National Institute for Health and Clinical Excellence

Centre for Health Technology Evaluation

Pro-forma Response

ERG report

Mifarmurtide for the treatment of osteosarcoma

Please find enclosed the ERG report prepared for this appraisal.

You are asked to check the ERG report from School of Health and Related Research (ScHARR), The University of Sheffield to ensure there are no factual inaccuracies contained within it. If you do identify any factual inaccuracies you must inform NICE by 5pm, **Wednesday 24 February 2010** using the below proforma comments table. All factual errors will be highlighted in a report and presented to the Appraisal Committee and will subsequently be published on the NICE website with the Evaluation report.

The attached proforma document should act as a method of detailing any inaccuracies found and how and why they should be corrected.

16 February 2010

Issue 1 ERG Report 2009

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 6 1.1 Scope of the submission "The manufacturer's submission (MS) generally reflects the scope of the appraisal issued by NICE, and is appropriate to the NHS. The majority of the MS reflects the use of mifamurtide in individuals with osteosarcoma who have undergone surgical resection; however, it does not reflect the broader population outlined in the NICE scope (individuals with osteosarcoma related to Paget's disease, individuals with metastatic disease and individuals with relapsed osteosarcoma)." With reference to the NICE Scope "Guidance Osteosarcoma - mifamurtide: final scope, 22nd October 2008) Guidance will only be issued in accordance with the marketing authorisation." Mifamurtide (Mepact, Takeda UK Ltd) is indicated for use in children and adults aged between two and thirty years of age for the treatment of high grade resectable	Takeda UK Ltd requests an update to the ERG comment on the submission meeting the population within the scope in line with the Mepact Marketing Authorisation, which states that Mepact is indicated for the treatment of children and adults aged between two and thirty years of age for the treatment of high grade resectable non-metastatic osteosarcoma after macroscopically complete surgical resection to remove the tumour. It is used in combination with post-operative multi-agent chemotherapy.	The submission meets the definitions within the scope in line with the Mepact Marketing Authorisation.	This issue is caused due to a discrepancy between the Marketing Authorisation for Mepact and the scope issued by NICE. Our comment is factually correct, however we acknowledge that the groups omitted from the NICE scope are outside of Mepact's marketing authorisation and have added text to reflect this.

non-metastatic osteosarcoma after macroscopically complete surgical resection to remove the tumour. It is used in combination with post-operative multi- agent chemotherapy. Takeda UK Ltd believes that the submission meets the need of scope as the marketing authorisation for Mepact does not include individuals with osteosarcoma related to Paget's disease, individuals with metastatic disease and individuals with relapsed osteosarcoma.			

Issue 2 ERG Report 2009

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 6 and throughout document. Manufacturer's Submission (MS) - The original submission was completed by IDM Pharmaceuticals Incorporated. The Addendum was submitted by Takeda UK Ltd.	Takeda UK Ltd suggests that "Manufacturer's" submission is annotated to reflect which company actually was responsible for the specific submission.	Annotation of which company submitted specific parts of the overall submission will ensure accuracy of the ERG Report and aid reviewers to understand where responsibility lies for specific statements, etc.	The addendum from Takeda UK Ltd focussed on the revised economic model which incorporated the patient access scheme. As no amendment was made to the clinical section, which is a requirement of an STA, the ERG had no option but to assume that Takeda were satisfied with the clinical section previously presented by IDM Pharmaceuticals. For clarity it is noted that the clinical section was originally written by IDM Pharmaceuticals, not Takeda UK Ltd,

			who had the chance to revise this, but choose not to.

Issue 3 ERG Report 2009

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 7 1.2 1.3 Summary of submitted clinical effectiveness evidence Point 2: "Additional post hoc analysis that compared the addition of mifamurtide to Regimen A (Regimen A+) with chemotherapy alone (Regimen A) showed non-significant improvements in overall survival (hazard ratio, 0.75; 95% CI, 0.49 to 1.16; p=0.1949) and disease-free survival (hazard ratio, 0.96; 95% CI, 0.67 to 1.38; p=0.8357)." INT0133 was a prospective, parallel group, four-arm, multi-centre, randomised and open-label design. The study posed two questions in a 2 X 2 factorial design. INT0133 was powered to assess whether addition of ifosfamide to doxorubicin, cisplatin, and HDMTX would improve event-free survival (EFS) and overall survival (OS). INT0133 was also powered to assess whether addition of mifamurtide to	The INT0133 study was powered to assess in a 2 X 2 Factorial Design the addition of ifosfamide and mifamurtide to doxorubicin, cisplatin and high dose methotrexate on OS and EFS. Post hoc analysis of separate arms is not possible as the trial was not powered to detect any differences in outcomes between arms. Takeda UK Ltd suggests that post-hoc analysis is removed from the ERG Report.	Post hoc analysis of separate arms in a 2 X 2 Factorial design is not possible due to lack of power. Conclusions cannot be drawn from this methodology and should be removed from the report.	This is not a factual error. We have provided the NICE appraisal committee with data the ERG believes pertinent to a UK decision. These data will be considered by the appraisal committee alongside those presented by Takeda UK Ltd.

chemotherapy would improve EFS and OS. The INT0133 study was not designed to analyze four arms in parallel fashion with adequate power and conclusions cannot be drawn in line with good clinical trial and statistical procedure. Post-hoc analysis of Regimen A vs. Regimen A+ does not allow conclusions to be drawn from this comparison. This course of action would also necessitate consideration of Regimen B vs. Regimen B+ which significantly increases Mepact impact on overall survival from 70 to 81% over 6 years. (Assessment of the B/B+ arms produces an ICER of £36,913 with PAS.)			

Issue 4 ERG Report 2009

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG Response**
Page 8 1.4.2 Weaknesses "The included RCT is not an absolute reflection of the population with osteosarcoma in the UK, so the	Takeda UK Ltd requests an update to the ERG comment on the submission reflecting the UK population with osteosarcoma in	Trial INT0133 forms the basis of the submission reflects the population of osteosarcoma patients in the UK – this is in line with the Mepact	This is not a factual error. As noted on page 32 of the ERG 2009 report, the INT-0133 trial only included

external validity may be questionable." As detailed in issue 1, trial INT0133 which forms the basis of the submission reflects the population of osteosarcoma patients in the UK that Mepact holds a Marketing Authorisation.	line with the Mepact Marketing Authorisation.	Marketing Authorisation. The participants in study INT-0133 trial are highly representative of patients likely to receive the intervention in the UK.	patients less than 30 years of age with high grade, resectable, non metastatic osteosarcoma of the bone. This comprises approximately 65% of all patients with osteosarcoma (no information to support its use for patients with osteosarcoma outside the eligibility criteria of this trial). In addition, the mean age of patients in the INT-0133 trial was slightly younger than the typical age of an osteosarcoma patient in England and Wales (mean age: 16 years in boys and 15 years in girls) (ERG 2009 report, p23)

Issue 5 ERG Report 2009

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG Response**
Page 9 1.4.3 Areas of uncertainty "There is uncertainty around the clinical- and cost-effectiveness of mifamurtide in combination with multi-agent chemotherapy (Regimens A+ and B+ combined) to multi-agent chemotherapy alone (Regimens A and B combined) in individuals with metastatic disease, recurrent disease, older patients (greater than 30 years of age) and	Takeda UK Ltd requests an update to the ERG comment on the submission and this area of uncertainty. The marketing authorisation for Mepact does not include individuals with osteosarcoma and metastatic disease, recurrent disease, older patients (greater than 30 years of age) and other osteosarcomas. It is therefore unclear what areas of	Trial INT0133 forms the basis of the submission reflects the population of osteosarcoma patients in the UK – this is in line with the Mepact Marketing Authorisation. The participants in study INT-0133 trial are highly representative of patients likely to receive the intervention in the UK under the terms of the marketing authorisation.	This is not a factual error. See response to issue 3.

other osteosarcomas."	uncertainty are referred to in the ERG report, as the patient groups described are irrelevant to the marketing authorisation under discussion.		

Issue 6 ERG Report 2009

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 9 1.4.3 Areas of uncertainty "Importantly, the addition of mifamurtide to multi-agent chemotherapy may not be effective if one assumes the RCT results for treatment arms which represent current UK practice (Regimens A+ versus A) hold." Please refer to Issue 3 relating to lack of power for 4 Arm Parallel comparisons. The standard of care within UK Clinical Practice is to enter patients into a prospective clinical trial such as the EURAMOS study. The dosage and timing of methotrexate, doxorubicin and cisplatin were essentially the same in study INT-0133 as in the comparator arms for the ongoing EURAMOS study. This reflects current clinical practice	The INT0133 study was powered to assess in a 2 X 2 Factorial Design the addition of ifosfamide and mifamurtide to doxorubicin, cisplatin and high dose methotrexate on OS and EFS. Post hoc analysis of separate arms is not possible as the trial was not powered to detect any differences in outcomes between arms. Takeda UK Ltd suggests that this stastictally underpowered post-hoc analysis is removed from the ERG Report. There is no evidence from the existing data that there is any difference between the 3 and 4 agent chemotherapy arms. The study was also not powered to compare anything besides the endpoints stated above. It would	Post hoc analysis of separate arms in a 2 X 2 Factorial design is not possible due to lack of power. Conclusions cannot be drawn from this methodology and should be removed from the report. The ERG report should reflect that current UK practice is to enter patients onto prospective clinical trials such as EURAMOS which reflects the trial design of INT0133.	This is not a factual error. Our clinical experts advised us that Regimen A was most representative of current UK practice. This issue will be discussed by the NICE appraisal committee with clinical experts.

in the UK as well as in many other geographical locations, such as Member States of the European Union. The regimen used represents the most effective chemotherapy combination currently available, as evidenced by use in the EURAMOS trial comparator treatment arms.	therefore be poor statistical practice to select out this group as the basis for a pharmacoeconomic analysis. As the four arms of the INT0133 trial reflect the comparator trail arms of EURAMOS, Takeda UK LTD suggest that INT0133 as a 2 X 2 Factorial design trial reflects current UK practice.		

Issue 7 ERG Report 2009

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 23 4.1.5 Paragraph 1 Description and critique of manufacturers approach to validity assessment "Although the sample size power calculations were adequately powered for the disease-free survival intermediate endpoint, the ERG notes that the INT-0133 trial was not powered to assess overall survival." In osteosarcoma disease free survival and overall survival are closely correlated similar to many other cancers. The INT0133 primary study end points were overall and disease free survival and were	Takeda UK Ltd suggests the statement "the ERG notes that the INT-0133 trial was not powered to assess overall survival." is removed as not accurate. It is clear from the clinical study reports that overall, as well as event free survival, were pre-specified primary objectives of this independent study.	Takeda UK Ltd suggests the statement "the ERG notes that the INT-0133 trial was not powered to assess overall survival." is removed as not accurate.	This is not a factual error. The sample size power calculations in the INT-0133 trial were based on the first planned analysis of the intermediate disease free survival endpoint (a recognised surrogate marker of overall survival in cancer trials).

adequately powered.			

Issue 8 ERG Report 2009

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 23 4.1.5 Paragraph 3 Description and critique of manufacturers approach to validity assessment "The MS suggest that the participants in the INT-0133 trial were similar to the UK population (p49, 52, MS). The ERG observed that the mean age of the participants in the INT-0133 trial was approximately 14 years (range 1.4 to 30.4 years). The ERG clinical advisors noted that the age of patients in the INT-0133 trial was slightly younger than the typical age of an osteosarcoma patient in England and Wales (mean age: 16 years in boys and 15 years in girls) (Dr J Whelan, University College Hospital, London: personal communication, 2008). In addition, Bielack et al.,14 suggest that the incidence of osteosarcoma is highest between the age of 15 and 19 years. The ERG notes that the INT-0133 trial is not an absolute reflection of the	In clinical practical terms, the difference between a 14, 15 and 16 year old patient with osteosarcoma is negligible; the statement that external validity may be questionable is unfounded. Takeda UK Ltd request that this statement is removed as it is unfounded and not based on statistically robust evidence.	Takeda UK Ltd request that this statement is removed as it is unfounded and not based on evidence.	This is not a factual error. The use of the word 'may' in the phrase 'may be questionable' indicates that it may also not be questionable. This is a decision for the NICE appraisal committee, and we have fulfilled our role as the ERG by mentioning that there was a slight discrepancy in the age of patients in the trial and those treated in practice.

population with osteosarcoma in the UK, so the external validity may be questionable." The references to ages above is academic as the difference between for example a 14 and 15 year old may be as small as one day. In clinical practical terms, the difference between a 14, 15 and 16 year old patient with osteosarcoma is negligible; the statement that external validity may be questionable is unfounded.			

Issue 9 ERG Addendum Report 2010

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 5 1.1 Scope of Submission "The manufacturer's submission (MS) generally reflects the scope of the appraisal issued by the National Institute for Health and Clinical Excellence (NICE), and is appropriate to the NHS. The majority of the MS reflects the use of mifamurtide in individuals with osteosarcoma who have undergone surgical resection; however, it does not reflect the broader population outlined in the NICE scope (individuals with	Takeda UK Ltd requests an update to the ERG comment on the submission meeting the population within the scope in line with the Mepact Marketing Authorisation.	The submission meets the definitions within the scope in line with the Mepact Marketing Authorisation.	See the response to Issue 1

osteosarcoma related to Paget's disease, individuals with metastatic disease and individuals with relapsed osteosarcoma)." Please refer to the response in Issue 1			

Issue 10 ERG Addendum Report 2010

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 6 1.2 Summary of submitted clinical effectiveness evidence "Additional supplementary data (requested by the Evidence Review Group (ERG)) also compared individual mifamurtide containing regimens (Regimen A+) to chemotherapy regimens most commonly used in the UK (Regimen A)." INT0133 was a prospective, parallel group, four-arm, multi-centre, randomised and open-label design. The study posed two questions in a 2 X 2 factorial design. INT0133 was powered to assess whether addition of ifosfamide to doxorubicin, cisplatin, and HDMTX	The INT0133 study was powered to assess in a 2 X 2 Factorial Design the addition of ifosfamide and mifamurtide to doxorubicin, cisplatin and high dose methotrexate on OS and EFS. Post hoc analysis of separate arms is not possible as the trial was not powered to detect any differences in outcomes between arms. Takeda UK Ltd suggests that post-hoc analysis is removed from the ERG Report.	Post hoc analysis of separate arms in a 2 X 2 Factorial design is not possible due to lack of power. Conclusions cannot be drawn from this methodology and should be removed from the report.	See response to Issue 3.

would improve event-free survival (EFS) and overall survival (OS). INT0133 was also powered to assess whether addition of mifamurtide to chemotherapy would improve EFS and OS. The INT0133 study was not designed to analyze four arms in parallel fashion with adequate power and conclusions cannot be drawn in line with good clinical trial and statistical procedure. Post-hoc analysis of Regimen A vs. Regimen A+ does not allow conclusions to be drawn from this comparison. This course of action would also necessitate consideration of Regimen B vs. Regimen B+ which significantly increases Mepact impact on overall survival from 70 to 81% over 6 years. (Assessment of the B/B+ arms produces an ICER of £36,913 with PAS.)			

Issue 11 ERG Addendum Report 2010

Description of problem	Description of proposed	Justification for amendment	ERG Response

	amendment		
Page 8 Commentary on the robustness of submitted evidence Weaknesses "The included RCT is not an absolute reflection of the population with osteosarcoma in the UK, so the external validity may be questionable." As detailed in issue 4, trial INT0133 which forms the basis of the submission reflects the population of osteosarcoma patients in the UK that Mepact holds a Marketing Authorisation.	Takeda UK Ltd requests an update to the ERG comment on the submission reflecting the UK population with osteosarcoma in line with the Mepact Marketing Authorisation.	Trial INT0133 forms the basis of the submission reflects the population of osteosarcoma patients in the UK – this is in line with the Mepact Marketing Authorisation. The participants in study INT-0133 trial are highly representative of patients likely to receive the intervention in the UK.	Whilst this is not a factual error, the ERG agree that this is not a weakness and have removed the bullet point

Issue 12 ERG Addendum Report 2010

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 9 Commentary on the robustness of submitted evidence Weaknesses "The ERG has concern regarding the lack of face validity of the model. The modelled survival rates are greater than the observed data with increases in the range of 3-4 percentage points. It is not known whether this discrepancy favours or	Takeda UK Ltd requests an update to the ERG comment on the submission meeting the population within the scope in line with the Mepact Marketing Authorisation.	The submission meets the definitions within the scope in line with the Mepact Marketing Authorisation.	Clearly there is a typographical issue with the manufacturer's comment to this Issue. Regardless, the ERG has reviewed the quoted text and remains content that it is factually correct. The observed rates were 80% and 73% for mifamurtide and no mifamurtide respectively; the modelled rates were 83% and 77% respectively.

disfavours mifamurtide but is likely to increase the uncertainty in the results." The 6-year Kaplan-Meier (KM) estimate of the survival rate in the mifamurtide arm is 78% and 70% in the arm without mifamurtide based on all 678 patients. It is important to note that this rate is different than the rate observed in patients who entered the adjuvant treatment phase of the INT-0133 trial. Alike to the previous Cost Effectiveness model submitted in the previous IDM Pharma Inc submission, the analyses in the Takeda cost effectiveness model is based upon an analysis of the 604 ITT patients who entered the maintenance phase. Seventy-four patients in the ITT group who did not enter the adjuvant phase were excluded from this analysis. In this patient population who received adjuvant treatment, the 6-year Kaplan-Meier estimate of the survival rate 80.4% in the mifamurtide arm and 72.9% in the arm without mifamurtide. This data has been submitted to NICE in response to Clarification questions submitted on the 14th			

January 2010 – Question A5.			

Issue 13 ERG Addendum Report 2010

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 9 Areas of uncertainty "The clinical advice provided to the ERG indicated that it is likely that a more clinically relevant assessment for a UK population would be derived from an analyses comparing Regimen A+ with Regimen A. The mathematical model submitted by the manufacturer also estimates that, on average, a patient being treated with Regimen A would accrue more QALYs at a lower cost than a patient receiving Regimen B." Please refer to the response to Issue 10.	The INT0133 study was powered to assess in a 2 X 2 Factoria Design the addition of ifosfamide and mifamurtide to doxorubicin, cisplatin and high dose methotrexate on OS and EFS. Post hoc analysis of separate arms is not possible as the trial was not powered to detect any differences in outcomes between arms. Takeda UK Ltd suggests that post-hoc analysis is removed from the ERG Report.	Post hoc analysis of separate arms in a 2 X 2 Factorial design is not possible due to lack of power. Conclusions cannot be drawn from this methodology and should be removed from the report.	This is not a factual error. See response to Issue 3 regarding power. The additional QALYs and lower costs associated with Regimen A compared with Regimen B is taken directly from the addendum submitted by the manufacturer.

Issue 14 ERG Addendum Report 2010

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 9 Areas of uncertainty "Importantly, the addition of mifamurtide to multi-agent chemotherapy may be substantially reduced if it is assumed that Regimen A represents current UK	The INT0133 study was powered to assess in a 2 X 2 Factorial Design the addition of ifosfamide and mifamurtide to doxorubicin, cisplatin and high dose methotrexate on OS and EFS.	Post hoc analysis of separate arms in a 2 X 2 Factorial design is not possible due to lack of power. Conclusions cannot be drawn from this methodology and should be	This is not a factual error. See the response to Issue 3 and Issue 6.

practice hold, rather than a combination of Regimen A and Regimen B." Please refer to the response to Issue 6.	Post hoc analysis of separate arms is not possible as the trial was not powered to detect any differences in outcomes between arms. Takeda UK Ltd suggests that post-hoc analysis is removed from the ERG Report. As the four arms of the INT0133 trial reflect the comparator trail arms of EURAMOS, Takeda UK LTD suggest that INT0133 as a 2 X 2 Factorial design trial reflects current UK practice.	removed from the report. The ERG report should reflect that current UK practice is to enter patients onto prospective clinical trials such as EURAMOS which reflects the trial design of INT0133.	

Issue 15 ERG Addendum Report 2010

Description of problem	**Description of proposed amendment**	**Justification for amendment**	**ERG Response**
Page 10 Areas of uncertainty Paragraph 2 "It is unclear whether the loss of hearing observed when mifamurtide was added to chemotherapy regimens is representative of actual events or whether these were chance events associated with cisplatin use." Also Key Issues Paragraph 2 "The rate of hearing loss assumed to	Takeda UK Ltd asks the ERG to remove the speculation that Mepact may cause loss of hearing; this is not supported by the data or previous patient exposure in Phase II trials.	The ERG report speculates that Mepact may cause hearing loss although the data does not support this. Ototoxicity is commonly associated with cisplatin therapy, and the frequency of hearing loss reported for patients treated with Mepact was within the range expected for cisplatin alone.	This is not a factual error. The text provided by the manufacturers show a significant effect on both objective and subjective hearing loss (p-value <0.05) when Mepact was added to standard treatment. The ERG has recognised that this may not be causal and have reflected this in our analyses.

be associated with the addition of mifamurtide to a current chemotherapy regimen." The addition of Mepact to chemotherapy significantly increased the incidence in objective (11.5% with Mepact vs. 7.1% without, p=0.048) and subjective (3.6% vs. 0.6%, p<0.01) hearing loss. However, the association between hearing loss and the study treatment was lost on comparison of the incidence of events in the individual Mepact treatment groups; specifically the incidence of auditory problems was lower in patients treated with chemotherapy plus Mepact than in those treated with chemotherapy alone. Ototoxicity is commonly associated with cisplatin therapy, and the frequency of hearing loss reported for patients treated with Mepact was within the range expected for cisplatin alone.			

Issue 16 ERG Addendum Report 2010

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 18 Table 1 Row 4 and 5 Scenarios described as "MBC but	Takeda UK Ltd recommends an update to row 5 with value for	Update accuracy of the table.	We acknowledge that this is an error. In Row 5, the discount rate for

discount rate for outcomes set to 0% per annum" –i.e. the same discount rate but the ICER values are different	outcomes set to "x"% per annum		outcomes should read 6% rather than 0%.

Issue 17 ERG Addendum Report 2010

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 28 7.1 "Whilst the submitted evidence generally reflects the decision problem as defined in the manufacturer's submission, it is not totally representative of all patients with osteosarcoma in the UK (e.g. individuals with metastatic disease, recurrent disease, older patients and osteosarcoma related to Paget's disease or other primary sites)." Please refer to the response in Issue 1.	Takeda UK Ltd requests an update to the ERG comment on the submission meeting the population within the scope in line with the Mepact Marketing Authorisation.	The submission meets the definitions within the scope in line with the Mepact Marketing Authorisation.	This is not a factual error. See response to Issue 1

Issue 18 ERG Addendum Report 2010

Description of problem	Description of proposed amendment	Justification for amendment	ERG Response
Page 28 7.1 "It is likely that a more clinically relevant assessment for a UK population would be derived from an analysis comparing individual	The INT0133 study was powered to assess in a 2 X 2 Factorial Design the addition of ifosfamide and mifamurtide to doxorubicin, cisplatin and high dose	Post hoc analysis of separate arms in a 2 X 2 Factorial design is not possible due to lack of power. Conclusions cannot be drawn from	This is not a factual error. See Response to Issue 3

mifamurtide containing regimens (Regimen A+) to chemotherapy regimens most commonly used in the UK (Regimen A). This additional post hoc analysis (requested by the ERG) that compared Regimen A+ with Regimen A showed a non-significant improvement in overall survival (hazard ratio, 0.75; 95% CI, 0.49 to 1.16; p=0.1949) and disease-free survival (hazard ratio, 0.96; 95% CI, 0.67 to 1.38; p=0.8357)." Please refer to the response in Issue 10. This course of action would also necessitate consideration of Regimen B vs. Regimen B+ which significantly increases Mepact impact on overall survival from 70 to 81% over 6 years. (Assessment of the B/B+ arms produces an ICER of £36,913 with PAS.)	methotrexate on OS and EFS. Post hoc analysis of separate arms is not possible as the trial was not powered to detect any differences in outcomes between arms. Takeda UK Ltd suggests that post-hoc analysis is removed from the ERG Report.	this methodology and should be removed from the report.	