

Additional analysis on the assessment report:

***“The Effectiveness and Cost
Effectiveness of Pimecrolimus
and Tacrolimus for the Atopic
Eczema”.***

Conducted by PenTAG.

Further Analysis of the Eczema Model Outputs

INTRODUCTION

Following submission of the PenTAG report; *The Effectiveness and Cost Effectiveness of Pimecrolimus and Tacrolimus for the Atopic Eczema* a number of issues have arisen about the outputs of the cost-effectiveness model included within this report.

These issues are explored below. Given the relatively large number of separately modelled scenarios in the PenTAG report, this is divided into the pimecrolimus and tacrolimus sections and is formatted in terms of responses given to questions raised about specific outputs from the model in order to focus the discussion.

PIMECROLIMUS

Question:

Why is the ICER for pimecrolimus vs emollient in the PenTAG model lower than the ScHARR estimate from Novartis?

Response:

Although superficially similar in structure the PenTAG model and the Novartis model are quite different since the PenTAG model is based on treatment states rather than health states and incorporates health states through weighted averages. Given this, it is unlikely that the PenTAG will replicate the results of the Novartis model. The results from the two models, however, do show the same trend.

If the PenTAG model is simplified by removing the distinction between mild and moderate levels of eczema severity (thereby increasing its similarity to the Novartis model) it is notable that the output ICERs converge considerably. The following results are obtained, for example, when the PenTAG model is simplified such that all treated patients are regarded as suffering from moderate eczema.

CHILDREN ECZEMA (All patients = moderate)

PIMECROLIMUS vs EMOLLIENT ONLY

| Treatment | Total Costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (Cost/QALY) |
|-----------------|--------------------|----------------|--------------------------|----------------------|---------------------|
| Emollient only) | 512619 | 11034 | | | |
| Pimecrolimus | 1987267 | 11136 | 1474648 | 102 | 14481 |

Reported PenTAG ICER (mixed severity)= £9083

Novartis ICER = £24,489

ADULT ECZEMA (All patients = moderate)

PIMECROLIMUS vs EMOLLIENT ONLY

| Treatment | Total Costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (Cost/QALY) |
|-----------------|--------------------|----------------|--------------------------|----------------------|---------------------|
| Emollient only) | 82449 | 789 | | | |
| Pimecrolimus | 393025 | 803 | 310576 | 13 | 23634 |

Reported PenTAG ICER (mixed severity)= £16,646

Novartis ICER = £27,350

TACROLIMUS MODEL

Data Entry Correction

A correction to a data point in one arm of the tacrolimus models leads to a revised output for the *Adult Body Moderate/Severe Eczema* modelled scenario. This revision does not alter the conclusions drawn from the model but goes someway to correct a perceived anomaly in the output from this particular model. The revision is as follows:

- Adult Body moderate/severe eczema - the first line treatment options for the *steroid only* arm have been set to the same pattern as for the *tacrolimus - second line treatment* arm

With this correction, the revised outputs from the model for tacrolimus comparisons in this arm are given below (the *adult facial* outputs are not changed but are included here for completeness).

ADULT BODY MODERATE/SEVERE

| Treatment | Total Costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (Cost/QALY) |
|------------------------|-----------------|-------------|-----------------------|-------------------|---------------------|
| No tacrolimus (CS) | 302113 | 863 | | | |
| <i>Previous values</i> | <i>265425</i> | <i>868</i> | | | |
| Tacrolimus Second Line | 284521 | 861 | -17592 | -2.25 | 7827.65 |
| <i>Previous values</i> | <i>284521</i> | <i>861</i> | <i>19069</i> | <i>-7</i> | <i>CS Dominates</i> |
| Tacrolimus First Line | 755367 | 875 | 453254 | 12.13 | 37362.48 |
| <i>Previous values</i> | <i>755367</i> | <i>875</i> | <i>489915</i> | <i>7</i> | <i>68428</i> |

Note: the relatively large changes in ICER values due to the data change shown here are explained to large degree by the small level of QALY differences between the modelled treatment arms (which makes ICER values relatively unstable).

ADULT FACIAL MODERATE/SEVERE

| Treatment | Total Costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (Cost/QALY) |
|------------------------|-----------------|-------------|-----------------------|-------------------|------------------|
| No tacrolimus (CS) | 131375 | 875 | | | |
| Tacrolimus Second Line | 202462 | 874 | 71087 | -1.65 | CS Dominates |
| Tacrolimus First Line | 326615 | 892 | 195240 | 16.43 | 11882.27 |

Question 1

Why, in the moderate/severe models is the ICER for body in children lower than that for facial whereas the reverse is true in adults.

Response:

This is explained by the data differences between modelled scenarios for clear-up rates from low potency steroid to disease controlled state (DCS). In the child facial model this probability is set to 0.35 whereas for child body eczema this is set to 0.147. These differences highlight the difficulties in classifying severity of eczema and its treatment leading especially when cross-comparing different areas of the body.

If the low-potency steroid to DCS clear-up rate (i.e. model transition probability) for child facial eczema is set to the same level as for child body eczema then the following outputs are given. These show a reversal of the ICER levels between child body and child facial eczema arms.

**CHILDREN BODY
MODERATE/SEVERE**

| Treatment | Total Costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (Cost/QALY) |
|------------------------|-----------------|-------------|-----------------------|-------------------|------------------|
| No tacrolimus (CS) | 956466.06 | 10850.48 | | | |
| Tacrolimus Second Line | 1209392.83 | 10868.32 | 252926.77 | 17.84 | 14175.22 |
| Tacrolimus First Line | 2446337.22 | 11014.51 | 1489871.16 | 164.03 | 9082.81 |

CHILDREN FACIAL MODERATE/SEVERE

| Treatment | Total Costs (£) | Total QALYs | Incremental costs (£) | Incremental QALYs | ICER (Cost/QALY) |
|------------------------|-----------------|--------------|-----------------------|-------------------|---------------------|
| No tacrolimus (CS) | 725870 | 10802 | | | |
| <i>Recorded values</i> | <i>624102</i> | <i>10997</i> | | | |
| Tacrolimus Second Line | 1383279 | 10803 | 657409.44 | 0.68 | 963498 |
| <i>Recorded values</i> | <i>1129347</i> | <i>10996</i> | <i>505244</i> | <i>-1</i> | <i>CS Dominates</i> |
| Tacrolimus First Line | 1784266 | 10980 | 1058396.28 | 177.62 | 5959 |
| <i>Recorded values</i> | <i>1737132</i> | <i>11028</i> | <i>1113030</i> | <i>31</i> | <i>35669</i> |

Note: in these models the costs for facial second line tacrolimus exceed body second line tacrolimus because far more patients are referred to tacrolimus use after failure with low potency steroids with facial excema).

Question 2:

Why is the ICER for second line lower than that for first line in all tacrolimus models?

Response:

This is due to the fact that utility gains from the use of tacrolimus in our model are greatest when it is used in first line treatment where patients have a more direct route back to Disease Controlled State. Tacrolimus as second line largely reduces the adoption of High Potency Steroids and Secondary treatments only after patients have spend time in the other steroid treatment states (with lower utilities), hence the effects for tacrolimus as second-line are likely to be lower.

These effects, however, are sensitive to the outcome parameters for tacrolimus. It might be argued, for instance, that the outcomes for tacrolimus as second line treatment will vary considerably to the outcomes when used as first line. Any alterations to these parameters would alter the outputs. Once again the outputs in general should be seen in the context of the very close QALY outputs from the different arms of the model and the high level of uncertainty in the data.

Question 3:

Why are there fewer QALYs on Tacrolimus in second line than in first line in all models?

Response

The first key point to make is that the QALY outputs are extremely close across these outputs. Any slight differences in QALY outputs should be seen in the context of the general levels of uncertainty which we know are inherent in the models.

That said, the explanation for the slight differences in QALY outputs is due primarily to 'severity mix' which controls the utility levels set for the treatment states in the different arms of the model. These have been adjusted to account for the fact that patients who receive

tacrolimus as first line treatment will contain a greater proportion of moderate patients (whereas when it is used as second line there are likely to be more severe). The precise ratios used in the model have been estimated from expert opinion etc and are hard to know exactly. However a sensitivity analysis of these ratios reveals their affect in terms of the QALY outputs in the different arms of the models. This is shown below for a range of severity mixes (note that the severity mix also affects the costs within the model – due to different levels of consultation used).

ADULT BODY ECZEMA

| | MOD % | SEV % | Cost dif | QALY dif | ICER | <i>Corrected</i> |
|---------|--------------|--------------|-----------------|-----------------|---------------|------------------|
| TAC 2ND | 15 | 85 | -17592 | -2.25 | 7827.65 | |
| TAC 2ND | 25 | 75 | -17460 | -1.28 | 13672.71 | DEFAULT |
| TAC 2ND | 50 | 50 | -17131 | 1.15 | Tac Dominates | |
| TAC 2ND | 75 | 25 | -16802 | 3.57 | Tac Dominates | |
| TAC 2ND | 85 | 15 | -16671 | 4.55 | Tac Dominates | |
| TAC 1ST | 15 | 85 | 480203 | -11.08 | CS Dominates | |
| TAC 1ST | 25 | 75 | 472761 | -4.45 | CS Dominates | |
| TAC 1ST | 50 | 50 | 454154 | 12.13 | 37436.64 | DEFAULT |
| TAC 1ST | 75 | 25 | 435548 | 28.71 | 15170.76 | |
| TAC 1ST | 85 | 15 | 428105 | 35.34 | 12113.54 | |

ADULT FACIAL ECZEMA

| | MOD % | SEV % | Cost dif | QALY dif | ICER | |
|---------|--------------|--------------|-----------------|-----------------|--------------|---------|
| TAC 2ND | 15 | 85 | 71087 | -1.65 | CS Dominates | DEFAULT |
| TAC 2ND | 25 | 75 | 71438 | 0.94 | 75729.73 | |
| TAC 2ND | 50 | 50 | 72317 | 7.42 | 9742.26 | |
| TAC 2ND | 75 | 25 | 73196 | 13.90 | 5264.88 | |
| TAC 2ND | 85 | 15 | 73548 | 16.49 | 4458.90 | |
| TAC 1ST | 15 | 85 | 222531 | -7.89 | CS Dominates | |
| TAC 1ST | 25 | 75 | 214733 | -0.94 | CS Dominates | |
| TAC 1ST | 50 | 50 | 195240 | 16.43 | 11882.27 | DEFAULT |
| TAC 1ST | 75 | 25 | 175746 | 33.80 | 5199.58 | |
| TAC 1ST | 85 | 15 | 167949 | 40.75 | 4121.69 | |

CHILD BODY ECZEMA

| | MOD % | SEV % | Cost dif | QALY dif | ICER | |
|---------|--------------|--------------|-----------------|-----------------|-------------|---------|
| TAC 2ND | 15 | 85 | 252927 | 17.84 | 14175.22 | DEFAULT |
| TAC 2ND | 25 | 75 | 253880 | 22.18 | 11448.41 | |
| TAC 2ND | 50 | 50 | 256264 | 33.01 | 7763.48 | |
| TAC 2ND | 75 | 25 | 258648 | 43.84 | 5899.58 | |
| TAC 2ND | 85 | 15 | 259602 | 48.17 | 5388.73 | |
| TAC 1ST | 15 | 85 | 1643784 | 79.89 | 20575.78 | |
| TAC 1ST | 25 | 75 | 1599809 | 103.93 | 15393.13 | |
| TAC 1ST | 50 | 50 | 1489871 | 164.03 | 9082.81 | DEFAULT |
| TAC 1ST | 75 | 25 | 1379933 | 224.13 | 6156.73 | |
| TAC 1ST | 85 | 15 | 1335958 | 248.17 | 5383.13 | |

CHILD FACIAL ECZEMA

| | MOD % | SEV % | Cost dif | QALY dif | ICER |
|---------|--------------|--------------|-----------------|-----------------|----------------------|
| TAC 2ND | 10 | 90 | 500916 | -0.86 | CS Dominates DEFAULT |
| TAC 2ND | 15 | 85 | 503280 | 6.30 | 79928.11 |
| TAC 2ND | 25 | 75 | 605774 | 20.60 | 29402.76 |
| TAC 2ND | 50 | 50 | 519825 | 56.37 | 9222.07 |
| TAC 2ND | 75 | 25 | 433876 | 92.13 | 4709.27 |
| TAC 2ND | 85 | 15 | 399496 | 106.44 | 3753.31 |
| TAC 2ND | 90 | 10 | 382307 | 113.59 | 3365.63 |
| TAC 1ST | 10 | 90 | 1426472 | -82.19 | CS Dominates |
| TAC 1ST | 15 | 85 | 1387869 | -68.11 | CS Dominates |
| TAC 1ST | 25 | 75 | 1319995 | -39.94 | CS Dominates |
| TAC 1ST | 50 | 50 | 1150309 | 30.47 | 37752.39 DEFAULT |
| TAC 1ST | 75 | 25 | 980623 | 100.88 | 9720.54 |
| TAC 1ST | 85 | 15 | 912749 | 129.05 | 7073.04 |
| TAC 1ST | 90 | 10 | 878812 | 143.13 | 6140.02 |

Question 4

Why is the ICER for as first line tacrolimus on body in children so much lower than that for adults?

Response:

Mainly because the usage of ointment is much smaller in children whilst the utility gains are comparable between adults and children. This means that in children less costs are incurred for equivalent QALY gains (hence lower ICER).

Question 5

Why is the ICER for first line tacrolimus. in child facial eczema so much higher than that for adults?

Response

This is explained by the data differences for clear-up from first-line tacrolimus to disease controlled state between adults and children (adults = 0.632 ,children = 0.39). If the tacrolimus clear-up for children is set to the adult clear-up level then the ICER for children falls to below the adult level.

Question 6

Why does tacrolimus as second-line cost less than the steroid only arm for Adults.

Response:

In general tacrolimus as second line treatment substitutes for secondary/systemic care in severe eczema. Secondary care is relatively expensive so that it therefore becomes possible for tacrolimus as second line arm to be cheaper for this reason. Output depends critically however on the cost levels for these types of treatment and the relatively clear up rates of each (ie transition probabilities to Disease Controlled State from each of these treatments).