NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

SINGLE TECHNOLOGY APPRAISAL

APPEAL HEARING

Advice on Single Technology Appraisal of trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane [ID603]

Decision of the Panel

Introduction

1. An Appeal Panel was convened on 13th October 2014 to consider an appeal against the Institute's Final Appraisal Determination, to the NHS, on the Single Technology Appraisal of trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane.

2. The Appeal Panel consisted of –

Mr Paddy Storrie	Chair
Dr Frank McKenna	NHS Representative
Professor Finbarr Martin	Non-Executive Director
Mr Patrick Hopkinson	Industry Representative
Mr John Morris	Lay Representative

3. None of the members of the Appeal Panel had any competing interest to declare.

4. The Panel considered appeals submitted by Roche Products Ltd.

5. Roche Products Ltd was represented by –

Ms Jennifer Cozzone	Head of Health Economics and Strategic Pricing
Ms Karen Lightning-Jones	Head of Business Development and Operational Pricing
Mr Simon McNamara	Group Health Economics Manager
Ms Heather Moses	Medical Manager
Dr Adela Williams	Legal advisor, Arnold & Porter (UK) LLP

6. All of the above declared no conflicts of interest.

7. In addition the following individuals involved in the appraisal were present and available to answer questions from the Appeal Panel -

Dr Jane Adam	Chair, Technology Appraisal Committee A
Mr Meindert Boysen	Programme Director, NICE

8. All of the above declared no conflicts of interest.

9. The Institute's legal adviser, Mr Stephen Hocking, was also present.

10. Under the Institute's appeal procedures members of the public are admitted to appeal hearings and several members of the public were present at this appeal. In addition, an observer was present, but took no part in the proceedings.

11. There are two grounds under which an appeal can be lodged:

    Ground 1(a) NICE has failed to act fairly
    Ground 1(b) NICE has exceeded its powers
    Ground 2 the recommendation is unreasonable in the light of the evidence submitted to NICE

12. The Vice Chair (Dr Maggie Helliwell) in preliminary correspondence had confirmed that the appellants had potentially valid grounds of appeal as follows:

    Ground 1(a):
    (i) The reasoning set out in the FAD to justify disregarding the 2014 PPRS is inadequate and does not explain the conclusion reached
    and
    (ii) The Appraisal Committee has failed to take into account relevant matters when reaching the decision set out in the FAD

13. Trastuzumab emtansine (Kadcyla, Roche) is an antibody-drug conjugate consisting of trastuzumab linked to mertansine, which is a cytotoxic agent. Because the antibody targets human epidermal growth factor receptor 2 (HER2), and HER2 is over expressed in breast cancer cells, the conjugate delivers the toxin directly to the cancer cells. Trastuzumab emtansine, as a single agent, has a UK marketing authorisation 'for the treatment of adult patients with HER2-positive, unresectable locally advanced or metastatic breast cancer who previously received trastuzumab and a taxane, separately or in combination.

14. The appraisal that is the subject of the current appeal provided advice to the NHS on the use of trastuzumab emtansine for treating HER2-positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane.

15. In opening the appeal, the Appeal Panel chair made clear that a third point of appeal from Roche Products Ltd (RPL) had been deemed not a valid appeal point. However, the Appeal Panel would be clear to consider in this hearing any unfairness in the appraisal process, however caused. Before the Appeal Panel inquired into the detail of the complaints, the Appeal Panel chair invited the appellant and the Appraisal Committee to make preliminary statements.

16. On behalf of RPL, Ms Cozzone explained that the appeal was unusual in focusing solely on process and was related to the implications of PPRS on current NICE appraisals. She said that there were important implications for patients including access to innovative treatments. In relation to trastuzumab emtansine, it had been accepted to be innovative and also to prolong survival with less toxicity. The issue precluding access was the price. She stated that price was not a matter for NICE but pricing for these products is complex and there are limited options for increasing price

after the launch of a new product. As a result RPL were not able to develop further pricing recommendations due to the uncertainty of how PPRS will be taken into account. She explained that PPRS 2014 was a major shift in the way that drug costs are controlled by the NHS with a change from price control to budget control. However, despite this change NICE have not changed their methodology to address the impact on evaluation of cost effectiveness of new products.

17. For the committee, Dr Adam stated that RPL had only introduced comments on the PPRS and its bearing on the appraisal following the publication of the ACD. RPL had not stated how they expected the PPRS to be taken into account ahead of the FAD. She explained that the Committee based their decision making in keeping with the 2013 Methods Guide and trastuzumab emtansine was not recommended as it was not cost effective. The PPRS post-dated the Methods Guide and she explained that it was not the role of the Appraisal Committee to develop new methodology. She explained that there was a brief discussion relating to PPRS, all the discussion took place in the public part of the meeting and this discussion was reflected in the FAD. The Committee had asked the Institute in the public part of the meeting whether PPRS superseded the Methods Guide and if they should change their approach. The answer from the Institute was unequivocal and is recorded in the FAD. She added that the PPRS is a complex scheme and it was difficult to see how the Committee could have taken it into account.

18. Mr Boysen, for the Institute, stated that NICE had liaised with the Department of Health (DH) in relation to PPRS and claimed the DH would be more than happy to issue a statement to the effect that the PPRS is not relevant to appraisal decisions.

19. Dr Williams suggested that if that information were to be taken into account the appeal hearing should be delayed, but the Chair of the Appeal Panel considered this would be unnecessary. For the purpose of this appeal the Panel could only proceed on the basis of the information already before it and the Methods Guide and any other relevant documents as they stood during the appraisal. If the DH were to issue a statement the effect of that statement on appraisals would have to be determined at the time.

20. Ms Lightning-Jones then gave a presentation on PPRS to the Panel of her interpretation of the PPRS. In summary she explained that 2014 PPRS is a major shift in that cost control of branded drugs has changed from price control to budget control. This then meant that because the DH had certainty of the total level of expenditure, it could provide access to new medicines without concern over cost. As there was an indirect effect on cost of medicines, RPL did not consider that the PPRS was a matter that could be fairly or logically disregarded by NICE. She explained the methodology of the new system and stated that total expenditure on branded drugs which exceeded a fixed budget (set by the DH) would be reimbursed pro-rata by the pharmaceutical companies that participate in the scheme. She explained that there was not quite a 1:1 correspondence between overspend and reimbursement, but that reimbursement would be very close to overspend. It was expected that there would be an overspend in each year, so that spend on trastuzumab emtansine would be largely reimbursed, although she acknowledged that reimbursement could not be formally attributed to any one product. The scheme is voluntary but those companies that do not participate have imposed on them a 15% mandatory reduction in price to

the NHS of all their branded products. RPL do not support the position that price of medicine is irrelevant but sought to understand how PPRS is incorporated in NICE's process so its effect could be incorporated in their submissions to NICE. The previous PPRS agreement was automatically incorporated into the appraisal process as it affected the headline price of the treatment upon which the cost effectiveness calculation was based.

21. The Panel asked whether RPL considered the system to be one of price control or budget control. For RPL, Dr Williams considered it was both as the companies were unable straightforwardly to increase the price of their products but in addition the purpose of PPRS was to control the total drugs budget. Ms Cozzone explained that price could only be changed through modulation where one product price was reduced in tandem with an increase in another product.

22. The Panel asked whether RPL had a proposal for how the cost effectiveness analysis could take PPRS into account. Dr Williams said that it was difficult to consider how this could be done in relation to the price of an individual product but the benefit to the health economy in reimbursing the NHS should be taken into account.

23. For the committee, Dr Adam said that they had looked at this as a comment to the committee but that consistency of approach is important in appraisals and the effects of PPRS may fluctuate over time. She also considered that it was not possible to attribute the rebate to the NHS through the PPRS to any single drug. Mr Boysen stated that the refunds from PPRS go to the Department of Health and not NHS. However, he clarified that they had told the committee not to disregard PPRS but rather that it doesn't supersede the 2013 Methods Guide. He also pointed out that NICE doesn't feature in the pricing and payment chapters of PPRS but does feature in other chapters.

24. Mr McNamara for RPL stated that the evaluation of opportunity costs was an efficient method of establishing the effective use of resources but that the nature of any opportunity cost had fundamentally changed with reimbursing excess cost to the DH. It is not that PPRS supersedes the methods guide but that the impact of its approval on budgets has not been understood. This is fundamental to the evaluation of opportunity cost and it is unfair not to have taken it into account. He said that the NICE technology appraisal process was founded on achieving effective use of NHS resources and with the PPRS 2014, the broader context had not been taken into account even though the opportunity cost of branded treatments has fundamentally changed. If capped expenditure is exceeded, money comes back to the DH. This capping must be a relevant factor, as previous PPRS provisions were taken into account within the cost-effectiveness calculation itself. He is aware that NHS resources are not unlimited but the appraisal has to consider the true costs and benefits now that a payment back to the DH would occur if there was a budget overspend. Mr McNamara said that RPL were careful in their wording of the appeal; they were not saying it is unreasonable to say no to a medicine but NICE must consider the impact of budget capping. If it was considered not to have an impact on decision making they needed to explain why not. RPL were not trying to solve the PPRS problem in the appeal but considered it could not be fair to consider that the budget being capped is not relevant. RPL need to understand how budget capping is incorporated into the process. They have not received an explanation as to why

committee thinks PPRS is not relevant to cost effectiveness and stated that RPL would have appreciated a discussion on this. However there was no consultation on how to incorporate PPRS and RPL feel disappointed in the process. Ms Cozzone added that there were potential solutions how this could be addressed for example by tolerating more uncertainty in the ICERs. Another approach would be to allocate the PPRS rebate funds to fund treatment for End of Life or rare conditions by raising the thresholds for those products. She was not recommending what NICE should do but explaining that there were options.

25. For RPL, Mr McNamara restated that the rebate must be incorporated somehow in the cost-benefit analysis. Dr Williams stated that it was important there was transparency and that NICE is mandated to take account of effective use of NHS resources, and that the rebate is a fundamental aspect of what NHS resources are available. Ms Cozzone expanded this point and argued that price control in the previous PPRS was reflected in cost-benefit analysis but the lack of clarity of the effect on price in PPRS 2014 prevented an accurate evaluation and this needed to be addressed. Ms Lightning-Jones added that NHS England documents record that PPRS payments will be handed back to the CCGs. Mr McNamara considered that an attempt could be made to attribute the rebate to individual drugs, or could be taken into account more broadly, but there was a failure to have this discussion.

26. For the committee, Dr Adam said that the Appraisal Committee has to make recommendations regarding clinical and cost effective use of treatments and should not recommend treatment that is not cost effective. They have some leeway in interpreting the Methods Guide for example around interpretation of "normally" or "robust" but they are not allowed to consider budget issues. The Committee had invited the manufacturer to comment on how to incorporate the PPRS into their deliberations at the second appraisal meeting but they didn't.

27. Dr Williams stated that the reason for the establishment of NICE is because there are limited NHS resources. NICE tries to allocate resources fairly, but where extent of NHS resources is impacted by PPRS, it is a factor to be taken into account. She argued that it was important to take into account the financial landscape and in this regard reduced opportunity costs as a result of the PPRS rebate were highly relevant. It was not necessary just to look at the impact of the PPRS on an individual product, as the committee could tolerate more uncertainty, or could conclude that PPRS rebates justify a higher threshold for End of Life products. The Appraisal Committee would then apply the Methods Guide in a purposive way.

28. For the Institute, Mr Boysen stated that Appraisal Committees take into account broad benefits and costs and that the Methods Guide mentions list prices and any price changes are taken into account. The Committee can also take other prices into account through Patient Access Schemes. The resulting cost per patient is then transparent to the Institute. In addition, the opportunity cost threshold will not change through life of the agreement, as stated in the PPRS 2014 document para 4.9. Finally he considered that the PPRS was not in effect a giant Patient Access Scheme. Patient Access Schemes give a cost that can be simply taken into account, but the PPRS does not. When asked by the Panel if these points were reflected in the FAD, Mr Boysen apologised that they were not but stated that he thought they are self-evident. He said that what must be taken into account were the relevant parts of

PPRS where NICE is mentioned. However, the PPRS is not a profit control or payment mechanism. The Committee can take account of issues such as uncertainty, but are careful to be clear that, for example, the Cancer Drugs Fund should not be taken into account. The appraisal system takes account of uncertainty in its evidence base. If there is information on the impact of PPRS 2014 on the price of a medicine then that could be taken into account, but it has to be transparent.

29. Dr Williams for RPL stated that the PPRS 2014 was not just a discount on price, but the wider picture had to be considered including the use of NHS resources.

30. Dr Adam said that it was difficult to take account of PPRS without inventing a way to do so and the manufacturer had not suggested anything. In order to develop a methodology it would have been necessary to suspend the appraisal. However there was little discussion in the Committee on PPRS because no one had anything to say. Mr Boysen stated that the Committee considers the impact of the decision when it considered uncertainty. It was also not unreasonable to be reminded that where the consequence of a budget impact is high, there is a reluctance to accept uncertainty. There needs to be certainty before allowing a gigantic movement of funds. He urged caution and restated that cost is not price, and that Committees can look more broadly. In relation to opportunity costs there is a threshold of £20-30k; a budget impact could be relevant to uncertainty, but the central estimate of ICER is not affected.

31. Mr McNamara discussed other costs included in the total cost of the drug and that if the cost of both the drug and administration are included then it is necessary to take the rebate into account. The real consequences for the NHS are that if there is a spend of £x and a rebate of £y, then there needs to be some account of the rebate. He stated that RPL were asking what NICE's position was on this but it was difficult for RPL to offer a view and they were never asked how to do this. Dr Williams said that it was also important for consistency of NICE appraisals, not just for RPL in the context of this appraisal. Ms Cozzone considered it was disappointing that because the new version of PPRS deals with affordability concerns in a different way, this is not factored into NICE's methods. The issue has arisen because the budget cap has been enacted in a new way leading to a lack of transparency in opportunity costs.

32. Mr McNamara said that the decision should be clear and transparent but no reasons were given in the FAD for disregarding PPRS, even though Mr Boysen had now outlined a number of them. RPL were therefore unable to understand how NICE considered that PPRS did not have an impact if it was not explained. RPL considered that it was inadequate to state that the Committee were not engaging with PPRS simply because it did not supersede the Methods Guide.

33. Dr Adam explained that the Committee were not in a position to change methods of appraisal in unspecified ways and they needed the Institute's guidance. They had been informed by the Institute that the refund did not go back to commissioners but they considered that to be immaterial. The considerations section is the considerations of the Committee not a vehicle for policy statements by the Institute.

34. RPL were invited to sum up their appeal. Dr Williams said that both the clinical need and benefits for trastuzumab emtansine were accepted and that the key issue was

price. She stated that there were difficulties in pricing new medicine in part because future indications were unknown. RPL want patients to have access for the initial indication but are handicapped by lack of transparency of whether and how PPRS is taken into account. The control of NHS budgets as a feature is a huge shift in how PPRS works and affects the availability of NHS resources. There needs to be consistency between Committees, so it would have been inappropriate for RPL to suggest how PPRS should have been taken into account. However, there were options open to the Committee. PPRS is a fundamental part of NHS environment and of how resources are allocated. In relation to the reasons given, the explanations in the FAD were very limited and that prejudiced RPL in the ability to respond both generally and in the appeal hearing.

35. In summing up for the Committee Dr Adam said it wasn't the price that the Committee looked at but cost effectiveness and all costs on the patient pathway. The suggestion that there was a need to address PPRS was of significance for the way the Committee worked and they sought and acted on advice. The manufacturer was allowed to suggest how to include PPRS in the process but did not do so, therefore the conversation was brief and that is what was reflected in the FAD.

36. The Panel considered the evidence presented to them. In relation to point (ii), the Panel appreciated the difficulty faced by the Committee in the lack of an approved method to take PPRS into account. It was not for the Panel to take a definitive view on the relevance or otherwise of the PPRS to the work of NICE at this time. In pre-appeal correspondence, Dr Helliwell had reminded the appellant that the role of the Panel was to consider (in this case) unfairness in the course of an appraisal, and not to judge or set down rules for the operation of NICE globally. The Panel reminded itself of its limited role and this decision must be read accordingly. Furthermore, the arguments before the Committee and before the Panel had been limited in scope, and insufficient for the Panel to reach a conclusion that goes beyond the subject matter of this appeal.

37. The Panel were persuaded that they could not rule out that the PPRS 2014 might have some influence on opportunity costs. Indeed, Mr Boysen had conceded that the Institute had not guided the Committee that the PPRS was irrelevant to their work; only that the Methods Guide still applied. The Panel did not consider that the failure of RPL to suggest a mechanism during the appraisal was a relevant consideration. Had RPL been unable to suggest a mechanism during the appeal, the Panel might have taken that as an indication that the PPRS could not be relevant or taken into account, but even if they do not eventually find favour, the suggestions put forward by RPL were sufficient for the Panel to be unable to conclude that it was impossible to operationalise taking the PPRS into account. The Panel concluded that the 2014 PPRS should have been taken into account, or, alternatively and sufficiently for this appeal, that the possibility of the PPRS being relevant had not been sufficiently considered and its irrelevance established. This does not imply an opinion of the Panel that taking it into account would or should have any material effect on the appraisal outcome. That would be a matter for the Institute and the Appraisal Committee.

38. The Appeal Panel therefore unanimously upheld ground 1 (a) point (ii).

39. In relation to point (i), the Panel recognised that the Committee discussion in relation to PPRS was brief and this was reflected accurately in the FAD. The Panel also recognised that the Committee received advice from the Institute that the 2013 Methods Guide was not superseded by the terms of PPRS, but also heard from Mr Boysen that the Committee were not told to disregard PPRS. However, this advice did not address how the PPRS could be taken into account. The Panel reflected on the comments by Mr Boysen on the reasoning why the PPRS might not lead the Committee to make a different decision to that taken, but also were conscious that this reasoning was not described in the FAD. Furthermore, save in the clearest case it was not possible to say with confidence that a factor would not have made a difference, when it had not in fact been discussed or considered at any length. The Panel had to deal with an appraisal as it was, not as it might have been.

40. The Panel recognised that in the PPRS 2014 document it states that the basic cost-effectiveness threshold by NICE will not be changed for the duration of the scheme. However, that was not the same as saying that the PPRS was not relevant to technology appraisals. The Panel were persuaded that the PPRS could potentially be relevant to the assessment of opportunity costs that underlies a NICE appraisal (see above). The reasons for the Committee's decision not to be swayed by the PPRS are not or not adequately described in the FAD. The lack of reasoning to justify disregarding the 2014 PPRS is unfair to the appellants.

41. The Appeal panel therefore unanimously upheld ground 1 (a) point (i).

Conclusion and effect of the Appeal Panel's decision

42. **The Appeal Panel therefore upholds the appeal on both Ground 1(a) points:**

    (i) The reasoning set out in the FAD to justify disregarding the 2014 PPRS is inadequate and does not explain the conclusion reached
    and
    (ii) The Appraisal Committee has failed to take into account relevant matters when reaching the decision set out in the FAD

43. To assist the Institute, the appellants, and others, the Panel wishes to make the following observations:

    a. It repeats that its role is to adjudicate on an appeal brought before it, and not to opine more widely on appraisal methodology. To begin with the second appeal point, to be a valid appeal point, the PPRS would have to be at least potentially relevant to the appraisal. The Panel was not persuaded that the operation of PPRS was necessarily irrelevant to the conduct of this appraisal and on that basis and given its concern about fairness the Panel felt logically compelled to find the appellant's second appeal point made out. Its accompanying concern in this case was that the committee's position on the PPRS was insufficiently explained and that this was unfair: this was the first appeal point. The Panel does not express a view either for or against the possibility of the Institute finding on further inquiry and open minded consideration that the PPRS is irrelevant, or that it is impossible to

operationalise taking the PPRS into account. Those would be matters for the Institute in the first instance.

b. The Panel also noted that the appellant was not arguing that the PPRS made consideration of the price of a product irrelevant, or that there should be a very profound effect on the technology appraisal. The Panel considered that those concessions were correctly made, having in mind in particular that any rebate under the PPRS is a global figure and cannot be attributed to any one product.

c. There may be some concern as to appraisals currently under way. Again this is not a matter for the Panel, but the Panel notes that it understands the considerable public interest in progressing appraisals without delay, and also that fairness in particular is context-dependant. If an interim solution were implemented to allow work to progress as scheduled pending a fuller consideration, the Panel would hope that potential appellants and, as the case may be, any future appeal panel would allow the Institute an appropriate margin of appreciation.

44. There is no possibility of further appeal against this decision of the Appeal Panel. However, this decision and NICE's decision to issue the final guidance may be challenged by applying to the High Court for permission to apply for a judicial review. Any such application must be made within three months of publishing the final guidance.