Case study 3

Glivec and Chronic Myeloid Leukaemia*

Summary

Need

- Glivec has benefitted patients: it has helped to prolong survival for those with CML.
- CML is not easy to identify, given this it's also likely to be difficult to predict patient numbers who will benefit from treatment.
- CML occurs in 0.9 per 10,000 people. Close to 2,700 people are diagnosed with CML across the UK.

R&D

- Glivec was initially developed outside of 'pharma' but was commercialized by Novartis. However the time taken from initial breakthrough in scientific knowledge to successful approval was over 40 years.
- Glivec successfully achieved orphan drug status for CML, but also treats other cancers. This illustrates that products for rare diseases can sometimes treat a number of conditions. This will drive higher sales, and correspondingly higher revenue over time.
- Novartis will need to re-coup R&D costs, but the effective patent life may be relatively short with the first patent for Glivec is due to expire between 2013 and 2015.

Regulatory approval

- Glivec's approved use in CML by EMA has been supported by a four main clinical studies, including 2,133 adults and one study of 54 children.
- Together these imply relatively high costs for development although we did not identify the costs from our searches.
- Glivec had been originally authorized under exceptional circumstances in 2001, but this status was removed in 2007 as new data become available. This illustrates that it can take some time to provide additional data, particularly survival benefits and this will also raise the costs of bringing a product to market.

Payer approval

- Glivec costs around £20,000 per patient per year, with cost effectiveness ratios ranging from £21,000 per QALY (considered within the bounds of value for money) to over £300,000. This illustrates the scale of uncertainties, reflecting uncertainties in the clinical evidence base and economic analysis.
- In 2002, the budget impact of Glivec was estimated between £8million to £11.8million for the NHS in England in the rising to £25 million to £15.8million per year after 5 years use. This illustrates a considerable uncertainty, both for the NHS budget but also for the manufacturers revenues.
- Decisions on Glivec's use in England and Wales were taken relatively quickly (within a year of approval) but NICE was initially cautious reflecting limited evidence. Views changed over time as the appraisal process continued.
- Similarly, decisions on Glivec's use in Scotland were taken relatively quickly, (just over a year after approval) and SMC was also cautious, by restricting use. No further updates have come from SMC.
- Further afield in Australia, Glivec is funded by the PBS, but is subject to planned review of survival data by PBAC, and requires individual funding applications.

** 2020health is grateful for all of the insights from experts; the content however of this report is independent and may not reflect the views of experts and sponsors but represents only the views of the 2020health project team. The research was funded by an unrestricted educational grant from Pfizer, Genzyme and Shire.*

Glivec and Chronic Myeloid Leukaemia

Prescription

- Over time, Glivec has become standard treatment, but must compete with new products that have become available within a decade of its launch. That has also necessitated ongoing appraisal by agencies such as NICE, and continued work for Novartis to support such appraisals.

- Novartis has been able to secure significant (and 'blockbuster' status) revenues over time from Glivec, across a number of indications, not just in CML.

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Glivec and Chronic Myeloid Leukaemia

Introduction

Glivec (imatibib) is an anticancer medicine, manufactured by Novartis (EMA, 2012f). Glivec has been shown in clinical trials to improve clinical outcomes for patients with chronic myeloid leukaemia (CML) in terms of surrogate outcome measures for survival, including: overall haematological and cytogenetic response rates, and progression-free survival. Glivec was the first in a new class of cancer drug, resulting in reductions in the uncontrolled proliferation of white blood cells which occurs in CML (NICE, 2002).

Glivec was awarded orphan drug designation for its use in CML and approved for use by the European Medicines Agency (EMA) in 2001 (COMP and EMASS, 2011). Glivec was therefore one of the earliest products to be able to benefit from incentives under the Orphan Drug Legislation.

Glivec and Chronic Myeloid Leukaemia

Need

CML is classified as a rare disease because it has a prevalence rate of 0.9 per 10,000 people (COMP and EMASS, 2011). Five hundred and sixty people in the UK are diagnosed with CML each year (NICE, 2012d). Some 2,660 people have CML across England and Wales (NICE, 2002). It can occur at any age but is more common in middle-aged and older people. It's rare in children (Macmillan Cancer Support, 2011b). CML accounts for more than one in six leukaemias in adults.

CML can often come without symptoms. The leukaemia is often found when doctor orders blood tests for an unrelated health problem or during a routine check-up, and even when symptoms are present, they are often vague and non-specific (America Cancer Society, 2012).

CML has three phases (NICE, 2002):

- The chronic phase is the initial phase of CML; it is usually relatively stable and benign, and typically lasts around 3–5 years following diagnosis.
- The accelerated phase is seen in about two-thirds of people affected; others progress directly to blast crisis. 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 and inevitably leads to death.

People with CML can experience abdominal discomfort, tiredness, weight loss, headaches and visual disturbances, night sweats and fever, bone pain and for men, persistent painful erection (Cancer Research UK, 2011). Those with CML can find it very difficult to cope with (Cancer Research UK, 2010). In short, having CML has a significant impact on quality of life, and shortens life expectancy.

Glivec is one of different treatment options for CML, including (NICE, 2002):

- allogeneic stem cell transplant (SCT);
- IFN-α;
- conventional chemotherapy (usually with hydroxyurea [HU; also known as hydroxycarbamide] or busulfan).

Not all patients can benefit from Glivec, with some intolerant or resistant (Gardner, 2012).

Research and development

Glivec's beginnings came from outside pharmaceutical companies. The discovery that led to the development of glivec came from two researchers (Peter Nowell, MD, of the University of Pennsylvania School of Medicine, and David Hungerford, MD, of the Institute for Cancer Research). They identified a genetic mutation in those with CML back in 1960 (Medical News Today, 2005).

Novartis then took on further development to build on previous discoveries. The team were able to build on the finding that CML could be caused by a single enzyme and design products which could target that single enzyme. Patents followed in 1993 and 1995 (Medical News Today, 2005).

Novartis is now competing with BMS with the development of Dasatinib, although Novartis also has its own alternative Nilotinib. NICE considers that both of these offer superior benefits to Glivec standard dose. (NICE, 2012d)

We haven't been able to find out exactly when Glivec will go off patent, although there is considerable interest and speculation that it may be sometime between 2013 and 2015 (Leukemia and Lymphoma Society, 2012).

Regulatory approval

Novartis built up the clinical evidence base to achieve an 'exceptional circumstances' approval from EMA in 2001 (COMP and EMASS, 2011). Glivec was licensed for the treatment of adult patients with Philadelphia-chromosome-(BCR-ABL)-positive CML in the chronic phase after failure of IFN-a therapy, and in the

accelerated and blast-crisis phases (NICE, 2012d). The exceptional circumstances related to the reliance on surrogate outcome markers, rather than direct evidence on survival. EMA noted that there was a lack of evidence and that: "the indications for which the medicinal product in question [imatinib] is intended are encountered so rarely that the applicant cannot reasonably be expected to provide comprehensive evidence/data on the quality, safety and efficacy of the medicinal product" (NICE, 2012d). As part of approval, Novartis agreed ongoing work to inform the risk/benefit of treatment with Glivec (NICE, 2012d).

EMA (2012f) approval was based on four main trials in CML. The trials involved 2,133 adults and one study of 54 children.

EMA (2012f) changed the approval status for Glivec from exceptional circumstances to approval in 2007. We've not found full details of the additional information that Novartis were able to supply.

Glivec is now approved in more than 110 countries (Novartis, 2012b).

Payer approval

Glivec costs £1724.39 for a 400 mg 30-tablet pack (2012 cost in UK) resulting in an annual cost of treatment of £20,980 per year, assuming a treatment regimen of 400 mg per day (NICE, 2012d). The individual costs per patient depend on the dose prescribed by clinicians (NICE, 2002), as well any discounts negotiated by the NHS with Novartis (NICE, 2012d).

Glivec is excluded from Payment by Results and hence the high cost has to be paid for outside of the national tariff (Medicines Management Team by Coastal West Sussex, 2012).

Glivec has been subject to consideration for both cost and clinical effectiveness by all the three key UK agencies: NICE, SMC and AWMSG (indirectly). Based on our research of the latest guidance from these agencies, their recommendations differ for the use of Glivec for CML:

- NICE recommends the use of Glivec.
- SMC recommends restricted use of Glivec.
- AWMSG does not explicitly recommend the use of Glivec, although it is taken as an appropriate comparator for consideration of new treatments in CML.

We look at each of these in more detail below.

NICE

NICE first considered Glivec close to its launch, producing final guidance in 2002 (TA50). At that point, NICE recommended use in restricted circumstances, recommending use in: "chronic phase in adults who are intolerant of interferon-alpha (IFN-a) therapy or in whom IFN-a is deemed to have failed to control the disease. Imatinib is recommended as an option for the treatment of adults with Philadelphia-chromosome-positive CML in accelerated phase or blast crisis provided they have not received imatinib treatment at an earlier stage" (NICE, 2012d). This means that the recommendation from NICE was more restricted than the license by linking use to the previous treatments received. However, provisional guidance consulted on earlier in 2002 had initially suggested that NICE would only recommend use in the accelerated phase, due to concerns about the limited evidence base (e.g. lack of survival data). In 2002 NICE called for a national registry to provide long-term data on the effectiveness of Glivec (NICE, 2010d).

NICE has re-considered Glivec over time. NICE's latest guidance, published in 2012 (TA251), recommends standard dose Glivec "as an option for the first-line treatment of adults with chronic phase Philadelphia-chromosome-positive chronic myeloid leukaemia (CML)" (NICE, 2012d). That guidance acknowledges an increase in the evidence base over time, with the IRIS clinical trial providing 7 years of survival data (based on 8 years of follow up) (NICE, 2012d).

However, NICE guidance is now concerned with three treatments and Glivec's use not just in terms of standard

dose but also at a high dose (NICE, 2012d). This illustrates how there are changes in the treatment options over time (in 10 years) and how that affects decisions: not just whether to use Glivec but rather Glivec versus other new medicines, as well as it's dose, and use in the broader pathway (first, second etc line positions).

In 2002 when NICE first looked at Glivec, Novartis produced estimates of the incremental cost-effectiveness ratio (ICER) for imatinib treatment when compared with hydroxyurea was (NICE, 2010d):

- between £33,225 per quality-adjusted life year (QALY) and £35,000 per QALY for the chronic phase;
- between £21,800 per QALY and £30,500 per QALY for the accelerated phase; and
- between £33,275 per QALY and £43,500 per QALY for the blast crisis.

These were low in comparison to re-worked analysis from an independent assessment group. When using the least favourable assumptions, they found (NICE, 2010d):

- between £45,600 per QALY and £301,500 per QALY for the chronic phase;
- between £35,600 per QALY and £56,000 per QALY for the accelerated phase; and
- between £52,300 per QALY and £64,750 per QALY for the blast crisis;

By 2012, the cost effectiveness question is about the use of Glivec with other products and in its relative treatment position, because Glivec is now part of routine clinical practice (NICE, 2012d). Thus it is about the cost effectiveness of adding or replacing Glivec with others, and not Glivec's own cost effectiveness *per se*.

In 2002, Novatis estimated the budget impact of Glivec to be £8million for the NHS in England in the first year, rising to £25 million per year after 5 years. This was uncertain however, with the potential for a higher impact of of £11.8 million for the first year, rising to £15.8 million for the upper estimates (NICE, 2010g).

SMC

The SMC (2003a) gave Glivec a restricted recommendation in 2003. Just as NICE did, SMC also wanted further data collection, recommending a central registry (SMC, 2003b). We haven't been able to find out more about SMC's recommendation.

AWMSG

The AWMSG has considered Glivec in the context of informing its recommendations on the use of dasatinib for CML in its 2011 guidance. Evidence considered by AWMSG (2011a) highlighted clinical benefits from both dasatinib and nilotinib verus Glivec at the standard dose. We did not find an earlier appraisal on Glivec alone.

Regional approaches

Glivec has also been subject to local scrutiny. For example, Glivec has been red rated by the Coastal West Sussex Traffic Light System (Medicines Management Team by Coatal West Sussex, 2012). The system is to provide guidance on the use of medicines between the interface between primary and secondary care. The red rating means that Glivec should be initiated by or under the explicit direction of specialists in secondary or tertiary care only.

International funding

Glivec is funded under Pharmaceutical Benefits Scheme (PBS) via applications for individual patients (Australian Governement, Department of Human Services, 2012). Although it is difficult to identify when the first decision was reached by the Phamaceutical Benefits Advisory Committee (PBAC), in 2002 Glivec was listed with the additional requirement that patients must achieve a major cytogenetic response within 18 months and

demonstrate that the response is maintained by testing every 12 months. Listing was accompanied by the intention for PBAC will review new survival data after 1 year, 2 and 5 years (Australian Government, Department of Health and Ageing, 2002).

Prescription

The benefits of Glivec are significant. For example, the latest NICE guidance notes that "the introduction of imatinib into routine clinical practice the 5-year relative survival increased from 27.1% in 1990–92 to 48.7% in 2002–04, for all age groups combined" (NICE, 2012g). This is a result of the routine prescription of Glivec.

In 2010 Glivec had global sales of US$4.3 billion (Credit.net, 2012). Based on our searches, we haven't found a breakdown for revenue from UK sales, or sales within the UK countries.