aHUSUK - RESPONSE TO THE ECD

1 INTRODUCTION

1.1 aHUSUK Patients' Response

Our members' reaction was one of deep disappointment when told that NICE was unable to recommend eculizumab for the treatment of aHUS and that it was seeking further information from the Company and advice from NHS England. Many told us they were shocked at what they saw as yet another hurdle placed in the way of guaranteed access to eculizumab. Some expressed deep concern at the prospect of their current treatment being withdrawn, although NHSE has since said it has no plans to do this. Some dialysis patients, whose hopes for a transplant had been raised, revealed real anguish over their potentially hopeless situation. As if having to deal daily with this dreadful disease was not bad enough, aHUS patients are in a unique situation. In the past two years they have experienced three high level evaluations, each of which has found eculizumab to be highly clinically effective with the potential to save and transform lives, and yet they find access still uncertain – because the cost issue is unresolved.

1.2 aHUSUK Trustees' Response

Our response to the ECD is in four parts and an Annex. In Part 2 we answer the questions posed by NICE in the preamble. Part 3 is our commentary on Paragraphs 1-8. We offer some additional observations on the HST process from a patient group perspective in Part 4 and conclude our response in Part 5. Annex 1 consists of our notes on the assumptions and workings for budget projection referred to in 3.3. .

The notation is ours. The sub-headings are the same as the ECD with references in parenthesis to the paragraphs we address.

2 THE NICE QUESTIONS *(Page 1)*

2.1 Has all of the relevant evidence been taken into account?

No. The Committee has asked for more evidence from the Company on the cost of the drug and further advice from NHSE, therefore all relevant evidence has not been taken into account
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2.2 Are the summaries of the criteria considered by the Committee and the clinical and economic considerations reasonable interpretations of the evidence?

Yes. There has been reasonable interpretation of the evidence that was called for and provided; but we are not clear about all the criteria the Committee was considering and why reasonable evidence to meet certain criteria was not gathered in the reasonable time given.

2.3 Are the provisional recommendations sound and a suitable basis for guidance on the use of eculizumab for the treatment of aHUS in the context of national commissioning by NHS England?

No. We cannot agree that the provisional recommendations provide a sound and sustainable guidance for aHUS patients whether coping with the illness now or yet to face onset. This is because we consider the conclusion skewed to one single issue out of several equally important criteria. We expected a more rounded approach.

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

Yes. If NICE does not make a final recommendation for permanent national commissioning, and as a result NHSE withdraws the drug from existing patients, it will create a new cohort of disabled people with kidney failure. Within that cohort will be patients who have had a transplant since 1 4 2013 who will have to revert to dialysis as their new kidneys fail. If NHSE continues to prescribe the drug for existing patients and those to whom it has promised

transplants, but fails to provide it for new onset patients, by default it will create a new cohort of disabled people and we suspect that this will breach its equality obligations.

3 OUR COMMENTARY ON THE ECD

3.1 Preliminary recommendations *(Paras 1.1, 1.2)*

We are bewildered by these. The high cost of eculizumab is well known and was first raised formally by AGNSS. It was the sole reason given for the DoH's referral to NICE. It should have been obvious that this would be a sticking point so we cannot understand why it was not confronted sooner. We would have thought it deserved the highest priority.

3.2 Evidence submissions

Nature of the Condition *(4.1, 4.2)*

We are pleased the Committee recognises the value of the "impact survey of eculizumab patients" of 2013 and that it accepts that financial problems, impaired quality of life due to dialysis and plasma exchange, and a burden on families arise directly from this disease.

Clinical Evidence *(4.3 – 4.16)*

This evidence proves the drug works and has very limited side effects.

Economic Evidence *(4.17 -4.21*)

Much of the health economics is incomprehensible to us as laypersons and we find it disturbing that professional commentators are so diverse in their manipulation of the same data. However, we take comfort from the Committee's comment that based on experience whichever economist's advice is taken, the expectation of eculizumab is that it will deliver high QALY by most drug standards.

Evidence Group Review *(4.22 – 4.24)*

We note that within its licensed indication that eculizumab is recommended to continue for a patient's lifetime, unless discontinuation of treatment is clinically indicated. We acknowledge the possibility of discontinuation of treatment when not needed because of definite clinically established diagnosis of a condition other than aHUS.

For those with a definite aHUS diagnosis as well those with an uncertain but likely diagnosis we believe that clinical judgement, based on good quality research into the risks and outcomes, supported by an aHUS Expert Centre concurrence, should underpin any dosage tailoring and exit strategies when needed. Patients must be counselled and should be listened to, and then should be given the best tools to monitor themselves for the earliest indication of renewed TMA, and with a suitable and direct pathway to clinical management.

We have observed good management practice elsewhere and would wish to be consulted on any similar framework adopted for England.

3.3 Consideration of the evidence

Nature of the Condition and Impact of the new technology *(5.2-5.6)*

We agree.

Cost to NHS and Personal Social Services *(5.7)*

Our view on the patient numbers underpinning the Committees' budget projection is that it results in an overestimate of between £64m and £109m over the period. The key reasons for the differences are firstly that the Committee assumed that all patients received an "adult dosage". Doses of 1200mg begin when the patient reaches

40kg weight. Although it is likely that an average 12 year old and above would need such an infusion there will be younger or lighter patients who need lower doses.

Secondly, the Committee's assumption that their estimate of the existing aHUS patient population is also the number who need eculizumab right now. Sadly, even today, there is no exact figure of the current aHUS population. Even though aHUS patients are so few, the NHS is incapable of counting them. This has been confirmed to aHUSUK by both the NHS Renal Registry where aHUS has been, and continues to be, incorrectly classified; and by NICE who have told us that it was impossible to know exact patient numbers for an evaluation like this. Furthermore the NHS has proven to be a barrier to collecting data to make aHUS specific registries valid.

As a result, discussions on aHUS patient numbers rely on data trawled before the First aHUS Patient Conference in 2011 which are in the public domain. Although the best available, this data is unreliable, due to under and mis-reporting of those deemed atypical within an overall aHUS/HUS patient population. Nevertheless it does provide some information on whether those patients were in need of eculizumab at that time.

In the nearly three years since the Conference, there has been some improvement in our knowledge, gleaned largely from our expanding membership. But this is far from complete so we have to accept that we can only rely on a "broad-brush statistical estimate" of incidence i.e. 0.4 incidents per million population.
Which is why we believe that there are about 205 (+/- 15) patients who would be regarded as having aHUS as at April 2014. Of these we estimate that there will be 111 (+/-5) (and not the often quoted 170) who are either receiving or are scheduled to receive eculizumab, as part of a planned transplant. Of these we estimate that 74 patients will require a 1200 mg dose and 37 will need a 600mg dose.

From that base we have produced projections of those who need eculizumab, with some sensitivity analysis to reflect the inherent uncertainties. Using the eculizumab prices stated in the ECD we have arrived at figures which suggest that NICE's "aunt sally" projections present a significant overestimate of gross health spend even compared to our higher level forecast. Our notes on the assumptions and workings are set out in Annex 1.

Value for Money *(5.8, 5.9)*

Because of the uncertainty and upset it has caused in delaying a positive recommendation, it's unfortunate that the Committee has had to seek extra evidence on cost from the Company but we understand its reasons ***(5.8).*** We understand too that the Company is making every possible effort to provide the information by 25 3 2014. We hope that, if necessary, dialogue on the point will be ongoing beyond that date.

We welcome the conclusion of the Committee ***(5.9)*** that omission of other health related costs of the alternative treatments has resulted in an underestimate of the value of eculizumab. We attempted to include as many of these as we could prove in our Patient Submission and indeed shared our information with the Company. We did not have access to other essential data nor the resource to turn what we had into reasonable financial estimates. We have asked other organisations such as Kidney Research UK if there is any generic research into the economics of long term dialysis, particularly where uninterrupted by occasional working transplants, but have been told that there is none.

We do not claim that all the related treatments face all patients every year, but most will be faced by many at some time; and in some cases more than once. Most of the treatments are expensive.

We also detect from the Company's response that the impact of these co-morbidities is partially reflected in the higher health utility and we agree. We also recognise that health state Chronic Kidney Disease Stage 5- End Stage Renal Failure can be further broken down into early and late ESRF, where many of these co-morbidities will eventually have taken their toll on all patients before a premature demise.

In conclusion aHUSUK is certain that that eculizumab's value for money is greater than it appears in the evidence presented.

Impact of the technology beyond health benefits and on delivery of the specialised service *(5.12)*

We agree.

Conclusions and Summary of Evaluation Committee's key conclusions *(5.13)*

Whilst welcoming the Committee's view of eculizumab as an effective and important treatment option and its recognition that it has significant value, we are disappointed that it does not consider the cost to the NHS is reasonable without further evidence. As we are not being asked for further evidence it would seem our case has persuaded the Committee sufficiently. This appears to be of no avail unless, finally, another single issue is resolved.

3.4 Proposed recommendations for further research *(6.1)*.

We agree. There are many questions left unanswered about the disease that need more study . Research should also address the possibility of controlled discontinuation from appropriate patients as practised successfully in at least one European country.

3.5 Proposed date for review of guidance *(8.1)* .

We agree.

4 ADDITIONAL OBSERVATIONS

4.1 Expert Centre.

We were surprised there was no mention of the desirability of an Expert Centre. As has been proved by the work done in Newcastle, these are essential to the success of the management and development of ultra-orphan therapies, enhanced by closer links with the patient organisation.

4.2 Existing patients using therapy under evaluation.

In future HST evaluations there may be some patients already benefitting from the drug under evaluation They should be given assurances that they will not be prejudiced by an adverse final decision.

4.3 Patient groups.

In future HST evaluations you may find that patient groups will need practical and perhaps even financial support if they are to make an effective contribution to such a complex and demanding process.

5 CONCLUSION

Although we were disappointed with the current lack of a positive recommendation from the Committee and we have raised some critical points above, we are grateful to have been given the opportunity to put our case, both in submissions and at the hearing. We have been treated fairly and professionally by NICE management and staff throughout. We would now welcome this long drawn out process being brought to a successful conclusion.

[redacted] and Len Woodward, .

on behalf of the trustees of aHUSUK.

aHUSUK is registered as a charity in England and Wales (1145953) and Scotland (SCO46232)

21 3 2014

ANNEX 1

aHUSUK Response to ECD

NOTES ON ASSUMPTIONS AND WORKING FOR BUDGET PROJECTION

1. 134 aHUS patients prevalent in England as at April 2011(www.ahus.org.uk)
2. 77 patients calculated as needing or receiving eculizumab as at April 2011 based on health states of UK prevalent population of 172 as at April 2011(www.ahus.org.uk)
3. 4 patients in England no longer in need of complement inhibitor in period 2011 to 2014 based on aHUSUK observation
4. 9 patients relapsed in period 2011 to 2014 based on aHUSUK membership experience.
5. 75 (+/-) new onset patients in period based on incident expectation of 0.4 per million and range of between 20 and 30 per annum
6. 45 of new onset prescribed eclizumab under trial ,PCT, interim or compassionate provision.
7. Health of remaining new onset, if they exist not know but will be added to the potential for transplant or relapse
8. 20 of the dialysis patients assumed with the treatable with eculizumab considered unfit for other reasons to undergo a transplant operation.
9. Base number of aHUS patients receiving or planned to receive eculizumab as at April is therefore 111.
10. Estimated patients over period 2014/15 to 2018/19 including provision for relapses and a second tranche of transplants in 2015/16 are shown in the table below:

Period	Base plus 25 new incidents	Base plus 20 new incidents	Base plus 30 new incidents	NICE Forecast in ECD
Base	111	106	116	170
2014/15	139	129	149	170
2015/16	177	162	192	190
2016/17	205	185	225	210
2017/18	233	208	258	230
2018/19	261	231	291	250

11. Based on the estimated patient numbers in the table above and from knowledge of aHUSUK members and other aHUS patients known to aHUSUK, that the ratio for less than 40kg patient and over 40kg patients is approximately 1:2 as shown in the table below:

	Base plus 25 new incidents	Base plus 25 new incidents	Base plus 20 new incidents	Base plus 20 new incidents	Base plus 30 new incidents	Base plus 30 new incidents
Period	Less than 40kg	More than 40kg	Less than 40kg	More than 40Kg	Less than 40kg	More than 40Kg
Base	37	74	35	71	38	78
2014/15	46	93	43	86	49	100
2015/16	58	119	53	109	63	129
2016/17	68	137	61	124	74	151
2017/18	77	156	69	139	85	173
2018/19	86	175	76	155	96	195

12 Based on the patient split in the table above and knowledge that the average weight dosage below 40Kg is 600mg the computed full dosage number per year is estimated to be as shown in the table below:

Period	Base plus 25 new incidents Computed doses	Base plus 20 new incidents Computed 1200 mg doses	Base plus 30 new incidents Computed 1200mg doses	NICE Estimated 1200mg doses
Base	93	89	97	170
2014/15	116	108	124	170
2015/16	148	135	160	190
2016/17	171	154	188	210
2017/18	195	174	215	230
2018/19	218	193	243	250

13 The estimated budget for the period, assuming that new on set are evenly spread through each year of onset and are therefore assumed to have an half year effect is shown in the table below

Period	Base plus 25 new incidents Computed 1200mg doses £ million	Base plus 20 new incidents Computed 1200 mg doses £million	Base plus 30 new incidents Computed 1200mg doses £million	NICE Estimated 1200mg doses £million
Base	33	31	34	58
2014/15	36	35	38	58
2015/16	45	42	48	63
2016/17	52	48	57	69
2017/18	59	53	65	75
2018/19	68	60	75	82
Period total	261	238	283	347

Len Woodward
Treasurer
aHUSUK
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