News on the progress of bosutinib through the NICE assessment system

Bosutinib (Bosulif, Pfizer Ltd.) began its rather long journey through the NICE system way back in mid-2011.

Cancer drugs enter the NICE HTA process with the hope that they will gain a 'positive recommendation' to allow routine use in the (now separate) NHS systems of England and Wales.

Scotland has its own NICE equivalent called the Scottish Medicines Consortium (SMC).

A positive recommendation for a drug means that the NHS must pay for it should a clinician offer it as an appropriate treatment to a patient, provided the patient meets certain profiling criteria set out by NICE.

These criteria sometimes limit a drug to only those patients in Chronic Phase CML or as a treatment following some other specified treatment.

Bosutinib has now almost reached the end of the NICE HTA process and as those of you who have read the Appraisal Consultation Document (ACD) on the NICE website will be aware, the news is less than encouraging.

The ACD (the draft rather than the final determination or FAD) has already outlined why the committee will not recommend bosutinib for the treatment of CML through the NHS.

The patient profile which the appraisal is considering is for the treatment of patients in all phases of CML, but only if they have been previously treated with both 1st and 2nd generation tyrosine kinase inhibitors (TKI) imatinib, dasatinib and nilotinib without success.

In essence, this means that treatment with bosutinib will almost invariably be reduced to a third or fourth line of treatment and would therefore only be used for the treatment of a very small number of CML patients in England and Wales.

Pfizer, the manufacturer of bosutinib, estimate this group of patients to amount to 19 (third line) and 49 (fourth line) each year. The NICE committee did not disagree with that estimate

The study evidence NICE used to judge the drugs clinical effectiveness was based on an equally small patient sample, because the outstanding success of existing TKIs means the patient population for whom there is an unmet need for an effective therapy is very small.

There were therefore very few patients who met the appraisal patient profile, recruited on to the single arm study of bosutinib. The 58 treatment centres in 27 countries involved in conducting the clinical trial managed to locate only 52 patients who matched this patient profile.

Despite this small sample size, the NICE Committee concluded in the ACD that there was evidence from the clinical study that showed clinical efficacy, in terms of both haematological and cytogenetic responses, following treatment with bosutinib.

Andrew Dillon, the CEO of NICE, agreeing with the Committee said in a press release *'there is evidence to suggest that bosutinib was considered clinically effective for the treatment of CML'*.

We agree that this is evident in the data, and have said so in our submissions to this NICE HTA.

No doubt the many CML patients across the world who are currently being treated with bosutinib, and who were previously treated with other TKIs, would also agree. One such patient, from London, testified as to the effectiveness of bosutinib to the Appraisal Committee meeting in June this year.

Obviously the problem that the committee has found concerns the cost of the drug rather than its clinical effectiveness. In particular the key issue is the price of bosutinib compared to the price of Hydroxycarbamide (HU), relative to both drugs clinical effectiveness.

A considerable amount of time has been spent debating how long a patient who has been previously treated with other TKIs would survive on an HU only regime in contrast to how long they would have survived had they been given bosutinib and then HU.

The Committee seemed to have concluded that it would be rational to offer patients previously treated with the other TKIs, HU in a 3rd or 4th line of treatment, rather than bosutinib. Even though they simultaneously unreservedly accept that HU is not a treatment in the same sense as a TKI, since it can have no clinical effect on the course of CML. To many of us this thinking seems irrational.

How do they reach this conclusion?

They have accepted the analysis of some health economists which assumes that the outcomes for patients who have been previously treated with other TKIs followed by HU, would be 'no different' to outcomes for those previously treated with other TKIs, followed by bosutinib and then finally HU.

'No different to' means, from a health economics viewpoint, that there would be no difference in the length of survival time between either group before death.

If you add to this assumption the much reduced cost of HU compared to the higher cost of bosutinib, you can guess the conclusion of their analysis.

In this scenario, bosutinib becomes a drug that is not '*an effective use of NHS resources*', whereas HU is. In other words, bosutinib, a drug that the Committee recognizes to be clinically effective is not a cost effective use of NHS resources, whereas HU, which is not have any clinical efficacy in CML, is viewed as a cost effective use of NHS resources.

We find that view to be perverse and not representative of the ethos underpinning the NHS.

What are the next steps?

The Appraisal Committee gathered in Manchester last week to discuss the manufacturer's (Pfizer) as well as CMLS group's written responses to the draft appraisal committee document (ACD).

I attended the meeting and in my opinion the committee is highly unlikely to change its preferred position, although they did appear ready to agree some minor concessions on some of the points raised regarding survival time on HU.

Pfizer have already offered a patient access scheme (PAS) which is a confidential discount on the price of bosutinib, but this failed to make a difference to the committee's initial conclusion in the ACD.

It's worth repeating a point I have made before, that the top price that is judged a 'willingness to pay' price for any drug undergoing an HTA has remained the same since NICE was formed, over ten years ago. Inflation has never been taken into account.
Cast your mind across all kinds of areas of expenditure and ask yourself where else this applies: food, house prices, petrol, gas, electricity and water prices, train fares?

You might also consider the following.

Not a single cancer drug has managed to get through the NICE HTA process over the last two years without the manufacturer agreeing a PAS, but only one that was acceptable to NICE and the Department of Health.
Note that there is a clear correlation of this timeline with the launch of the Cancer Drugs Fund (CDF) in 2010, the year before this situation arose.

Are the two connected?

I would say that they are, and it is no surprise that dasatinib has been joined by bosutinib, and more recently ponatinib, on the list of CDF drugs, allowing patients who meet certain criteria access.

The problem is that drugs can move out of, as well as into, the CDF list.

The first ejections are scheduled for September this year, although patients who are currently being treated with a drug via the CDF will continue with their treatment.

However an ejection of a drug from the CDF will obviously affect patients who might need that particular drug at some future date.

Bosutinib and ponatinib are not likely to face ejection in September since they have only just been accepted onto the CDF list. It is doubtful that dasatinib will be ejected because it is such an effective drug, but there is no certainty here.

We hope nothing changes with CDF drugs list for CML, and we also hope that the NICE Committee sees the irrationality of its draft decision on bosutinib and reverses it.

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