Vasculitis UK – Response to the Second NICE Appraisal Consultation Document for use of rituximab in treating ANCA vasculitis.

1) Vasculitis UK is the only UK national patient support charity which supports and represents those suffering from **all** types of vasculitis.

2) As a patient group, we do understand that NICE has an obligation to ensure that the treatment regimes which it approves are both effective and cost effective, representing Best Value for Money. In this context, it is inappropriate for a more costly regime to replace a cheaper one without there being significant demonstrable additional benefit. We consider that the relative benefits of the use of rituximab in treating AAV, as an alternative to cyclophosphamide, can be very well demonstrated, especially when **all** the socio-economic factors are taken into consideration and that in most cases the additional cost is easily justified.

3) We welcome the fact that in this second ACD, NICE are now minded to approve the use of rituximab in treating major relapse after exposure to a second course of cyclophosphamide. However we consider that this reconsidered conclusion does not go far enough and will leave certain groups of patients seriously disadvantaged.

4) We are also mindful that earlier this year, Vasculitis UK made a similar submission to the Scottish Medicines Consortium to assist their deliberations on the use of rituximab for treating ANCA vasculitis. The SMC final decision was more pragmatic than the current position adopted by NICE – we would consider more realistic – and it addresses the issues described below. If this divergence between NICE and SMC persists, there will be a cross-border tension reminiscent of the "postcode lottery".

5) We consider that, following the development of rituximab, its off-label use for treating ANCA (and other types) of vasculitis has convincingly demonstrated it to be at least as effective as the only other proven reliable induction medication, cyclophosphamide, albeit without most of the serious side effects associated with such a potent cytotoxic drug.

6) We consider it to be a step change as this is a targeted drug with a very different pharmacological action to cyclophosphamide and other less potent immune suppressing drugs (mycophenolate, methotrexate, azathioprine).

7) We consider that as rituximab is now licensed for the treatment of ANCA vasculitis, failure to make it available for certain categories of patients listed below, who are in the care of the NHS and who suffer disability due to their ANCA vasculitis will represent an **inequality** and constitute **discrimination** against them.

8) The categories of patients are listed below:-

a) Patients who have been given a full maximum cycle of 10-12 pulses without evidence of remission. In these cases there is no reason to expect a further cycle of cyclophosphamide would improve the outcome, whereas rituximab is shown to be highly effective in these cases.

b) Patients with pre-existing endothelial conditions where exposure to the toxic excretory metabolites of cyclophosphamide will increase the probability of developing carcinoma of the endothelial lining of ureter, bladder or urethra..
c) Patients with infections where the use of cyclophosphamide is contra-indicated.
d) Patients who are intolerant to, or show adverse reaction to cyclophosphamide or to mesna (used to reduce endothelial toxicity).
e) Young adult females who may be unnecessarily rendered infertile or brought into a state of premature menopause through exposure to cyclophosphamide.
f) Young adult males whose fertility and potency may similarly be affected.
g) ANCA vasculitis does affect children as young as five, occasionally younger. This group have a lifetime risk of recurrent relapse, involving retreatment and of the long term effects associated with cyclophosphamide exposure.
h) Pubertal and post-pubertal adolescents are believed to be at particularly high risk of infertility due to cyclophosphamide exposure. For this group, cyclophosphamide should certainly be the exception rather than the rule.
i) For a very small refractory group who suffer recurrent relapse despite conventional maintenance therapy, rituximab administered as a single dose at fixed intervals has proved to be a highly effective maintenance regime.

9) <u>As ANCA vasculitis is a rare disease affecting **mainly** those aged 40+ and these categories listed above are exceptions, the total numbers of individuals in these categories is relatively small, consequently the total increased cost to the NHS of treating them with rituximab is correspondingly relatively small.</u>

10) We most certainly consider that failure to include these categories of patients in any restricted list of applications that NICE might be minded to approve for initial induction, in new cases or relapsing cases , would be an unconscionable and grave omission. <u>At the very least, at the point where informed patient consent is being sought, there should be **an informed choice** between cyclophosphamide and rituximab for those whose fertility is at risk.</u>

11) We understand that the deterministic concept of a “safe” limit of 25gms for exposure to cyclophosphamide is not firmly evidence based and that the stochastic effect of exposure to the metabolites of cytotoxic drugs can induce somatic mutation leading to cancer. This increases with the level of exposure<u>, but no level can be considered “safe”.</u>

12) Despite the published AAV treatment guidelines , which advocate induction using pulsed intravenous infusions, many patients have been and continue to be treated with oral cyclophosphamide which results in exposure to very much higher cumulative doses of cyclophoshamide. This does not seem to have been addressed in the context of “2 full cycles of cyclophosphamide” stated in the current ACD.

13) The committee does not appear to have taken note of the strong evidence that when used for a second round of induction, <u>cyclophosphamide is significantly less effective for inducing remission.</u>

14) We accept that, for most patients other than those in the categories listed above, pulsed IV cyclophosphamide is an effective and slightly cheaper agent than rituximab for initial induction remission in new cases.

15) However we noted at the first appraisal that the treatment regime for rituximab which was quoted in the manufacturer's submission was at odds with that which we know to be practised in the UK. We understand that when this is taken into account, the additional cost of administering a full course of rituximab (usually 2-4 infusions) relative to a full course of cyclophosphamide (7-10 infusions) is significantly reduced from those figures used in the health economic studies, thus distorting the ICER result. Thus, inclusive of drug and administration costs, the true difference between the overall cost of rituximab and cyclophosphamide is not as great as has been represented.

16) With all rare diseases, it is very difficult to produce evidence based on adequate sizes of cohort to be statistically significant. Unlike more common diseases, such as cancer or vascular disease, there is little in the way of coherent collection of data and statistics, making it impossible to produce some of the evidence demanded by NICE.

17) With the inception of the new NHS Commissioning process involving Specialised Clinical Reference Groups and the development of new rare disease registries,such as that for vasculitis (which is funded by this charity), these data will soon be increasingly available, so the true value of expensive new biological drugs will be more readily assessed.

18) As a fundamental issue, we consider the concept and use of QUALYS to be inappropriate, simplistic, narrowly focussed and a flawed measurement in diseases such as AAV which may not be curable but can usually be effectively controlled with appropriate treatment and brought into full long-term remission.
As we understand, QUALYS fail to take into account the full socio-economic impact of induction failure or relapse. Patients with AAV may be in early or middle stages of life and effective treatment routinely enables them to continue with a normal working and personal life. Conversely, repeated relapse with associated cumulative organ damage renders them unable to work, dependant on social welfare, requiring ongoing medical and community care, with a consequent substantial cost to the both the NHS and national economy. When all this is taken into account, the case for the use of rituximab as the treatment of choice for all cases of relapse and for maintenance in selected cases is very strong.

19) As a further fundamental consideration, we consider it unfortunate that the NICE STA process for a new drug is largely driven by an application made by the manufacturer of that drug, rather than by the clinicians who have gained experience in use of the drug. This tends to make the NICE appraisal process into an adversarial process rather than an inquisitorial one, which one might consider more appropriate for healthcare considerations. In the case of this appraisal, the motivation for the manufacturer is not great as the potential market for treating AAV is not large, especially in comparison to that for other applications for this drug.

20) **In conclusion**: we consider the introduction of rituximab to be a step change in the treatment of ANCA vasculitis. As a targeted, "biological", manufactured, monoclonal antibody it is a fore-runner of a rising generation of similar tailored antibodies. Failure to give adequate market access for innovative use of existing drugs or of new drugs for treating rare diseases such as AAV provides a strong disincentive for manufacturers to develop other such drugs, or to support new uses for existing drugs, in the future.

21) Rituximab has now been used in the treatment of ANCA vasculitis for over 8 years, with great success. Its use has been enshrined in recommendations by NHS England and its use is core to the newly revised British Society of Rheumatologists' "Guidelines for the Treatment of Adult ANCA Vasculitis". Severely restricting access to this new drug will most certainly be viewed by those with vasculitis as a retrograde step.

John Mills; chairman, Vasculitis UK (on behalf of Vasculitis UK).
October 2013

Those named below are trustees of Vasculitis UK (all of whom have vasculitis) who have read the above response and endorsed it:-

Professor Lorraine Harper (Consultant Nephrologist, Birmingham University Hospital)

(23 letters describing personal experience of rituximab were included in an appendix to the original submission. These are available on request).

See also:
Appended lists of over 1000 signatories. (Appendix 2)
These have all seen a summarised version of the essential points in the above submission (see Appendix 1). They are:-

a) **members of Vasculitis UK who may be currently receiving rituximab or have received it in the past or fear that it might not be available to them in the event of future relapse.**
b) **Family members, carers and relatives of the above.**
c) **Friends and work colleagues of the above.**

Appendix 1 - Letter circulated to Vasculitis UK members.

AN IMPORTANT MESSAGE ABOUT NICE & RITUXIMAB

We, at Vasculitis UK, urgently need **your** help in preparing yet another submission to NICE to influence their decision about the use of Rituximab in treating vasculitis.

Please read the information below, then if you would like to offer your support to the Vasculitis UK submission, please send an email to nice@vasculitis.org.uk.
Put "NICE" in the "subject" line for the email.
Send me your full name including:

1) title (Mr, Miss etc),
2) initials & last name,
3) postcode.

(these details will be on the letter to NICE but will not be made public)

– The Story So Far

As many of you will be aware, the National Institute for Health and Clinical Excellence (NICE) has been carrying out an "Appraisal" of the use of the new "biologic" drug, Rituximab in treating ANCA vasculitis. Until now, its use has been restricted to certain hospitals where research is taking place and in certain other cases, where approval for its use has been on an individual basis.

The usual initial treatment for ANCA vasculitis (Wegeners, MPA & Churg Strauss) and some other non-ANCA types of vasculitis has been cyclophosphamide, which is a very powerful and toxic chemotherapy drug which has saved thousands of lives since its introduction 40 years ago. But cyclo is not suitable at all for use in certain cases and is not sufficiently effective in about 10% of cases. There is a maximum cumulative "safe" dose of 25gms. Serious potential side-effects of cyclophos are bladder cancer and leukaemia. It can also cause infertility in both females and males and can induce premature menopause.

Rituximab is (at present) an expensive drug when compared to cyclophosphamide, but it has been proved to be just as effective without the serious side effects associated with cyclophosphamide. Rituximab has been used for about 10 years for treating other diseases such as Rheumatoid Arthritis, and the side effects are generally not serious, but of course it is not yet known if there are going to be significant long-term side effects.

Rituximab can be used as an alternative to cyclophos as an initial induction drug, to bring the disease under control, or for treating cases of major relapse or for use as a long term maintenance drug. It can be used in cases where cyclophosphamide is unsuitable or where it might impact on fertility. However Rtx has proved to be **especially** useful in treating relapsing cases of vasculitis, whereas cyclophosphamide is less effective second time around.

Vasculitis UK and many medical clinicians made a submission to the initial NICE Appraisal, supporting the use of Rtx in treating vasculitis. The result of this first appraisal was a total rejection of the use of this new drug in the treatment of vasculitis.

Medical professionals and Vasculitis UK then made a second submission. This submission was taken into account in the second appraisal. The decision this time was that Rtx would be approved for use, but **only** in severely relapsing cases and **only** after a second course of treatment with cyclophosphamide. This would bring the total amount of cyclophos up to just below the so called "safe" limit of 25gms.

No consideration or allowance was made for those cases where cyclophosphamide is contra-indicated or cases where there are fertility issues, especially young women. So the failure to approve use of Rtx in these cases is a severe blow.

(Vasculitis UK also made a submission to the Scottish Medicines Consortium for their appraisal of Rituximab. Unlike NICE, they have approved its use for these special cases and for severe relapse, without the requirement for a second dose of cyclophos. So now it is available in Scotland but may not be available in England).

We are now in the third and final stage of the appraisal process and need all the "muscle" we can muster. This decision may not affect you **now**, but it will affect some of our fellow vasculitis sufferers and might affect any of us in the future. ANCA vasculitis tends to be a relapsing disease

If you would like to lend your support and your weight, to the efforts to get Rtx approved for these essential cases, please let me know by email, putting "nice" in the subject title and including **your first and last name and postcode**. This will go in a "petition" to accompany our submission, but the list of names will be confidential to the NICE appraisal.

If NICE rejects the use of Rtx for these cases, vasculitis patients will be worse off than before the appraisal.

All of us who have ANCA vasculitis live with the risk of relapse, so it can affect all of us.

The more vasculitis patients who give their support to this submission, the more influence it may have on the final decision taken by NICE.

Best wishes to all

John Mills (Chairman, Vasculitis UK)

Appendix 2. – List of signatories. This list comprises 2 Excel files containing over 1000 Names and postcodes. For reason of personal confidentiality/data protection, these files have been submitted separately to NICE