NICE Single Technology Appraisal of Mifamurtide for the treatment of osteosarcoma:

New submission of evidence 8th February 2010.

In the NICE Single Technology Appraisal of mifamurtide for the treatment of osteosarcoma, Takeda UK submitted new evidence on the 10th December 2009 to support this appraisal. On the 16th November 2009, Takeda UK also submitted a Patient Access Scheme (PAS) to NICE PASLU & the Department of Health for assessment. The proposed scheme stated that Takeda UK would provide mifamurtide treatment to patients, with no charge to the NHS, beyond the average treatment length (as defined by the INT-0133 trial) up to the defined SPC regimen amount.

In the final assessment of the PAS, the free stock provision as part of the scheme was requested by NICE PASLU to be changed from the end of the treatment regimen to the beginning of the PAS. This submission is to provide supportive economic evidence for the amended PAS. All details of the economic model (with the exception of the PAS) are inline with the original Takeda UK submission of evidence on the 10th December 2009 and answers to questions provided to NICE on the 29th January 2010.

Details of the new PAS are provided in accompanying documentation. In summary, the amended PAS allows Takeda UK to provide mifamurtide treatment to patients, for the first 7 doses, with no charge to the NHS.

The contents of this new submission of evidence are to detail the amended cost effectiveness results and sensitivity analyses.

Key Points:

- The new base case ICER is £68,734. When a mifamurtide PAS is introduced the ICER is £56,683.
- Assessment of the A/A+ arms of the INT-0133 arms produce an ICER of £158,485 (£130,814 with PAS). Assessment of the B/B+ arms produce an ICER of £44,812 (£36,913 with PAS). Given the documented imbalances of the patient population in the, "A" arms, it is accepted from clinical opinion (communication with Prof Ian Lewis) that efficacy presented in the, "B" arm may be more representative of the overall treatment efficacy of three or four regimen chemotherapy in combination with mifamurtide, and as a result, the ICER presented from the B arm may be an appropriate upside for assessment.
- The model is also very sensitive to modification of the discount rate for outcomes. When this is changed to 1.5% for the total treatment population, the ICER is £34,581 when a mifamurtide PAS is introduced.
- Even when the model is set to a super pessimistic scenario, the ICER is £91,442, this is dramatically reduced to £66,951 when the efficacy of the B/B+ arms are viewed as generalisable for the total population and a PAS is introduced. Alternatively, when the discount rate is adjusted to 1.5% for outcomes and a PAS are introduced, the ICER is £56,694.
- This analysis validates the base case ICER and demonstrates the general robustness of the base case analyses. The upside from the discount rate for outcomes ameliorates any uncertainty in the model that may come from non inclusion of other model assumptions such as limb salvage maintenance costs or adverse events associated with hearing loss.
- It is the opinion of Takeda UK that mifamurtide offers good value for money with an ICER in the region of £56,683 when a PAS for mifamurtide is introduced. On the upside a realistic upside ICER may be as high as £36,913 per QALY gained when the efficacy demonstrated in the B/B+ arms are assumed generalisable for the total population.

1 Results

The new base case cost per incremental QALY gained is £68,734. This is presented below in Table 1 along with ICERs for all treatment regimens from the INT-0133 trial.

Table 1: ICERs for all treatment regimens from the INT-0133 trial.

Outcome	A+/B+	A/B	Diff	A+	A-	Diff	B+	B-	Diff
Total costs	£123,852	£31,481	£92,371	£122,604	£29,709	£92,895	£125,121	£33,244	£91,877
Mifamurtide Drug costs	£91,189	–	£91,189	£91,189	–	£91,189	£91,189	–	£91,189
Adjuvant Chemotherapy costs	£26,205	£26,205	–	£26,205	£26,205	–	£27,625	£27,625	–
Resource costs	£6,458	£5,277	£1,181	£6,631	£4,925	£1,706	£6,307	£5,619	£687
QALYs	16.72	15.38	1.34	16.69	16.10	0.59	16.71	14.66	2.05
Incremental Cost-effectiveness Ratios									
Incremental cost per QALY gained	**£68,734**			**£158,435**			**£44,812**		
ICER with PAS	**£56,683**			**£130,814**			**£36,913**		

These results are based on the following assumptions, as per the previous submission (8th December 2009, and amendments requested and answered January 19th 2010):

- 60 year time horizon.
- 100% of the population starting in the Disease-free health state;
- Clinical data as previously described;
- Resource and Cost inputs as outlined in Tables x & x, patients receive on average 38.4 doses of mifamurtide;
- No Amputation or limb salvage costs;
- Hearing loss adverse event not included;
- Mortality risk reverting to general population after a given time period not included;
- Age related utility weights not included;
- Discounting rates of 3.5% for both costs and outcomes applied.

Assessment of the A/A+ arms of the INT-0133 arms produce an ICER of £158,435 (£130,814 with PAS). Assessment of the B/B+ arms produce an ICER of £44,812 (£36,913 with PAS). Given the documented imbalances of the patient population in the, "A" arms, it is accepted from clinical opinion (communication with Prof Ian Lewis) that efficacy presented in the, "B" arm may be more representative of the overall treatment efficacy of three or four regimen chemotherapy in combination with mifamurtide, and as a result, the ICER presented from the B/B+ arms may be an appropriate upside for assessment.

Regimens A & B are considered the standard of care within UK clinical practice. The decision to use ifosfamide in addition to cisplatin, doxorubicin and high dose methotrexate (regimen B in preference to regimen A) is dependent on patient status and physician preference. In addition, many UK patients are entered into the Euramos 1 trail which reflects both Regimen A and B as principle treatment arms.

In exploring subgroup analyses, an imbalance in histological response was also noted in patients older than 16 and this is a particular problem in the A/A+ arms. In the INT-0133 trial, randomization occurred before induction chemotherapy pre-surgery, but mifamurtide was used post surgery, so there is a potential for differences in patient allocation.

The group of patients aged 16 years and older had a marked imbalance in necrosis. This imbalance was completely absent in the patients 15 and younger. Examination of the entire intent to treat cohort did not identify a noticeable imbalance in good and poor necrosis between patients assigned to receive or not to receive mifamurtide. Examination of the patients aged 16 or older showed that there was an excess of poor necrosis in the patients assigned to receive Mepact in the A+ arm. Kaplan-Meier analysis of the 15 and younger cohort demonstrates perfect concordance between EFS and survival and both demonstrate improvement with the addition of Mepact to chemotherapy with no hint of interaction between the two study interventions. However this does not mean to suggest that the benefit of Mepact is limited to the younger cohort of patients.

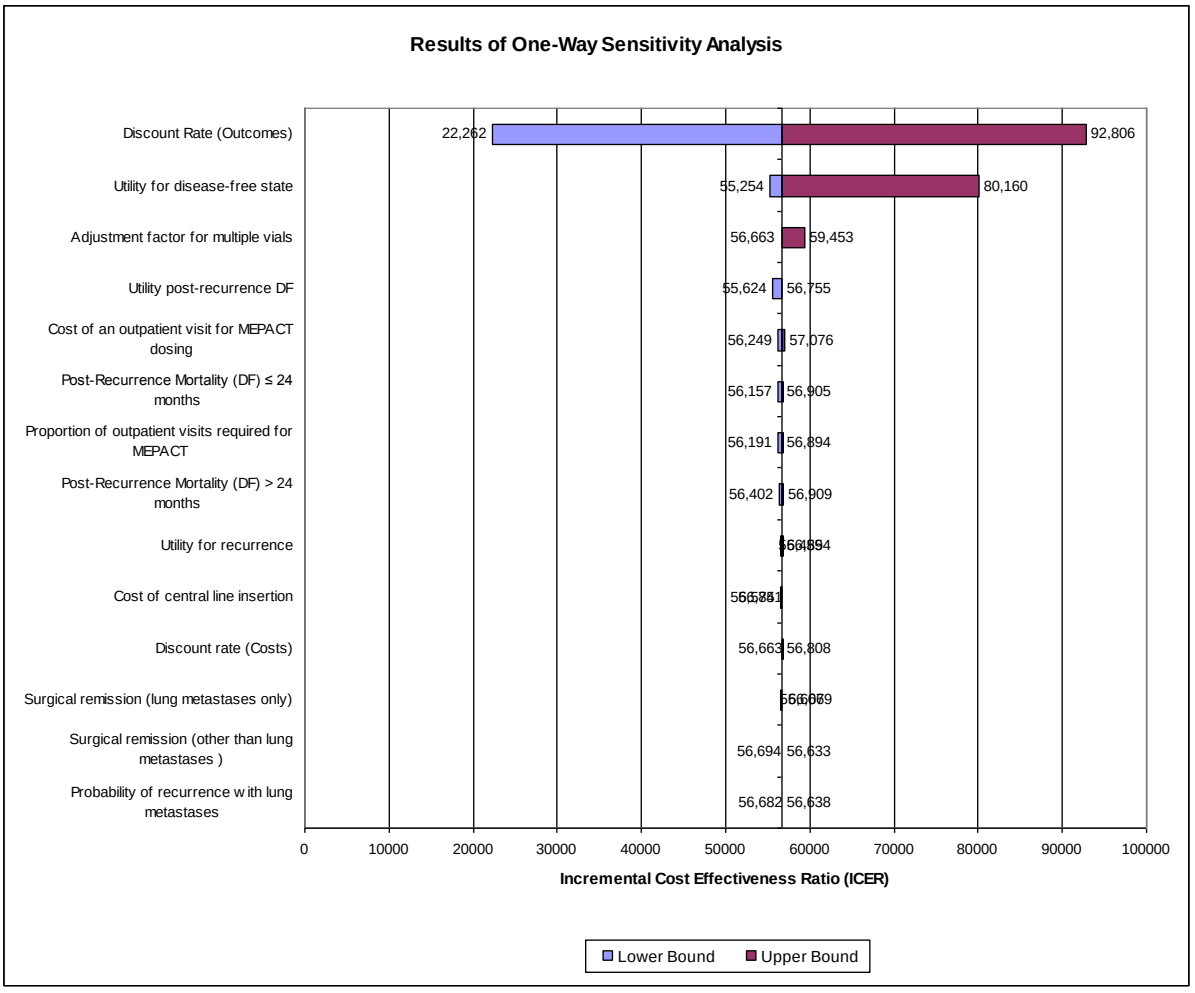
2 Sensitivity Analyses

To ascertain the robustness of the new Takeda cost effectiveness model we have undertaken a range of sensitivity analysis including one-way sensitivity analysis and probabilistic sensitivity analysis (PSA).

2.1 Standard One-way Sensitivity Analysis

One way sensitivity analyses is presented below in Figure 2.1.

Figure 2.1: One Way Sensitivity Results



2.2 Probabilistic Sensitivity analysis

The probabilistic sensitivity analysis was run over 10,000 model iterations using the default scenario (with PAS) with both 3.5% discounting rates for both cost and outcomes. In each probabilistic sensitivity analysis iteration, the model simultaneously sampled parameter values from assumed statistical distributions.

The results of the probabilistic sensitivity analysis are shown in Figure 2.2 and Figure 2.2.1. Both analyses have assumed a willingness to pay (WTP) threshold of £50,000. Both analyses also reflect the affect of having the treatment cost primarily in the early years (mainly year 1) by the flatness of the cost-effectiveness scatter plot.

The summary cost per QALY derived from the PSA is £54,830.

Figure 2.2: PSA Cost-effectiveness Plot

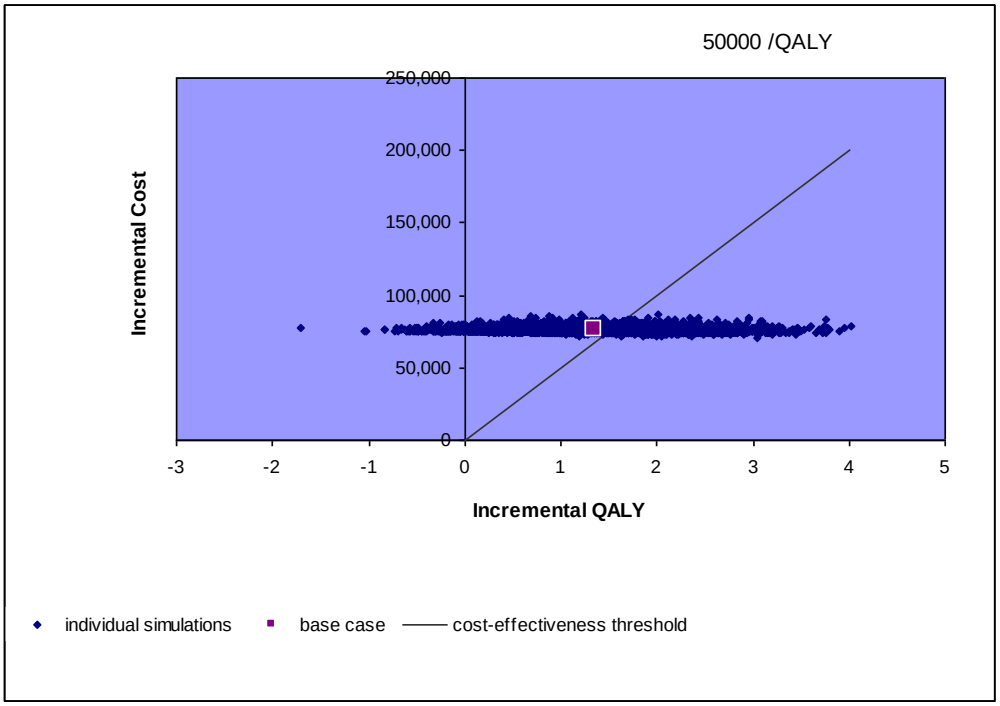
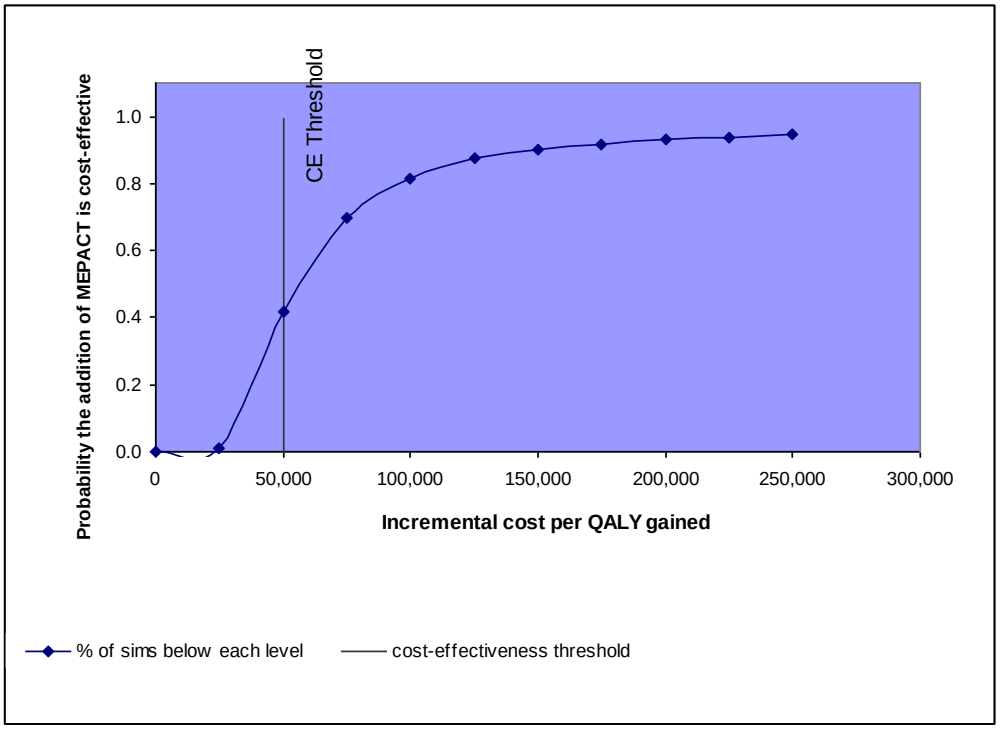


Figure 1.2.1: Cost-effectiveness Acceptability Curve:



The results of the cost effectiveness acceptability curve shows that the probability of mifamurtide being a cost effective use of NHS resources at a willingness to pay of £50,000 is 40%.

3 Scenario Analysis: PSA for the B/B+ arms

As a credible upside ICER, a PSA is presented below when assuming the efficacy of the B/B+ arm of the INT-0133 is generalisable to the total population and the mifamurtide PAS is applied. The summary cost per QALY derived from the PSA is £35,181. The results of the probabilistic sensitivity analysis are shown in Figure 3.1 and Figure 3.2 below.

Figure 3.1: PSA Cost-effectiveness Plot

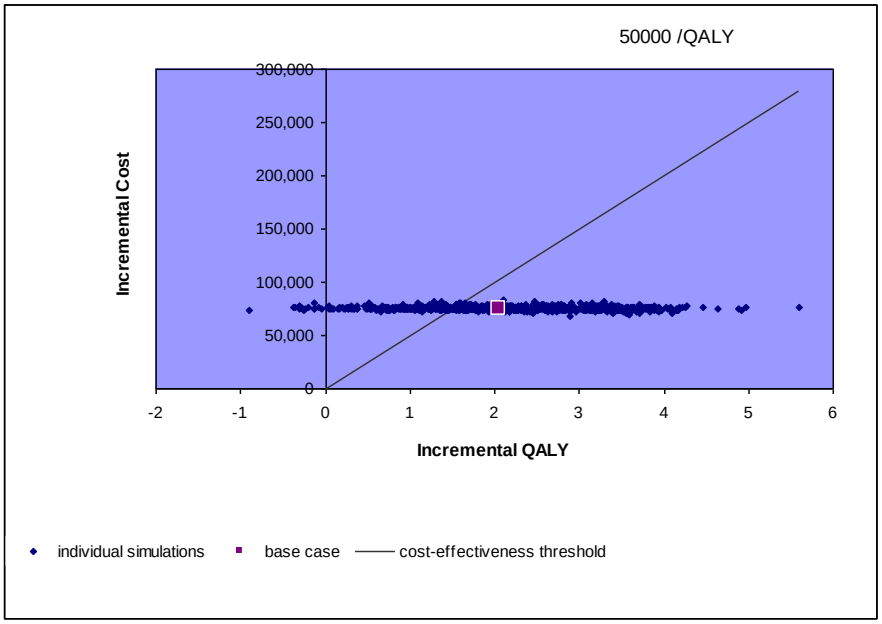
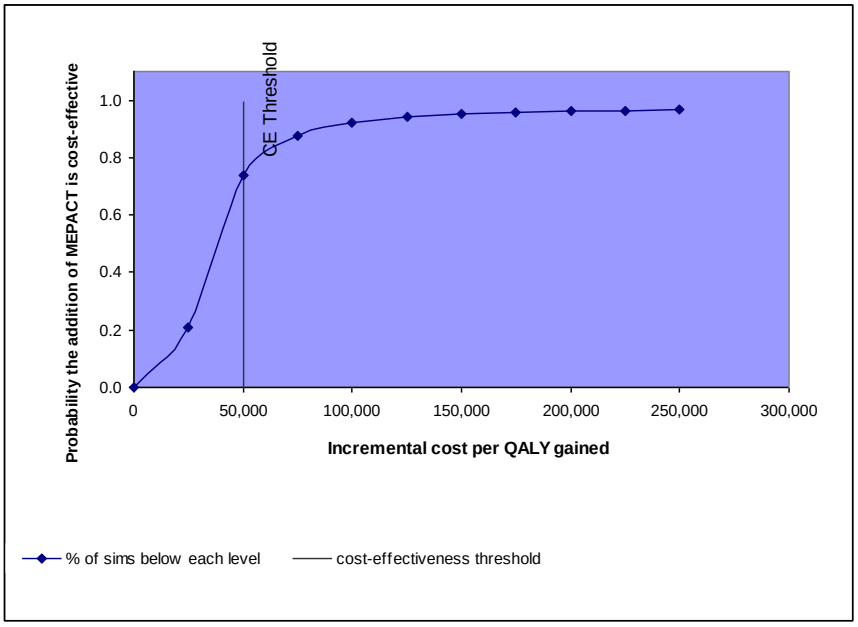


Figure 3.2: Cost-effectiveness Acceptability Curve



The results of the cost effectiveness acceptability curve shows that the probability of mifamurtide being a cost effective use of NHS resources at a willingness to pay of £50,000 is greater than 70%.

4 Scenario Analysis: Variation of the discount rate for outcomes

As per the original Takeda UK submission of evidence on the 9th December 2009, the model is very sensitive to the discount rate for outcomes. The primary reason that the discount rate for outcomes has a significant effect on the ICER is that the majority of the treatment costs are incurred within the first few years of the model but the clinical outcomes are obtained throughout the whole time horizon and thus discounting the outcomes (benefits) reduces the QALY difference between the treatments which adversely affects the cost-effectiveness of mifamurtide. Table 4 below presents the sensitivity of the ICER to varying the discount rate for outcomes whilst holding the discount rate for costs constant at 3.5%. This analyses assumes the introduction of the mifamurtide PAS.

Table 4: Sensitivity of the ICER to varying the discount rate for outcomes whilst keeping the discount rate for costs at 3.5%.

Discount rate for outcomes	ICER
0%	£22,262
1%	£30,070
1.5%	£34,581
2%	£39,502
3%	£50,559
3.5%	£56,683
4%	£63,191
5%	£77,308
6%	£92,806

A discount rate for outcomes of 1.5% could be applied for this appraisal, which would be inline with the previous NICE reference case where costs and outcomes were discounted at differential rates of 6% and 1.5% respectively. In this situation then the cost per incremental QALY gained would be £34,569.

5 Scenario Analysis: Evaluating the Effect of Incorporating other Model Assumptions.

The results detailed in this section assess the impact of including other model assumptions either individually or simultaneously. In particular these include:

- Incorporating Amputation and Limb Salvage costs;
- Incorporating Hearing Loss AE's;
- Allowing the post-recurrence mortality rate to equate to the general population mortality rate for patients who remain disease-free after a given time period;
- Applying Age-related utility rates.

The results of including these assumptions can be found in Table 5.1 below. These results assume the inclusion of the mifamurtide PAS.

Table 5.1: Sensitivity Analysis; Inclusion of other Model Assumptions.

Parameter	Mifamurtide + Neo adjuvant Chemotherapy	Neo Adjuvant Chemotherapy Alone	Difference
Default	£107,657	£31,481	£76,176
	16.72	15.38	1.34
			£56,683
Incorporate Amputation and Limb Salvage costs	£148,393	£68,793	£79,600
	16.72	15.38	1.34
			£59,231
Incorporate Hearing Loss AE's	£107,817	£31,564	£76,253
	16.19	15.11	1.07
			£71,065
Post-recurrence mortality rate equal Gen pop rate after 5 years DF	£107,591	£31,408	£76,183
	17.73	16.49	1.24
			£61,580
Apply Age-related utility rates	£107,657	£31,481	£76,176
	15.60	14.38	1.23
			£62,112

As per the previous analyses, simultaneous addition of these other model assumptions increases the ICER. In this analyses the model was to include all of the other model assumptions as in Table 5.1. These results are presented below in table 5.2.

Table 5.2: Most pessimistic scenario.

Parameter	Mifamurtide + Neo adjuvant Chemotherapy	Neo Adjuvant Chemotherapy Alone	Difference
Default (without mifamurtide PAS)	£107,657	£31,481	£76,176
	16.72	15.38	1.34
			£56,683
• Amputation and Limb Salvage costs, • Hearing Loss AE's, • Post-recurrence mortality rate equal Gen pop rate after 5 years DF, • Apply Age-related utility rates	£151,054	£71,638	£79,416
	15.96	15.09	0.87
			£91,442
Assumption that efficacy demonstrated in the B/ B+ arm are generalisable to the total INT-0133 trial population	£152,097	£72,200	£79,898
	15.88	14.69	1.19
			£66,951
Use discount rate of 1.5% for outcomes and 3.5% for costs (assuming Total INT-0133 trial population)	£151,054	£71,638	£79,416
	23.68	22.28	1.40
			£56,694

Table 5.2 above shows that when all of the other model assumptions as assessed in Table 5.1are applied simultaneously, then the ICER is £91,442. This can be viewed as a worst case scenario. This ICER is dramatically improved to £66,951 when the efficacy demonstrated from the B/B+ arms are understood to be generalisable to the total population. Alternatively, for the total population, when the discount rate is adjusted to 1.5% for outcomes, and the discount rate for costs held constant, the ICER is improved to £56,694. This analyses validates the base case ICER and demonstrates the general robustness of the base case analyses.

6 Conclusion

The Takeda cost effectiveness model shows that the deterministic ICER is between £56,683 and £36,913 per QALY gained (with mifamurtide PAS) for the total and B/B+ populations. When the discount rate for outcomes is amended to 1.5% in assessment of the overall population, the ICER is £34,581 per QALY gained.

The results of the B/B+ arm provide a realistic upside for assessment, whereas the results for variation of the discount rate shows that this is the most sensitive variable in the model.

Even when the model is set to include all of the other model assumptions as assessed in Table 5.2 and then applied together for a worst case scenario the ICER is £91,442, this is dramatically reduced to £66,951 (for the B/B+ analyses) and £56,694 when the discount rate is adjusted to 1.5% for outcomes. This analyses validates the base case ICER and demonstrates the general robustness of the base case analyses.

In this case, the sensitivity of the discount rate and impact that can be made through modifying the discount rate for outcomes to 1.5% ameliorates any uncertainty in the model that may come from non inclusion of other model assumptions such as limb salvage maintenance costs or adverse events associated with hearing loss.

It is the opinion of Takeda UK that mifamurtide offers good value for money with an ICER in the region of £56,683 when a PAS for mifamurtide is introduced. On the upside a realistic upside ICER may be as high as £36,913 per QALY gained when the efficacy demonstrated in the B/B+ arms are assumed generalisable for the total population.