NATIONAL INSTITUTE FOR HEALTH AND CLINICAL EXCELLENCE

Trastuzumab emtansine for treating HER2-positive, locally advanced or metastatic breast cancer after treatment with trastuzumab and a taxane

Patient Access Scheme Submission

11th June 2014

1 Introduction

The 2009 Pharmaceutical Price Regulation Scheme (PPRS) (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS) is a non-contractual scheme between the Department of Health and the Association of the British Pharmaceutical Industry. The purpose of the 2009 PPRS is to ensure that safe and cost-effective medicines are available on reasonable terms to the NHS in England and Wales. One of the features of the 2009 PPRS is to improve patients' access to medicines at prices that better reflect their value through patient access schemes.

Patient access schemes are arrangements which may be used on an exceptional basis for the acquisition of medicines for the NHS in England and Wales. Patient access schemes propose either a discount or rebate that may be linked to the number, type or response of patients, or a change in the list price of a medicine linked to the collection of new evidence (outcomes). These schemes help to improve the cost effectiveness of a medicine and therefore allow the National Institute for Health and Clinical Excellence (NICE) to recommend treatments which it would otherwise not have found to be cost effective. More information on the framework for patient access schemes is provided in the 2009 PPRS (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS.

Patient access schemes are proposed by a pharmaceutical company and agreed with the Department of Health, with input from the Patient Access Schemes Liaison Unit (PASLU) within the Centre for Health Technology Evaluation at NICE.

2 Instructions for manufacturers and sponsors

This document is the patient access scheme submission template for technology appraisals. If manufacturers and sponsors want the National Institute for Health and Clinical Excellence (NICE) to consider a patient access scheme as part of a technology appraisal, they should use this template. NICE can only consider a patient access scheme after formal referral from the Department of Health.

The template contains the information NICE requires to assess the impact of a patient access scheme on the clinical and cost effectiveness of a technology, in the context of a technology appraisal, and explains the way in which background information (evidence) should be presented. If you are unable to follow this format, you must state your reasons clearly. You should insert 'N/A' against sections that you do not consider relevant, and give a reason for this response.

Please refer to the following documents when completing the template:

- 'Guide to the methods of technology appraisal' (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp)
- 'Specification for manufacturer/sponsor submission of evidence' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/singletechnologyappraisalsubmissiontemplates.jsp) and
- Pharmaceutical Price Regulation Scheme 2009 (www.dh.gov.uk/en/Healthcare/Medicinespharmacyandindustry/Pharmaceuticalpriceregulationscheme/2009PPRS).

For further details on the technology appraisal process, please see NICE's 'Guide to the single technology appraisal (STA) process' and 'Guide to the multiple technology appraisal (MTA) process' (http://www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/technology_appraisal_process_guides.jsp). The 'Specification

for manufacturer/sponsor submission of evidence' provides details on disclosure of information and equality issues.

Make the submission as brief and informative as possible. Only mark information as confidential when absolutely necessary. Sufficient information must be publicly available for stakeholders to comment on the full content of the technology appraisal, including details of the proposed patient access scheme. Send submissions electronically to NICE in Word or a compatible format, not as a PDF file.

Appendices may be used to include additional information that is considered relevant to the submission. Do not include information in the appendices that has been requested in the template. Appendices should be clearly referenced in the main submission.

When making a patient access scheme submission, include:

- an updated version of the checklist of confidential information, if necessary
- an economic model with the patient access scheme incorporated, in accordance with the 'Guide to the methods of technology appraisal' (www.nice.org.uk/aboutnice/howwework/devnicetech/technologyappraisalprocessguides/guidetothemethodsoftechnologyappraisal.jsp).

If you are submitting the patient access scheme at the end of the appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

3 Details of the patient access scheme

3.1 Please give the name of the technology and the disease area to which the patient access scheme applies.

The patient access scheme (PAS) applies to the purchase of trastuzumab emtansine (Kadcyla). The PAS proposed covers all populations for which trastuzumab emtansine has an EMA marketing authorization.

3.2 Please outline the rationale for developing the patient access scheme.

The scheme is designed to bring the cost of trastuzumab emtansine down to a level at which it can be considered more cost-effective.

3.3 Please describe the type of patient access scheme, as defined by the PPRS.

The PAS is a simple discount (a [redacted]% discount below the current list price of trastuzumab emtansine).

This equates to a net price of [redacted] per 160mg vial (compared to a list price of £2,625.62) and [redacted] per 100mg vial (compared to a list price of £1,641.09).

3.4 Please provide specific details of the patient population to which the patient access scheme applies. Does the scheme apply to the whole licensed population or only to a specific subgroup (for example, type of tumour, location of tumour)? If so:

- How is the subgroup defined?
- If certain criteria have been used to select patients, why have these have been chosen?
- How are the criteria measured and why have the measures been chosen?

The PAS is a simple discount applied at the point of invoice. The PAS will apply to all patients for whom trastuzumab emtansine is indicated.

3.5 Please provide details of when the scheme will apply to the population specified in 3.4. Is the scheme dependent on certain criteria, for example, degree of response, response by a certain time point, number of injections? If so:

- Why have the criteria been chosen?
- How are the criteria measured and why have the measures been chosen.

See above. The scheme is not dependent upon any criteria and is simply applied at the point of purchase.

3.6 What proportion of the patient population (specified in 3.4) is expected to meet the scheme criteria (specified in 3.5)?

The scheme will apply to all patients for whom trastuzumab emtansine is indicated.

3.7 Please explain in detail the financial aspects of the scheme. How will any rebates be calculated and paid?

The discount will be applied at the point of invoice.

3.8 Please provide details of how the scheme will be administered. Please specify whether any additional information will need to be collected, explaining when this will be done and by whom.

The discount will be applied at the point of invoice.

3.9 Please provide a flow diagram that clearly shows how the scheme will operate. Any funding flows must be clearly demonstrated.

See below:

3.10 Please provide details of the duration of the scheme.

The scheme will remain in place until the publication of any revised NICE guidance relating to trastuzumab emtansine. After any review, the scheme may be withdrawn or modified or carried on in its current form depending upon the outcome of the re-review.

3.11 Are there any equity or equalities issues relating to the scheme, taking into account current legislation and, if applicable, any concerns identified during the course of the appraisal? If so, how have these been addressed?

There are no equity or equality issues relating to the scheme taking into account current legislation.

3.12 If available, please list any scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians and patient information documents. Please include copies in the appendices.

Not applicable.

3.13 In the exceptional case that you are submitting an outcome-based scheme, as defined by the PPRS, please also refer to appendix B.

Not applicable.

Cost effectiveness

3.14 If the population to whom the scheme applies (as described in sections 3.4 and 3.5) has not been presented in the main manufacturer/sponsor submission of evidence for the technology appraisal (for example, the population is different as there has been a change in clinical outcomes or a new continuation rule), please (re-)submit the relevant sections from the 'Specification for manufacturer/sponsor submission of evidence' (particularly sections 5.5, 6.7 and 6.9). You should complete those sections both with and without the patient access scheme. You must also complete the rest of this template.

The PAS applies to the population considered in our primary evidence submission.

3.15 If you are submitting the patient access scheme at the end of the technology appraisal process, you should update the economic model to reflect the assumptions that the Appraisal Committee considered to be most plausible. No other changes should be made to the model.

Not applicable.

3.16 Please provide details of how the patient access scheme has been incorporated into the economic model. If applicable, please also provide details of any changes made to the model to reflect the assumptions that the Appraisal Committee considered most plausible.

The PAS has been applied by reducing the price of trastuzumab emtansine to [redacted]% below the list price stated in the primary evidence submission.

This equates to a net price of [redacted] per 160mg vial (compared to a list price of £2,625.62) and [redacted] per 100mg vial (compared to a list price of £1,641.09).

3.17 Please provide the clinical effectiveness data resulting from the evidence synthesis and used in the economic model which includes the patient access scheme.

As the PAS is a simple discount the clinical effectiveness data provided in the primary evidence submission is unaffected by the proposal.

3.18 Please list any costs associated with the implementation and operation of the patient access scheme (for example, additional pharmacy time for stock management or rebate calculations). A suggested format is presented in table 1. Please give the reference source of these costs. Please refer to section 6.5 of the 'Specification for manufacturer/sponsor submission of evidence'

The PAS is a simple discount introduced at the point of invoicing. It is therefore not subject to operational or implementation costs.

3.19 Please provide details of any additional treatment-related costs incurred by implementing the patient access scheme. A suggested format is presented in table 2. The costs should be provided for the intervention both with and without the patient access scheme. Please give the reference source of these costs.

Not applicable.

Summary results

Base-case analysis

3.20 Please present in separate tables the cost-effectiveness results as follows.[1]

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

[1] For outcome-based schemes, please see section 5.2.8 in appendix B.

Table 1: Base-case cost-effectiveness results without PAS

	Trastuzumab emtansine	Lapatinib and capecitabine	Trastuzumab and capecitabine	Capecitabine	Vinorelbine	Trastuzumab and vinorelbine
Technology acquisition cost	£90,831	£20,594	£21,811	£2,400	£559	£18,720
Other costs	£20,331	£13,576	£15,818	£10,773	£18,315	£20,326
Total costs	£111,162	£34,170	£37,629	£13,173	£18,874	£39,047
Difference in total costs	-	£76,992	£73,533	£97,989	£92,288	£72,115
LYG	3.16	2.53	2.27	1.87	1.87	2.27
LYG difference	-	0.63	0.89	1.29	1.29	0.89
QALYs	1.91	1.45	1.31	1.03	1.03	1.31
QALY difference	-	0.46	0.60	0.88	0.88	0.60
ICER	-	£167,236	£122,076	£111,095	£104,632	£119,722

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio.

Table 2: Base-case cost-effectiveness results with [redacted]% discount

	Trastuzumab emtansine	Lapatinib and capecitabine	Trastuzumab and capecitabine	Capecitabine	Vinorelbine	Trastuzumab and vinorelbine
Technology acquisition cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Other costs	£20,331	£13,576	£15,818	£10,773	£18,315	£20,326
Total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Difference in total costs	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
LYG	3.16	2.53	2.27	1.87	1.87	2.27
LYG difference	-	0.63	0.89	1.29	1.29	0.89
QALYs	1.91	1.45	1.31	1.03	1.03	1.31
QALY difference	-	0.46	0.60	0.88	0.88	0.60
ICER	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

LYG, life years gained; QALY(s), quality-adjusted life year(s); ICER, incremental cost-effectiveness ratio.

3.21 Please present in separate tables the incremental results as follows.

- the results for the intervention without the patient access scheme
- the results for the intervention with the patient access scheme.

List the interventions and comparator(s) from least to most expensive. Present the incremental cost-effectiveness ratios (ICERs) in comparison with baseline (usually standard care), and the incremental analysis ranking technologies in terms of dominance and extended dominance. A suggested format is presented in table 4.

The base case results from the original submission have been used since the ERG's estimated base case results could not be replicated due to a lack of detailed information on the modifications made. This is not expected to lead to a significant difference in the effect on ICERs of the PAS since the final base case ICERs for Roche and the ERG were very similar (for lapatinib and capecitabine, £49,798 (Roche) versus £50,620 (ERG); and for trastuzumab emtansine £167,236 (Roche) versus £166,429 (ERG)).

Table 3: Base-case incremental results – without PAS

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Capecitabine	£13,173	1.87	1.03				
Vinorelbine	£18,874	1.87	1.03	£5,701	0.00	0.00	Dominated
Lapatinib and capecitabine	£34,170	2.53	1.45	£15,296	0.66	0.42	£49,798
Trastuzumab and capecitabine	£37,629	2.27	1.31	£3,459	-0.26	-0.14	Dominated
Trastuzumab and vinorelbine	£39,047	2.27	1.31	£1,418	-0.26	-0.14	Dominated
Trastuzumab emtansine	£111,162	3.16	1.91	£72,115	0.89	0.60	£167,236

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Table 4: Base-case incremental results – with [redacted]% discount

Technologies	Total costs (£)	Total LYG	Total QALYs	Incremental costs (£)	Incremental LYG	Incremental QALYs	ICER (£/QALY gained)
Capecitabine	[redacted]	1.87	1.03	[redacted]			[redacted]

Vinorelbine	[redacted]	1.87	1.03	[redacted]	0.00	0.00	[redacted]
Lapatinib and capecitabine	[redacted]	2.53	1.45	[redacted]	0.66	0.42	[redacted]
Trastuzumab and capecitabine	[redacted]	2.27	1.31	[redacted]	-0.26	-0.14	[redacted]
Trastuzumab and vinorelbine	[redacted]	2.27	1.31	[redacted]	-0.26	-0.14	[redacted]
Trastuzumab emtansine	[redacted]	3.16	1.91	[redacted]	0.89	0.60	[redacted]

LYG: life-year gained; QALY: quality-adjusted life-year; ICER: incremental cost-effectiveness ratio.

Sensitivity analyses

3.22 Please present deterministic sensitivity analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal. Consider using tornado diagrams.

The incremental cost per QALYs from the deterministic sensitivity analyses are shown in Table 5 below. Vinorelbine monotherapy and trastuzumab in combination with vinorelbine have not been included in the table for ease of reading, since these treatment options are always dominated by capecitabine monotherapy and trastuzumab in combination with vinorelbine respectively.

Table 5: Parameters varied in deterministic sensitivity analysis (with PAS)

	Capecitabine	**Lapatinib and capecitabine**	**Trastuzumab and capecitabine**	**Trastuzumab emtansine**
Costs				
Progression-free survival supportive care cost (weekly)				
£43.45 = BCV £86.91 (BCV x2) £21.73 (BCV x 0.5)	[redacted]	[redacted]	[redacted]	[redacted]
Progressed disease supportive care cost (weekly)				
£63.08 = BCV £126.17 (BCV x2) £31.54 (BCV x 0.5)	[redacted]	[redacted]	[redacted]	[redacted]
Post-progression lines (2L/3L) of treatment duration				
4.3 months (18.63 weeks) = BCV 8.6 months (37.27 weeks) 2.15 months (9.32 weeks)	[redacted]	[redacted]	[redacted]	[redacted]
Treatment dose				
Planned treatment dose = BCV Actual treatment dose observed in the trial for all whole duration of progression-free survival	[redacted]	[redacted]	[redacted]	[redacted]

Drug costs				
Including wastage = BCV Excluding wastage (full vial sharing) for all drugs (except vinorelbine as generic and assumed to be made up through compounders)	[redacted]	[redacted]	[redacted]	[redacted]
Outcomes (Results from the MTC)				
PFS HR: Tra+Cap vs T-DM1				
0.68 = BCV 0.50 (95% CI) 0.91 (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
PFS HR: Cap vs T-DM1				
0.39 = BCV 0.29 (95% CI) 0.55 (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
OS HR: Tra+Cap vs T-DM1				
0.68 = BCV 0.46 (95% CI) 0.98 (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
OS HR: Cap vs T-DM1				
0.55 = BCV 0.41 (95% CI) 0.75 (95% CI)	[redacted]	[redacted]	[redacted]	[redacted]
PFS HR: Tra+Cap vs T-DM1				
0.68 = BCV 0.54 (excluding CEREBEL and Martin)	[redacted]	[redacted]	[redacted]	[redacted]
PFS HR: Cap vs T-DM1				
0.39 = BCV 0.35 (excluding CEREBEL and Martin)	[redacted]	[redacted]	[redacted]	[redacted]
OS HR: Tra+Cap vs T-DM1				
0.68 = BCV				

0.58 (excluding CEREBEL and Martin)	[redacted]	[redacted]	[redacted]	[redacted]
OS HR: Cap vs T-DM1				
0.55 = BCV 0.52 (excluding CEREBEL and Martin)	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free survival utility				
Different values in arms = BCV 0.74 (same values as Lap and Cap arm in all arms)	[redacted]	[redacted]	[redacted]	[redacted]
Progression-free survival utility T-DM1				
0.78 = BCV 0.71 (T-DM1 PFS utilty from TH3RESA trial)	[redacted]	[redacted]	[redacted]	[redacted]
Progressed utility				
0.50 = BCV 0.70 (BCV +0.2) 0.30 (BCV -0.2)	[redacted]	[redacted]	[redacted]	[redacted]
Progression free utility T-DM1				
0.78 = BCV 0.98 (BCV +0.2) 0.58 (BCV -0.2)	[redacted]	[redacted]	[redacted]	[redacted]
Progression free utility Lap + cap				
0.74 = BCV 0.94 (BCV +0.2) 0.54 (BCV -0.2)	[redacted]	[redacted]	[redacted]	[redacted]
Progression free utility Tra + cap/Tra + vin				
0.73 = BCV 0.93 (BCV +0.2) 0.53 (BCV -0.2)	[redacted]	[redacted]	[redacted]	[redacted]
Progression free utility Cap/Vin				
0.72 = BCV 0.92 (BCV +0.2) 0.52 (BCV -0.2)	[redacted]	[redacted]	[redacted]	[redacted]

Parametric functions				
Progression free survival				
Kaplan-Meier data with log-normal tail = BCV Kaplan-Meier data with other parametric tails (1) Weibull (2) Exponential (3) Log-logistic (4) Gamma (5) Piecewise exponential tail (one piece)	[redacted]	[redacted]	[redacted]	[redacted]
Overall survival				
Gamma distribution = BCV Other parametric distributions (1) Weibull (2) Log-logistic (3) Log-normal (4) KM data with piecewise exponential tail (one piece) (5) KM data with piecewise exponential tail (two pieces)	[redacted]	[redacted]	[redacted]	[redacted]
Other				
Cost discount rate				
3.5% = BCV 6% 0%	[redacted]	[redacted]	[redacted]	[redacted]
Health outcomes discount rate				
3.5% = BCV 6% 0%	[redacted]	[redacted]	[redacted]	[redacted]
Health and cost discount rates				
3.5% both arms = BCV 6% both arms 0% both arms	[redacted]	[redacted]	[redacted]	[redacted]
Time horizon				
10 years = BCV 15 years	[redacted]	[redacted]	[redacted]	[redacted]

5 years	[redacted]	[redacted]	[redacted]	[redacted]

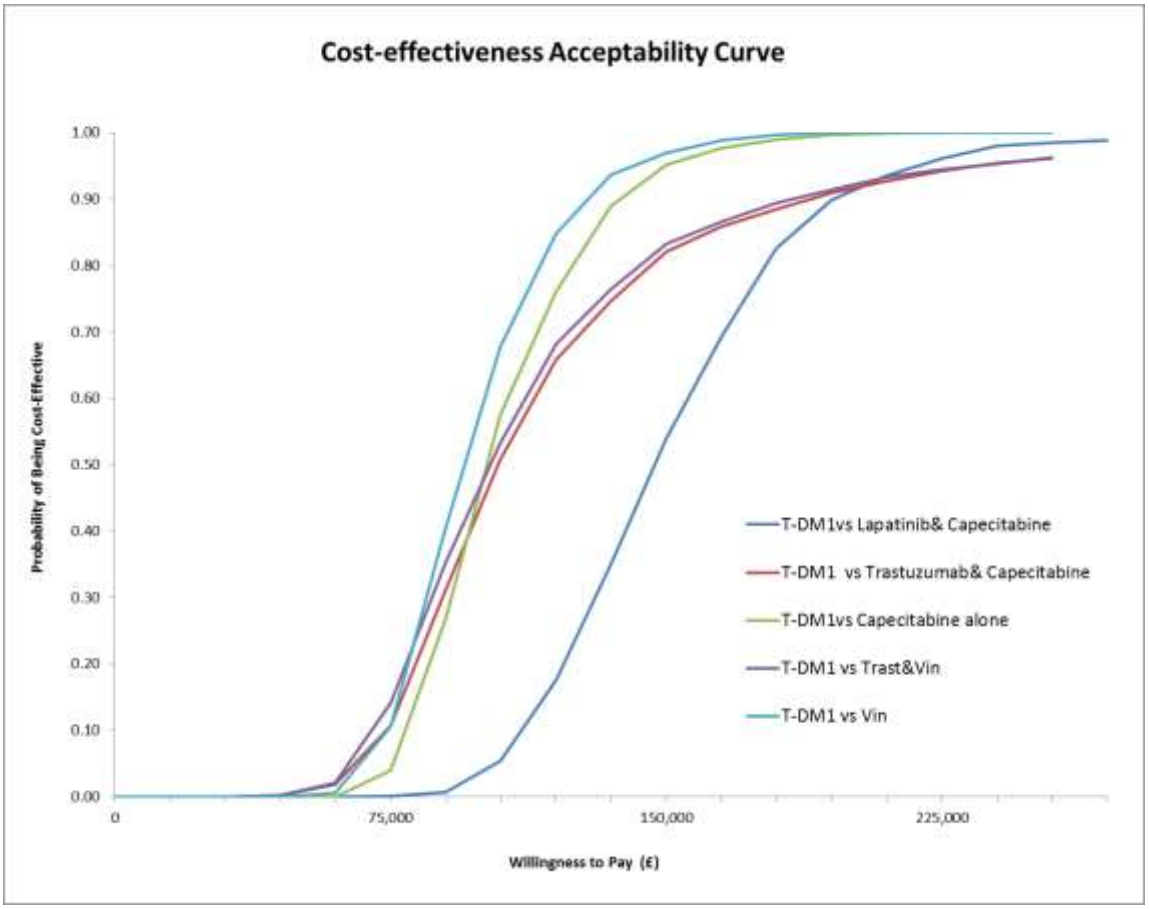
Budget Impact of NICE approval of trastuzumab emtansine

Table 6: Budget Impact of NICE approval (with [redacted]% discount)

Year	1	2	3	4	5
Mean drug cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Mean non-drug cost	£2,488,696	£5,823,548	£10,012,957	£12,978,659	£15,704,447
Mean total cost	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

3.23 Please present any probabilistic sensitivity analysis results, and include scatter plots and cost-effectiveness acceptability curves.

Figure 1: Cost Effectiveness Acceptability Curves



3.24 Please present scenario analysis results as described for the main manufacturer/sponsor submission of evidence for the technology appraisal.

See above.

3.25 If any of the criteria on which the patient access scheme depends are clinical variable (for example, choice of response measure, level of response, duration of treatment), sensitivity analyses around the individual criteria should be provided, so that the Appraisal Committee can determine which criteria are the most appropriate to use.

Not applicable.

Impact of patient access scheme on ICERs

3.26 For financially based schemes, please present the results showing the impact of the patient access scheme on the ICERs for the base-case and any scenario analyses. A suggested format is shown below (see table 5). If you are submitting the patient access scheme at the end of the appraisal process, you must include the scenario with the assumptions that the Appraisal Committee considered to be most plausible.

See above.

4 Appendices

4.1 Appendix A: Additional documents

4.1.1 If available, please include copies of patient access scheme agreement forms, patient registration forms, pharmacy claim forms/rebate forms, guides for pharmacists and physicians, patient information documents.

Not applicable.