18th March 2010

By First Class Post and Email

[redacted]
National Institute for Health and Clinical Excellence
MidCity Place
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London
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Dear [redacted],

Appeal of NICE Final Appraisal Determination: Azacitidine (VIDAZA) for the Treatment of Myelodysplastic Syndromes, Chronic Myelomonocytic Leukaemia and Acute Myeloid Leukaemia

We wish to appeal against the recommendations in the above final appraisal determination and try to provide the Appeal Panel with a better understanding of myelodysplastic syndromes (MDS) from the patient's perspective. The negative recommendation is a return to hopelessness for UK MDS patients who have glimpsed hope in the EU-approval of the first therapy for malignant bone marrow disease that is a significant advance in medical treatment for this condition. The recommendations also create an ethical dilemma for doctors treating this condition. How can it be in the patient's best interest to deny them an average of an extra nine months of life? Some patients have their lives extended by much longer than the average nine months.

We believe strongly that the underlying appraisal methodology is unfair and lacks transparency. We also believe that the recommendations are perverse as the appraisal committee completely ignored evidence presented to it on quality of life and does not understand the nature of this very rare disease. NICE has also exceeded its powers by making a recommendation that is incompatible with the Human Rights Act 1998 and doctors' ethical obligations. You will find below an overview of MDS followed by our detailed grounds for appeal.

Myelodysplastic Syndromes and Treatment

MDS is a complex group of malignant diseases that cause the bone marrow to malfunction and produce too few or poorly functioning, malformed blood cells. A person with MDS will suffer from chronic, severe fatigue and weakness due to the often extremely low levels of haemoglobin. This is debilitating in itself and often requires regular blood transfusions. Transfusions are time consuming, restrictive, costly and many MDS physicians believe that chronic transfusions shorten patients' lives. In MDS, platelet numbers, which prevent

bleeding and bruising, can often be very low. This can result in spontaneous bleeding and bruising. If an injury is sustained blood loss may be excessive. Clearly these factors result in many constraints and difficulties for patients. Platelet transfusions may be required on a regular basis and once again these are time consuming and restrictive. The average usefulness of a platelet transfusion is counted in hours not weeks and transfusion of platelets can lead to adverse reactions.

When white cells numbers become very low (as they often do in MDS) the body is unable to fight off infection normally. This results in a greater than usual incidence of infections which take longer than usual to clear. Medication is frequently required, as is hospitalisation. Some common illnesses, e.g., chickenpox, can be very serious for a person with MDS. White cells cannot be given by transfusion. The risk of contracting infections from crowded, public places obviously imposes severe restrictions on a person's participation in life and on the life of their family.

The only potential cure for MDS is a bone marrow transplant for those patients who are young enough and who have a suitable donor. Recovery may take months or even years and during this time the patient has to be monitored regularly and where necessary be supported with transfusions, blood growth hormones, pain killers (also known as best supportive care or BSC), and/or active treatment with various forms of chemotherapy. Chemotherapy is particularly important for patients who are unable to receive blood transfusions.

BSC compares very unfavourably with azacitidine. BSC does not represent a treatment as such for intermediate 2 and high-risk MDS. BSC merely deals with chronic symptoms of the condition and with acute events. Transfusions have to be administered with increased frequency and rapidly lead to a much worse quality of life, and decline in health. Each transfusion at the hospital is increasingly taxing for these patients. BSC does not slow or stop the progression of this fatal disease.

Active treatment with chemotherapy is used by many clinicians and can influence the natural history of the disease. Patients who are treated with azacitidine, however, experience haematological improvement, and significantly improved quality of life and overall survival, as explained in our evidential submission to NICE and our response to the appraisal consultation document.

The Institute has failed to act fairly and in accordance with the appraisal procedure set out in the Institute's Guide to the Technology Appraisal Process

The Appraisal Committee Ignored Key Evidence on Quality of Life

The FAD is unfair because the appraisal committee completely ignored evidence available to MDS UK Patient Support Group (MDS UK) on quality of life – in particular fatigue – and patient and carer views of MDS and existing treatments. This evidence clearly demonstrates that quality of life is improved immensely for patients receiving azacitidine. Had the committee been provided with this evidence, then we consider that a greater weight would have been applied to the ICERs (Incremental Cost-Effectiveness Ratio) for azacitidine either comparing to best supportive care alone or to chemotherapy, and that it would be recommended for use on the NHS. This is particularly important when considering end of life treatments, such as azacitidine, for rare, fatal illnesses. NICE's end of life guidance states:

> *"The impact of giving greater weight to QALYs achieved in the later stages of terminal diseases, using the assumption that the extended survival period is experienced at the full quality of life anticipated for a healthy individual of the same age."*

We repeatedly informed NICE that the MDS Foundation, of which MDS UK is a member, is preparing this quality of life data for submission to a peer-reviewed journal and that we would be happy to share with NICE all the quality of life information that we have at our disposal. In our original submission, we responded to the question of whether we were aware of any research carried out on patient or carer views of the condition or existing treatments that is relevant to this appraisal by stating:

> *"The MDS Foundation has conducted more than 60 Patient and Family Forums worldwide. Many patients who attended these Forums have been treated with VIDAZA both inside and outside clinical trials. Our patient questionnaires and recorded discussions have yielded information reflecting an overwhelmingly positive attitude about this therapy and the hope that patients experience with this treatment. While this is not as yet published in a peer-review journal that publication is being readied for submission".*

Similarly, in our response to the ACD dated 24 August 2009, we made clear to NICE that we were willing to provide the quality of life and other data to NICE for this appraisal.

> *"The MDS Foundation (an international patient advocacy organization) will be happy to share quality of life data gathered worldwide with NICE. In addition, the Foundation has developed a quality of life tool that is currently undergoing validation. The Foundation will be happy to provide NICE with all data gathered from MDS patients on an ongoing basis for future support of azacitidine use."*

The above data includes information from more than 1,000 patients gathered from more than 100 Patient and Family Forums worldwide through both written questionnaires administered to MDS patients and through verbal, taped and transcribed quality of life conversations at these. The data provide strong evidence that fatigue is the major reason that MDS patients experience an extremely diminished quality of life.

Blood transfusions rank second only to fatigue in their effect on patients' quality of life. The time involved in travel to the transfusion centre, to receive the transfusions, and the necessity to have an accompanying caregiver imposes a hardship on patients' lives and those of their caregivers. With repeated transfusions, the burden becomes higher as the disease progresses as does the risk of end organ complications arising from iron overload. Patients treated with azacitidine report that their quality of life both from the standpoint of relief from debilitating fatigue and freedom from transfusions has a huge impact on their quality of life and their ability to function in normal activities of daily living.

Given the importance of this information and the appraisal committee's apparent lack of understanding about MDS, NICE is obliged to follow-up with MDS UK regarding the additional evidence. This is consistent with the Coughlan intelligence test[1] and can be

[1] *R (Coughlan) v N&ED Health Authority* [1999] EWCA Civ 1871

evidenced, for example, section 4.14 of the FAD which states that "no representations had been made or evidence received about the pathway of care for patients with myelodysplastic syndromes, chronic myelomonocytic leukaemia or acute myeloid leukaemia who are unable to receive blood transfusions, or about the effectiveness of azacitidine in this patient population". This type of information would be available from our patient forums. To date, however, we have not received a response from NICE on this issue. This unfairly prejudices patients in the UK with MDS, particularly those unable to tolerate transfusions for clinical or religious reasons. NICE also appears to have relied heavily on assumptions in determining the effect of reduced symptoms and fatigue rather than expert patient testimony, for example, submitted by [redacted].

The Appraisal Committee Failed to Consult in an Open and Transparent Manner

During the appraisal committee meeting on 7 January 2010, [redacted], vice chair, who was chairing the Appraisal Committee, stated publicly that he had asked his local haematologist whether he used chemotherapy for his high-risk MDS patients. According to [redacted], that colleague told him that he did not use any chemotherapy to treat these patients. Their apparently informal and off-the-record discussion was then determinative of [redacted]'s position. His reference to this conversation was a discussion stopper at the meeting and seemed to end any debate on the issue.

The view that chemotherapy is not used to treat MDS is simply not true. A significant number of patients receive chemotherapy with BSC. For example, the survival study that formed the basis for the centralised approval of azacitidine by the European Commission following a review by the European Medicines Agency details the use of "conventional care" as one of the arms of this trial. Conventional care is clearly stated to include generally accepted chemotherapeutic regimens:

- low-dose cytarabine;
- intensive chemotherapy (induction with cytarabine followed by IV daunorubicin or idarubicin or mitoxantrone idarubicin); and
- if successful, this was followed by consolidation chemotherapy with reduced drug doses.

Despite this study being submitted to NICE, these treatment pathways were not considered by the Appraisal Committee.

In addition, [redacted]'s anecdotal report of his discussion with his colleague is outside the open and transparent appraisal process. Consultees and other members of the appraisal committee have been deprived of the ability to see the basis for this opinion or to challenge it. This unfairly prejudices patients with MDS as it has led to a reliance by the appraisal committee on BSC as the only comparator and is contrary to NICE's consultation procedures. We refer the Appeal Panel to the observations of Lord Halsbury LC in *Sharp v Wakefield*[2] on the scope of discretion that can be exercised by a public authority in a consultation:

[2] [1891] AC 173 at 179, 55 JP 197, [1886-90] All ER Rep 651

> ". . . discretion means, when it is said that something is to be done within the discretion of the authorities, that that discretion is to be done according to the rules of reason and justice, **not according to private opinion**: . . . according to law, and not humour. It is to be not arbitrary, vague and fanciful, but legal and regular. And it must be exercised within the limit, to which an honest man competent to the discharge of his office ought to confine himself."

The Institute has prepared guidance which is perverse in light of the evidence submitted

NICE's recommendation is perverse as the Appraisal Committee ignored key evidence

NICE's negative recommendation is unreasonable and perverse given that our evidence on quality of life and other information on MDS and treatment with azacitidine described above was not reviewed by the committee despite our clear willingness to share it with them.

Misunderstanding of MDS led to a perverse reliance on BSC as the only comparator

The Appraisal Committee does not fully understand the diseases under consideration and this has led to a perverse reliance on best supportive care (BSC) as the only applicable comparator technology. Chemotherapy is routinely used in conjunction with BSC by many clinicians, particularly in patients who are unable to tolerate blood transfusions. Some choose not to administer chemotherapy because they will simply prescribe azacitidine. Had the appraisal committee not ignored key evidence on quality of life and treatment of patients with MDS available to it from MDS UK, we believe that the more favourable chemotherapy ICERs would have been taken into account rather than simply ignored.

The recommendation is perverse given the 9.5 months extension to life

MDS UK considers that a negative recommendation for azacitidine is unreasonable given the 9.5 month average extension to life – more than three times that required to engage NICE's end of life criteria and it appears much longer than the extensions to life that NICE has accepted in the past – and the very small patient population. There are approximately 700 people with higher risk MDS in the UK and any financial burden on the NHS, regardless of whether the BSC alone ICER or the chemotherapy ICER is used, is unlikely to be significant. We also believe strongly that NICE must apply considerably more weight to the benefits of this drug given the ultra-orphan nature of this treatment.

The Institute has exceeded its powers

The Institute has exceeded its powers by making recommendations that are incompatible with the Human Rights Act 1998 and the General Medical Council's code of ethics that doctors must comply with. The FAD states that azacitidine offers an **average** of nine months extension to life compared with conventional care (BSC or standard/low-dose chemotherapy). This is a significant extension to life and means that patients with MDS can spend longer with their families, have a greatly improved quality of life, continue to work and keep active and ultimately have hope for the future in light of the enormous amount of new drug development research being conducted in MDS.

The prospect of not being able to offer azacitidine to patients and the chance of an extra 9.5 months on average extension to life flies in the face of doctors' ethical obligations. For

example, GMC states in "Ethical Guidance: Withholding and withdrawing- guidance for doctors" (part 1, paragraphs 9,10):

> *"**Doctors have an ethical obligation to show respect for human life; protect the health of their patients; and to make their patients' best interests their first concern.** This means offering those treatments where the possible benefits outweigh any burdens or risks associated with the treatment, and avoiding those treatments where there is no net benefit to the patient...Benefits and burdens for the patient are not always limited to purely medical considerations, and doctors should be careful...to take account of all the other factors relevant to the circumstances of the particular patient...**Prolonging life will usually be in the best interests of a patient**, provided that the treatment is not considered to be excessively burdensome or disproportionate in relation to the expected benefits."*

Bearing this in mind, we suspect that a doctor who does not prescribe azacitidine to appropriate MDS patients may be increasing the risk of negligence claims against the NHS, particularly as the overwhelming evidence is that azacitidine is clinically effective and given the very small numbers of patients with MDS in this country, unlikely to be a significant burden on NHS finances. In addition, UK MDS patients may be inclined to obtain therapy in France or other countries on a case by case basis with their physicians' recommendation.

To this end, we query whether an appropriate risk assessment has been conducted by NICE in conjunction with the NHS Litigation Authority.

Further, the Institute, as a public body, has not acted in accordance with Articles 2, 3, 8 and 14 of the European Convention for the Protection of Human Rights and Fundamental Freedoms (as incorporated in the UK by the Human Rights Act 1998). We note that neither NICE's Social Value Judgements (2008) nor its Equality Scheme and Action Plan 2007-2010 take account of or provide any guidance on NICE's duties under Articles 2, 3 and 8 of the Convention. Rather, those documents attempt to explain NICE's duties under Article 14 of the Convention relating to discrimination.

MDS UK agrees with the Parliamentary assessment by the Joint Committee on Human Rights[3] that, to date, NICE has not taken human rights fully into account in its decision making. We also agree with the recommendation of the committee that NICE should demonstrate in all its publications that it has expressly taken into account the Convention rights of any patients who may be affected, as required by the Human Rights Act. For example, NICE should demonstrate that it has taken into account rights under Article 2, 3 and 8 of the Convention.

In this case, the 9.5 month on average extension to life is a right to life that MDS patients are entitled to under Article 2 of the Convention. Article 2 places a positive obligation on states to prevent foreseeable loss of life. This is particularly where an individual's life is put at risk through the denial of healthcare to newly identified patients with higher risk MDS as the

[3] Joint Committee on Human Rights, The human rights of older people in healthcare, 2007, at page 56. See http://www.publications.parliament.uk/pa/jt200607/jtselect/jtrights/156/156i.pdf

government will be obliged to make funding available to patients already treated with azacitidine according to section 1.1 of the FAD.[4]

The denial of azacitidine to appropriate MDS patients also amounts to inhumane or degrading treatment which is a breach of Article 3 of the Convention. Although we recognise that the threshold for engaging this Article is high in circumstances where there is no "deliberate" infliction of pain or suffering, we believe that the threshold is met given that patients with high risk MDS are in a life-threatening situation.[5] In any event, knowingly refusing treatment that has been established to extend life, as is the case here, amounts to a deliberate act.

In addition, the negative recommendation infringes MDS patients' rights under Article 8 to the private and family life that an additional 9.5 months of life would provide, particularly as the Appraisal Committee has failed to give due or any regard to the wishes and fears of MDS patients as demonstrated by NICE ignoring MDS UK's data on MDS and quality of life. Further, the recommendations discriminate against newly diagnosed patients with MDS who will not be able to access treatment and it also discriminates on the basis of age given that the vast majority of patients with higher risk MDS are over 70 years of age, which is contrary to principles of equality and fairness and Article 14 of the Convention.

We strongly urge the Appeal Panel to ask NICE to look again at its recommendations in the context of the fundamental freedoms above and the ethical dilemma for doctors, bearing in mind that each case needs to be looked at on its own merits.

The Leukaemia Society and Rarer Cancers Forum (which are both consultees in this HTA) are joining MDS UK Patient Support Group in this appeal.

We remain available for any further assistance that we can give you.

Yours sincerely

[redacted]
Chairman, MDS UK Patient Support Group

[redacted]
Deputy Chairman, MDS UK Patient Support Group

[4] *R (on the application of Rogers) v Swindon NHS Primary Care Trust,* [2006] EWHC 171 (Admin).

[5] *Id.* and *Limbuela and others v Secretary of State for the Home Department* [2005] 3 WLR 1014