Reponse to ACD - Mifamurtide for the treatment of osteosarcoma

The Appraisal Committee seeks answers to the following questions:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound and a suitable basis for guidance to the NHS?
- Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

This response is from:

Sarcoma UK

Rarer Cancers Foundation

Has all of the relevant evidence been taken into account?

The evidence is limited to one clinical study which took place over 14 years. It accrued patients in one of the rarest cancers, including teenagers – a notoriously difficult group to convince about entering clinical trials.

The study produced one over-riding conclusion – that mifamurtide resulted in long-term survival for an additional 7-8% of the patient group, reducing the number at risk of dying by about one-third. This was the study's primary endpoint and its statistical design was intended to arrive at a conclusion of this nature. It is worth recalling the opinion of EMA when granting marketing approval "Mepact significantly increased the overall survival of patients…"

It is worth noting that average survival in the UK is lower than in the study group comparison arms (which were largely recruited in the USA) although there is no evidence to suggest that the treatment effect in the UK might be higher as a result.

Whatever else is taken into account this result is fact, it is inarguable, and is a significant statistical outcome.

Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?

It is acknowledged that the single study has weaknesses and that there are many valid questions which remain unanswered. The study was powered to produce an overall survival result, which it did successfully. It was not powered for sub-group analyses yet the Evidence Review for this appraisal entered into extended analysis and discussion about sub-groups. Such analysis was gratuitous. It could never deliver significance because the original study design was not powered to deliver it, and attempting to power the study to do so would have extended the duration of the trial into decades.

It is notable that in other technology appraisals NICE has avoided similar sub-group analyses BECAUSE there was no statistical power. Why is NICE inconsistent on this issue ?

The main difference between sub-groups is one agent in the adjuvant chemotherapy (ifosfamide) and patients in these arms (b and B+) attained a better response with mifamurtide, although this was non-significant. This additional chemotherapy is currently only available in the UK to patients entered in the EURAMOS1 clinical trial. The Committee accepted the assurance of the clinical experts that there was no biological reason for assuming that ifosfamide had a significant effect on the efficacy of mifamurtide.

Given this acceptance there is no rational reason for the emphasis given to the sub-group analyses by the Appraisal, especially when the overall result is so clear.

This is the kind of inconsistent statistical jiggery-pokery of which NICE is more usually able to accuse pharmaceutical companies. That NICE should do it in an apparent attempt to create a fog of added uncertainty around a simple and clear overarching fact is at best contrived, at worst devious.

Are the provisional recommendations sound and a suitable basis for guidance to the NHS?

This treatment is high-cost. Given the very small patient group to which it is applicable (estimated at a maximum of 60-70 a year in England and Wales) the costs of the drug are inevitably high. We welcome the willingness of the manufacturer to agree a patient access scheme with the Department of Health and express some surprise that such an agreement carries no weight with NICE, especially as there is no secret that NICE staff are closely involved with negotiating these schemes. This approach has a two-faced quality to it – it also looks devious and dishonest. Without the support of such a scheme there was never much likelihood of an ICER for mifamurtide coming within the range that NICE usually accepts for approval.

Requiring NICE to undertake a study of this kind was a mistake. NICE processes are inarguably biased against rare diseases and this is an ultra-orphan condition; NICE has never appraised a children's cancer drug before and does not have the contextual experience to do so; nor does NICE have the moral, clinical or scientific authority to pick apart the trial data in the way it has with this review. NICE has moved into an area for which its appraisal processes are unsuited and has once again demonstrated that it is incapable of operating appropriate flexibility with a rarer cancer.

Given the age range of the patient group and the fact that primary treatment for osteosarcoma is nationally commissioned, there is a huge question about the sense of NICE appraising this treatment in the first place. It clearly lies within the scope of national specialist commissioning.

In addition we would draw attention to the NICE Citizen's Council meeting of November 2008 which considered where exceptionality to usual cost-per-QALY rules should apply. More than two-thirds of the members considered exceptional circumstances apply where:

- the patients are children
- the intervention will have a major impact on the patient's family
- the illness under consideration is extremely severe
- the intervention will encourage more scientific and technical innovation
- the illness is rare 20
- there are no alternative therapies available

On this basis we believe that the Department of Health should accept that the Appraisal is not sound, nor is it a suitable basis for guidance to the NHS because it conflicts which society's expectations, as independently expressed through NICE's own consultation methods. NICE must recommend that the Department should use alternative routes which recognise the clinical efficacy of the treatment and are appropriately empowered to approve it for use.

Are there any aspects of the recommendations that need particular consideration to ensure we avoid unlawful discrimination against any group of people on the grounds of gender, race, disability, age, sexual orientation, religion or belief?

The Appraisal Committee's discussion of this issue makes interesting reading. Whether the law on discrimination when drafted, was intended to cover the denial of effective healthcare to children threatened by a potentially fatal disease, is a pertinent question. We might expect the NHS as a whole to reflect the moral and ethical standards of society with regard to children, and we can retain the hope that it will do so. It is, however, a sad day when NICE demonstrates that it has no duty to reflect society's expectations and is prepared to sacrifice children on its self-justified altar of cost-effectiveness.

The self-justification extends to the press release which accompanied the public announcement of the ACD. The wording of this release seems to have been designed to mislead people reading it into believing that there is an effective alternative to mifamurtide in the treatment of osteosarcoma. This is not true and NICE should state this fact unequivocally.

Why should NICE seek to tell an untruth of this kind ? It is clearly intended to explicitly support its negative decision for a treatment which is clinically effective. Using an untruth as self-justification is a reprehensible turn of events and we have separately sought a full explanation.

Thus, we must ask why this appraisal should have been discriminated against to receive such treatment from NICE: is the first drug to be appraised for children's cancer the first to be treated in this way ?