td>
<td>There were 7 (88%) complete haematological responses seen in 9 evaluable patients with relapsed Ph+ ALL (n=7) or CML (n=2). There were 7 (58%) complete haematological responses seen among 12 de-novo Ph+ ALL – all 12 patients showed a major cytogenetic response.</td>
<td></td>
</tr>
<tr>
<td>AJP01</td>
<td>Open label non-randomised study assessing imatinib combined with dose-intensive chemotherapy</td>
<td>80 patients received imatinib (600mg/day) for 8 weeks combined with dose intensive chemotherapy (cyclophosphamide, daunorubicin, vincristine, prednisolone) during an induction phase. Patients then went on to receive a consolidation phase of alternating course of chemotherapy (high-dose methotrexate and cytarabine) and imatinib (600mg/day for 28 days). Patients received a total of 8 courses.</td>
<td>Induction therapy resulted in complete remission in 77 (96.2%) and PCR negativity in 71.3%. Relapse occurred in 20 patients (26%) after a median duration of 5.2 months. HSCT was performed in 41 patients. The estimated one-year overall survival rate was 76.1%.</td>
</tr>
<tr>
<td>AUS01</td>
<td>Open label non-randomised study assessing imatinib combined with intensive hyper-CVAD chemotherapy</td>
<td>32 patients (26 with active disease – previously untreated (n=21) or refractory after one induction course (n=5) and 6 were in complete remission were treated with up to 8 induction-consolidation courses alternating hyper-CVAD with high dose methotrexate and cytarabine. Imatinib (400mg daily) was given for 14 days at the start of each cycle.</td>
<td>25 (96%) of patients with active disease achieved complete remission. Complete molecular remission was seen in 12 (60%) of the 20 evaluable patients. Allogenic stem cell transplant was carried out in 13 patients (i.e. 50%) in complete remission. A two year disease free survival rate of 87% is reported and this compares favourably with historical control cohort data of patients treated with VAD (12%) or hyper-VAD (28%), although this difference was not significant if data were censored at the time of SCT.</td>
</tr>
</tbody>
</table>

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March 2009

London New Drugs Group—APC/DTC Briefing
### Appendix 2

<table>
<thead>
<tr>
<th>Study Code</th>
<th>Study Design</th>
<th>Patients</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>AFR09</td>
<td>Open label non-randomised study assessing imatinib plus corticosteroids as a post-induction therapy</td>
<td>30 patients (aged 58 to 78 years) were treated with imatinib (600mg/day) plus intermittent steroids following induction treatment with steroids, cyclophosphamide, daunorubicin and vincristine.</td>
<td>5 of the 6 patients that survived induction treatment but did not achieve complete remission achieved it after salvage treatment with imatinib. Overall 27 out of 30 patients (90%) achieved complete remission and the projected one year overall survival rate was 68%. Historical control group data presented within this trial showed that 28.5% achieved complete response after induction increasing to 47.6% after salvage therapy and the projected overall survival rate at one year was 43%.</td>
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<tr>
<td>AIT04</td>
<td>Open label non-randomised study assessing imatinib and corticosteroids as an induction therapy in 19 elderly patients.</td>
<td>18 out of 18 evaluable patients achieved a complete haematological response and 3 out of 18 (17%) a complete molecular response. Six patients relapsed after a median time of 6 months (range 3 to 14.7 months) and the projected overall survival rate at one year was close to 80%</td>
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</tbody>
</table>

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

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