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22 August 2014

Re: Appeal against Final Appraisal Determination – Trastuzumab emtansine for treating HER2- positive, unresectable locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane

Dear Margaret

This letter sets out the appeal by Roche Products Limited in respect of the Final Appraisal Determination ("FAD") for the above mentioned technology appraisal on the ground that in making the assessment that preceded the recommendation, NICE has failed to act fairly, as permitted in accordance with NICE's Guide to the technology appraisal and highly specialised technologies appeal process.

EXECUTIVE SUMMARY

Roche's appeal arises from the determination of the Appraisal Committee that there was no requirement to take into account the Pharmaceutical Price Regulation Scheme ("PPRS") in the context of its appraisal of trastuzumab emtansine. We believe this decision and the resulting failure to consider the PPRS, was procedurally unfair.

- The 2014 PPRS represents a substantial change from previous price control schemes; in that it acts to ensure that the NHS does not exceed the budget set each

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year in respect of expenditure on branded medicines supplied by scheme members. To the extent that the NHS does exceed this budget, such overspend is repaid to the Department of Health by PPRS member companies.

- By guaranteeing the NHS budget for medicines, the PPRS therefore represents a key factor to be taken into account when assessing whether use of a particular treatment represents a good use of NHS resources. In particular:
    - The costs to the NHS associated with use of a particular technology cannot be assessed without taking into account the arrangements under the PPRS.
    - NICE's Guide to the Methods of Technology Appraisal 2013 emphasises the need to adopt a UK perspective when assessing the costs and benefits associated with use of a technology within the NHS' this includes the PPRS.
    - Failure to take into account the PPRS discriminates against PPRS member companies.
    - A stated purpose of the PPRS is to improve access to innovative new medicines; this requires that the arrangements under the PPRS be taken into account by NICE in conducting appraisals of products supplied by scheme members.
- In these circumstances, the Appraisal Committee's refusal to take into account the implications of the PPRS in the context of its appraisal of trastuzumab emtansine or at all is procedurally unfair, because:
    - the reasoning set out in the FAD to justify this decision is inadequate and does not explain the conclusion reached;
    - the Appraisal Committee has failed to take into account relevant matters when reaching the decision set out in the FAD; and
    - NICE has issued no guidance or statement explaining how the PPRS should be taken into account during appraisals.

Roche therefore asks the Panel to direct that NICE should consider and issue guidance to its appraisal committees in relation to their consideration of the PPRS in the context of health technology appraisals and that, following such guidance, the Appraisal Committee in this appraisal, should reconsider its recommendations for trastuzumab emtansine in that context.

INTRODUCTION

Roche Products Limited is responsible for the UK supply of Kadcyla (trastuzumab emtansine), authorised under the centralised procedure by the European Commission on 15 November 2013, for the following indications:

> "Kadcyla, as a single agent, is indicated 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. Patients should have either:
>
> - Received prior therapy for locally advanced or metastatic disease, or
> - Developed disease recurrence during or within six months of completing adjuvant therapy."

PROCEDURAL HISTORY OF THE APPRAISAL

Roche was notified of the proposed single technology appraisal of trastuzumab emtansine for the treatment of HER2+, unresectable locally advanced or metastatic breast cancer in September 2013. The subsequent history of the appraisal is as follows:

4 April 2013: Draft Scope issued.

22 October 2013: Final Scope issued, setting out the remit for the appraisal:

> "To appraise the clinical and cost effectiveness of trastuzumab emtansine within its licensed indication for the treatment of unresectable locally advanced or metastatic HER2-positive breast cancer after treatment with trastuzumab and a taxane."

10 December 2013: Roche provides its submission for the appraisal. NICE requested some additional clarification in relation to this submission and, on 28 January 2014, such clarification was provided by Roche.

25 February 2014: The University of Sheffield School of Health and Related Research ("ScHARR"), appointed as Evidence Review Group (ERG) for the purposes of this appraisal, issues its report assessing trastuzumab emtansine.

6 March 2014 Roche provides factual comments on ERG report

25 March 2014: The first meeting of the Appraisal Committee to consider trastuzumab emtansine.

23 April 2014: Appraisal Consultation Document ("ACD") is issued, stating at paragraph 1.1:

> "Trastuzumab emtansine is not recommended within its marketing authorisation for treating adults with human epidermal growth factor receptor 2 (HER2) positive, unresectable locally advanced or metastatic breast cancer previously treated with trastuzumab and a taxane."

19 May 2014: Roche submits its response to the ACD, with additional clarification provided as a result of the preliminary conclusions of the Appraisal Committee. The ERG produces an Addendum to its report.

24 June 2014: The second meeting of the Appraisal Committee to consider trastuzumab emtansine.

1 August 2014: Final Appraisal Determination ("FAD") issued to Roche. The conclusions at paragraph 1 of the FAD are unchanged from those set out in the ACD.

OVERVIEW OF THE TECHNOLOGY

Breast cancer is the most frequently diagnosed cancer and the leading cause of cancer death among females worldwide. Metastatic breast cancer is incurable, and an estimated 450,000 patients globally die from breast cancer per annum. Of these, approximately 15%-20% (60,000~90,000) are likely to be due to HER2-positive (HER2+) disease. Each year approximately 2,000 people in the United Kingdom die of HER2+ metastatic breast cancer. The majority of the people diagnosed are women, with an average age at diagnosis of 55 years. The primary objective of the management of HER2+ metastatic breast cancer is to extend the person's length of life, whilst maintaining or improving quality of life. People with metastatic disease are unlikely to be cured.

Kadcyla (trastuzumab emtansine, also known as T-DM1) is a novel , antibody-drug conjugate. It comprises three parts:

> (i) trastuzumab, a HER2-directed antibody with proved anti-tumour effect in HER2+ breast cancer;

(ii) derivative of maytansine-1 (DM1), a potent cytotoxic from the maytansinoid family; and

(iii) a thioether bond linker.

Trastuzumab emtansine provides the mechanisms of action of both trastuzumab and DM1. When it binds to the HER2 receptor on the tumour cell, the trastuzumab moiety reduces HER2-related signalling and targets the cell for antibody-dependent cellular cytotoxicity. Trastuzumab emtansine is then internalised by endocytosis and undergoes lysosomal degradation, releasing DM1 into the cell. DM1 is a microtubule inhibitor and, by binding to tubulin, disrupts intracellular tubulin networks, causing inhibition of cell division and cell growth and, eventually, cell death. Trastuzumab emtansine is therefore able specifically to target HER2+ tumour cells, delivering targeted chemotherapy to these cells and reducing the systemic toxicity seen with systemic chemotherapy. This has been shown to result in increased efficacy and a reduction in toxicity for patients, compared with more conventional treatment with chemotherapy alone, or a targeted therapy in combination with chemotherapy, e.g. lapatinib plus capecitabine.

GROUNDS OF APPEAL

1.1. The Appraisal Committee's refusal to take into account the Pharmaceutical Price Regulation Scheme ("PPRS") in the context of its consideration of trastuzumab emtansine was procedurally unfair

The Pharmaceutical Price Regulation Scheme ("PPRS") is a voluntary agreement for the control of prices of branded NHS medicines negotiated between the Department of Health and the Association of the British Pharmaceutical Industry (ABPI) as the appropriate industry body for the purposes of section 261 of the National Health Service Act 2006. The PPRS is typically renegotiated every 5 years; the current scheme is the 2014 PPRS. The 2014 scheme is stated to be a non-contractual agreement; however the parties have stated that "The scheme will operate for five years from 1 January 2014 until and including 31 December 2018. It is a fundamental condition of the scheme that it will continue to operate for five years starting from 1 January 2014 and ending on 31 December 2018".(paragraph 3.2 of the 2014 PPRS).

The 2014 PPRS represents a radical change from previous voluntary agreements between the Department of Health and the ABPI, acting on behalf of the innovative pharmaceutical industry, to control the prices of branded NHS medicines. The key change from previous versions of the PPRS is that, instead of imposing mandatory price reductions on prices of products within the scheme, the 2014 PPRS is designed to ensure that the NHS does not exceed the budget set each year in respect of expenditure on medicines. In summary, to the extent that the NHS does exceed the medicines budget, such excess sums are paid by way of rebate to the Department of Health by PPRS scheme members, via PPRS Payments, on a quarterly basis.

The benefit of the new agreement so far as the Department of Health is concerned is that medicines expenditure is certain and controlled within the defined budget. From the perspective of industry a critical result of the 2014 PPRS, and a reason why Roche agreed to participate in the scheme, is that it includes a commitment by the Department of Health to increase access to innovative new medicines within the NHS.

Accordingly, the 2014 PPRS states:

At paragraph 4.1:

> "The role of the pharmaceutical industry in the development of healthcare and medical advances is of crucial importance. It is in the interests of patients, the NHS, the Government and the industry that any pricing system encourages research and rewards innovation that delivers valuable new treatments. It is an objective of the Department and NHS England to improve overall outcomes for patients including through access to effective medicines. Innovation Health and Wealth (IHW) set out an ambition subscribed to by the Department and by NHS England "for an NHS defined by its commitment to innovation, demonstrated both in its support for research and its success in the rapid adoption and diffusion of the best, transformative, most innovative ideas, products, services and clinical practice". This is reflected in NHS England's statutory duties to promote research and innovation which are in turn translated into a specific requirement in the NHS England Mandate. To these ends, the Department, NHS England and the industry have committed to a number of specific initiatives aimed at encouraging and rewarding innovation and assisting better access to effective medicines."

At paragraph 6.1:

> "Recognising the current state of the global economy, the Department and ABPI have agreed that instead of the headline price adjustments which have been a feature of recent PPRSs a limit is introduced on growth in the overall cost of the branded medicines purchased by the NHS from members of the scheme. An important purpose is to provide Government with surety on the level of NHS expenditure on branded health service medicines supplied by scheme members".

The 2014 PPRS includes special provisions relating to the application of the PPRS Payment mechanism to new products, defined, at paragraph 6.10, as "products introduced after 31 December 2013 following the granting of an EU or UK new active substance marketing authorisation from the appropriate licensing authority". Kadcyla is classified as a new product under the PPRS as it was not available on the market in the UK until after 1st January 2014. However and for the avoidance of doubt, costs incurred by the NHS in relation to such new products are included as part of "Measured Spend" by the NHS and are therefore taken into account when evaluating whether and by what percentage the NHS has exceeded the defined medicines budget and in determining the PPRS Payments to be made by PPRS member companies to cover the overspend.

The introduction of the 2014 PPRS represents a fundamental change in the control of prices of branded NHS medicines in the UK, and one that Roche firmly believes should be reflected in NICE's appraisal methodology. Our reasons for this view include the following:

(a) The costs to the NHS associated with use of a particular technology cannot be assessed without taking into account, in some way, the PPRS Payment mechanism and the arrangement under the 2014 PPRS that the NHS medicines budget (insofar as this relates to branded health service medicines supplied by scheme members) is capped and effectively underwritten by member companies. Failure to take account of the arrangements under the 2014 scheme, therefore disregards an important benefit provided by scheme members and overestimates the true costs of the technology to the NHS.

(b) NICE's Guide to the Methods of Technology Appraisal dated 2013 ("the Methods Guide") emphasises the need to adopt a UK perspective when assessing the costs and benefits associated with use of a technology within the NHS (see e.g. paragraphs 3.2.2, 5.1.9, 5.3.4, 5.10.11). The PPRS Payment mechanism now represents a key element of the UK environment so far as supply of PPRS products is concerned. The current requirement by NICE for the benefits of a treatment to be demonstrated in a population reflecting the situation of patients in the UK, for comparators to be selected based on standard practice within the NHS in England (even if such products are viewed by NICE as cost-ineffective and are available only on a temporary basis via the Cancer Drugs Fund) and for costs to be assessed based on the anticipated usage

within the UK, is inconsistent with an approach that disregards a central element of the costs control regime as applied to medicines in the UK.

(c) Failure to take into account the PPRS Payment mechanism discriminates against PPRS member companies. The mandatory reduction in the list price of products covered by the Statutory Scheme (the parallel price control mechanism applied to all companies who supply branded health service medicines, but are not members of the voluntary PPRS) is a factor taken into account by NICE in assessing their cost-effectiveness. Similarly, the reductions in the list prices of medicines covered by previous versions of the PPRS were also taken into account by NICE. In circumstances where the new arrangements under the 2014 PPRS are intended to have a comparable effect to list price reductions (see paragraph 6.1 of the PPRS set out above) it is illogical and unfair that PPRS Payments are disregarded by NICE.

(d) It is implicit as a result of the Department of Health's commitment under the 2014 PPRS to improve access to innovative new medicines, that NICE must take the arrangements under the scheme into account in conducting appraisals. Access to medicines recommended by NICE was already guaranteed, prior to the 2014 PPRS coming into effect, as a result of the National Institute for Health and Care Excellence (Constitution and Functions) and the Health and Social Care Information Centre (Functions) Regulations 2013 (previously NHS Directions imposed the same requirements). Accordingly, if a stated purpose of the 2014 scheme is to improve access to innovative new medicines (see paragraph 4.1 of the PPRS set out above), we believe this must mean more than the "standard" approach to appraisals previously adopted by NICE and necessarily requires that the arrangements under the 2014 PPRS are taken into account by NICE in conducting appraisals of products supplied by scheme members.

NICE's consideration of the PPRS

At paragraph 4.21 of the FAD for trastuzumab emtansine, the Appraisal Committee considers Roche's response to the ACD dated 19 May 2014 and to our submission that the PPRS 2014 and the implications of the PPRS Payment mechanism "must be considered by the Committee if the decision reached is to be reasonable". In response to Roche's submission, the Appraisal Committee expresses the view that the 2014 PPRS is not a

material factor to be taken into account in its appraisals either generally or in the context of this technology:

> "The Committee considered the company's response to the appraisal consultation document. This response stated that the Committee should take into account the Pharmaceutical Price Regulation Scheme (PPRS) 2014. The Committee sought guidance from the Guide to the methods of technology appraisal 2013. It noted paragraph 6.1.2, which states that it is the role of the Committee not to recommend treatments if the benefits to patients are unproven, or if the treatments are not cost effective. The Committee heard from NICE that this advice had not been superseded by the terms of the PPRS. The Committee concluded that its remit and methods of appraising the clinical and cost effectiveness of technologies had not changed".

Roche's appeal in relation to the 2014 PPRS

It is not Roche's position, as asserted by Sir Andrew Dillon in his press release dated 8 August 2014, that "the 2014 Pharmaceutical Price Regulation Scheme (PPRS) agreement includes an expectation that NICE will ignore the price a company asks for its product" as a consequence of the PPRS Payment mechanism[1]. However, it is our firm belief that the Appraisal Committee's conclusion that the 2014 PPRS is not a material factor to be taken into account when assessing the cost effectiveness of health technologies is procedurally unfair. The procedural unfairness arises, in particular, from three aspects of the appraisal: (i) the reasoning set out in the FAD to justify disregarding the 2014 PPRS is inadequate and does not explain the conclusion reached; (ii) the Appraisal Committee has failed to take into account relevant matters when reaching the decision set out in the FAD; and (iii) NICE has issued no guidance or statement explaining how the 2014 PPRS should be taken into account during appraisals. These are considered in more detail below.

(i) *The reasoning set out in the FAD to justify disregarding the 2014 PPRS is inadequate and does not explain the conclusion reached*

The reasons given by the Appraisal Committee at paragraph 4.21 of the FAD for its decision to disregard the 2014 PPRS when appraising health technologies may be summarised as:

[1] Roche is aware of paragraph 4.29 of the 2014 PPRS, which states that "The basic cost-effectiveness threshold used by NICE will be retained at a level consistent with the current range and not changed for the duration of the scheme".

- The Appraisal Committee considered the Methods Guide, specifically paragraph 6.1.2, which states that it is the role of the Committee not to recommend treatments if the benefits to patients are unproven, or if the treatments are not cost effective.
- NICE indicated that this advice had not been "superseded" by the 2014 PPRS.

However the issue is not whether paragraph 6.1.2 of the Methods Guide continues to be applicable, but whether the consideration of a health technology by the Appraisal Committee, including the assessment of cost effectiveness, should take into account the arrangements under the PPRS.

Paragraph 1.4.2 of the Methods Guide states, under the heading "Fundamental Principles":

> "A technology can be considered to be cost effective if its health benefits are greater than the opportunity costs of programmes displaced to fund the new technology, in the context of a fixed NHS budget".

The implications for the NHS budget, and the potential displacement of other therapies if a technology were to be used, is therefore a key element of any assessment of cost-effectiveness. In circumstances where the 2014 PPRS provides for any excess expenditure over and above the NHS medicines budget to be rebated by scheme members, Roche believes it is impossible for the Appraisal Committee to conduct an appraisal consistent with paragraph 1.4.2 of the Methods Guide, if the price control mechanisms under the scheme are disregarded.

The reasons provided at paragraph 4.21 of the FAD do not, however, explain the Committee's conclusions in relation to this matter.

(ii) *The Appraisal Committee has failed to take into account relevant matters when reaching the decision set out in the FAD*

The Committee's conclusions in relation to the relevance of the 2014 PPRS in the context of its appraisals, as set out at paragraph 4.21 of the FAD, fail to address the matters set out at paragraphs (a) - (d) above. As a consequence, the Committee's consideration of the relevance of the PPRS was inadequate and the procedure followed in this appraisal was unfair.

(iii) *NICE has issued no guidance or statement explaining how the 2014 PPRS should be taken into account during appraisals*

For the reasons set out above, Roche believes the relevance of the 2014 PPRS in the context of NICE's appraisal of products supplied by scheme members to be unarguable. In these circumstances, the Institute's failure to issue a statement advising Appraisal Committees how the 2014 PPRS should be taken into account and informing stakeholders accordingly, so that submissions may be appropriately directed, constitutes a serious lack of transparency and procedural unfairness.

A clearly defined process, which informs stakeholders how the assessment will be carried out and the target they have to meet, is a basic requirement of a fair procedure. In this case however, there is no transparency as to how the PPRS arrangements should be considered, with resulting confusion among both stakeholders and the Appraisal Committee. This situation is patently unfair.

Finally, following Sir Andrew Dillon's statements in the media, it is possible that NICE will claim that, because of the size of the ICER for trastuzumab emtansine accepted by NICE, taking into account the PPRS Payment mechanism would make no difference to the outcome of this appraisal. We assume that the Appeal Panel will recognise that such an argument does not answer the inherent unfairness of the procedure, as outlined above or address the prejudice to Roche as a result of its resulting inability adequately to consider the implications of alternative pricing arrangements for the product.

Conclusion

For the reasons set out above, Roche believes that the Appraisal Committee's assessment of trastuzumab emtansine was procedurally unfair. Roche requests an oral hearing for the determination of this appeal.

Sincerely,

[redacted]

[redacted]
Head of Health Economics and Strategic Pricing