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Pharma Mar
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27 January 2015

Dear [redacted]

Appeal against Final Appraisal Determination: Topotecan, pegylated liposomal doxorubicin hydrochloride, paclitaxel, trabectedin and gemcitabine for advanced ovarian cancer (for recurrent disease only) (Review of TA 91 & TA 222)

Thank you for lodging Pharma Mar's appeal against the above Final Appraisal Determination.

Introduction

The Institute's appeal procedures provide for an initial scrutiny of points that an appellant wishes to raise, to confirm that they are at least arguably within the permitted grounds of appeal ("valid"). The permitted grounds of appeal are:

- 1(a) NICE has failed to act fairly,[1] or
- 1(b) NICE has exceeded its powers;[2]
- (2) the recommendation is unreasonable in the light of the evidence submitted to NICE

This letter sets out my initial view of the points of appeal you have raised: principally whether they fall within any of the grounds of appeal, or whether further clarification is required of any point. Only if I am satisfied that your points contain the necessary information and arguably fall within any one of the grounds will your appeal be referred to the Appeal Panel.

[1] formerly ground 1
[2] Formerly ground 3

It is important to stress than an appeal is not a re-run of the appraisal. In particular, it is not appropriate to expect an appeal panel to engage with and form its own judgement on detailed scientific evidence, in the way that would be expected for an appraisal committee. As I will elaborate below, your appeal letter contains a great deal of detail which is suggestive of simple disagreements with the appraisal committee's judgement rather than unreasonableness in particular. The appeal process is not charged with resolving such disagreement.

You have the opportunity to comment on this letter in order to elaborate on or clarify any of the points raised before I make my final decision as to whether each appeal point should be referred on to the Appeal Panel.

Initial View

Ground 1 (a)

1.1. Exclusion of the appraisal committee of relevant covariates in the adjusted analysis of trabectdin is unjustified.

I have not taken account of your speculation as to what the ERG of TA222 would have done if different data had been given to it, as the issue is the procedural fairness of this appraisal.

This committee were clearly aware of and considered your adjustments (see FAD 4.3.15). It felt there was no relevant DSU guidance and that it should not consider your adjustments (4.3.16). There seems to be considerable discussion of this (4.3.15-4.3.20). It may be that reasonable people could differ on these judgements, but I cannot see any signs of a failure to consider relevant evidence, to consult properly, or any other procedural unfairness.

I am not minded at this time to regard this as a valid appeal point.

1.2 Different interpretation of the evidence by the same appraisal committee for the MTA and TA222 regarding the use of head to head data for trabectedin to address the decision problem for the non-platinum network is irrational and unfair

An appeal panel considered the requirement of consistency in 2014, in connection with an appeal concerning "aflibercept in combination with irinotecan and fluorouracil-based therapy for treating metastatic colorectal cancer that has progressed following prior oxaliplatin based chemotherapy". The panel said:

It accepted that there was an overall requirement of consistency, between relevantly similar cases. It observes that this requirement must be reasonably applied, in particular having regard to the fact that NICE has four appraisal committees who cannot be expected to be familiar with the minutiae of each others' work. (In this case the same committee was involved in both appraisals, but the Panel does not feel that can impose a higher obligation of consistency.) The details of each appraisal will differ, and the details are usually important. Further there has to be room for committees to exercise their judgment afresh in each case. Therefore for guidance to be unreasonable on the grounds of inconsistency the Panel feels the inconsistency needs to be very clear indeed.

NICE has repeatedly made the point that one appeal panel does not bind another. However panels have consistently adopted this approach and I have little doubt that they would do so again.

Further, your complaint is of unfairness rather than unreasonableness. You were aware of the committee's approach and drew attention to the difference with TA222 in the consultation. TA222 was an STA published in 2011. I do not find it particularly surprising that a committee might take a different approach in certain respects when it is conducting an MTA to be published in 2015. Fairness would require the committee to make its approach clear so that you could comment on it, and that was done. What you are arguing for is a substantive benefit, that this committee must take the same view as the committee took in an appraisal conducted under a different process some four years ago. I am not minded to agree that is a valid appeal point.

Ground 2

2.1 The appraisal committee's rationale for not using adjusted clinical effectiveness results for the cost effectiveness evaluation of trabectedin in the MTA is flawed and inconsistent with the previous TA222 appraisal and NICE DSU guidance

As to consistency with TA222 I repeat my observations above. As we are now considering reasonableness rather than fairness, it seems to me that the fact that an earlier committee took one reasonable approach has very little if any weight in supporting an argument that this committee's different approach was unreasonable. The scope of an MTA is different to an STA and it does not seem surprising per se if the methods adopted vary. The decision problems will also vary. Your point appears to be a complaint that there was not a simple read across from TA222 but even assuming that that might have been a reasonable

approach (as to which I have my doubts, since this committee has to make up its own mind) I am unclear as to why you argue that that would have been the only possible reasonable approach.

I am not minded at this time to agree that is a valid appeal point.

2.2 The Appraisal Committee failed to take into account key differences in baseline characteristics and trial design of relevant studies that have informed the clinical and cost effectiveness results and subsequent recommendations for the FAD including that of trabectedin

It seems to me that these factors were taken into account (FAD 4.3.7 et seq). A decision not to analyse a blend of adjusted and unadjusted ratios seems likely to be rational, on the basis that the committee would have been analysing or comparing two different things. It appears to me that the committee have not determined that adjusted hazard ratios might not be desirable, but that the data did not exist to allow consistent use of adjusted ratios. If my understanding is correct and it is correct that the data do not exist, I do not see how this judgement could be challenged as unreasonable.

I am not minded at this time to agree that is a valid appeal point.

2.3 the different interpretation of the evidence by the same appraisal committee for the MTA and TA222 regarding the use of direct head to head data for trabectedin to address the decision problem for the non-platinum network is irrational and unfair.

I have commented above on the limitations of an expectation of consistency.

I am not minded to agree that is a valid appeal point

2.4 An incorrect adjustment by the assessment group of drug costs for trabectedin and PLDH has been applied resulting in an inaccurate ICER being calculated

A valid appeal point

2.5 Recommendations within the FAD for the use of paclitaxel within its marketing authorisations are based on extrapolated off label data and costs in the monotherapy platinum resistant/refractory patients

A valid appeal point.

2.6 Recommendations for the use of off label PLDH in combination with platinum are unlawful

Although placed in ground 2, this is a ground 1b) point.

It seems to be common ground that NICE was required to carry out this appraisal by a request from the Department of Health. I note that argument that the Department of health was unable to require that assessment as a result of case C185/10 European Commission v Republic of Poland.

NICE's appeal process cannot come to a ruling on what the Department of Health is or is not legally able to do.

NICE has fulfilled the remit made to it. These is nothing inherently unlawful in its doing so and it is not obvious to me that it had any choice but to do so. If the effect of that remit is contrary to the Poland case, at the least it would be necessary to obtain the Department's views on the issue, and it seems likely to me that it is the Department you should complain to. I will make arrangements to copy the relevant part of your letter to the Department for comment, although as this is your complaint I would suggest you also take up the matter with them directly.

I would also point out that the appraisal has been allowed to proceed to completion and as far as I am aware you have not raised this objection before.

At present I would not be minded to regard this as a valid appeal point.

As I am minded to rule that at least some of your appeal points are valid, I will pass your appeal to an Appeal Panel for consideration. However it seems to me that it may be possible to deal with your points in writing, and I would invite your views on this.

If you wish to make any further comment on the points that I have indicated that I do not, at this preliminary stage, view as valid, please provide this to me by **5pm, Wednesday 11 February 2015**. I will then reach a final decision on the validity of those points

Yours sincerely

[redacted]

Appeals Committee
National Institute for Health and Care Excellence