Xolair for the treatment of chronic spontaneous urticaria (CSU)

Evaluation of the Health Economic Model – Dutch version

Confidential report – version 2.0

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Introduction

This report was commissioned by the Dutch Association for Dermatology and Venereology (NVDV) in order to evaluate the health economic model for omalizumab (Xolair®), a novel drug against chronic idiopathic/spontaneous urticaria. Xolair has been registered since February 2014 for the indication of urticaria. Since European and American guidelines have provided guidance on its use in the treatment of urticaria. In general, use of omalizumab is advised, along with Cyclosporin A and leukotriene receptor antagonists (LTRAs), as the third step in a stepped-care model. First and second steps included the use of H_1-antihistamines in standard dose (step 1) or up to four times standard dose (step 2). Several countries have published own guidance on the use of omalizumab. The UK National Institute for Health and Clinical Excellence published guidance in July 2015, advising the use of omalizumab only in more severely affected patients who have not responded to H_1-antihistamines and leukotriene receptor antagonists.[1] Several other conditions apply in order to get reimbursement through the NHS. In the Netherlands, NVDV has prepared new guidelines for the treatment of chronic urticaria, including recommendations for the use of omalizumab. In the guidelines, omalizumab is proposed as a third step in the stepped-care approach, only when treatment in previous steps has failed. Previous steps in this stepped-care model include a regular dose of H_1-antihistamines (step 1) or up to a 4-fold increase of regular dose, possibly in combination with leukotriene receptor antagonists or short-term use of oral corticosteroids (step 2). Cyclosporin A is advised as a fourth step, after omalizumab as a third step, while a number of other medications, such as azathioprine and methotrexate, should only be considered if all other treatment steps have failed.

As the cost-effectiveness of Xolair has not yet been published in peer-reviewed papers, NVDV wants an independent review of the evidence on the cost-effectiveness of Xolair for this indication, before releasing these new guidelines. This report describes the process and outcomes of this independent review of the health economic model of omalizumab for urticaria.

A health-economic model to estimate the cost-effectiveness of Xolair has been developed by the manufacturer, Novartis. RTI Health Solutions has prepared this health economic model for the manufacturer, along with a report describing the health economic performance of omalizumab in the treatment of chronic spontaneous urticaria.[2] As many countries, including the Netherlands, have own country-specific health economic guidelines, country-specific adaptations of this international health-economic model are necessary for the submission of reimbursement dossiers. The Dutch adaptation of this international model has been prepared by the Institute of Medical Technology Assessment (iMTA) in Rotterdam, the Netherlands. The Dutch adaptations are described in a short report, as an add-on to the international report describing the health economic model for Xolair®.[3] Before including economic information, e.g. cost-effectiveness of omalizumab, in the final version of the urticaria treatment guidelines, NVDV issues an independent review of the international model and, in

[1] Omalizumab for previously treated chronic spontaneous urticaria. NICE National Institute for Health and Care Excellence, Technology Appraisal guidance, 3 September 2015. www. Nice.org.uk/guidance/ta339
[2] Cost-effectiveness model for Xolair in chronic idiopathic/spontaneous urticaria. Report prepared for Novartis by RTI Health Solutions, January 2014.
[3] Addendum Country adaptations for the Dutch system. Report prepared by iMTA for Novartis, 2014.

particular, of the Dutch adaptations of this international model. This report describes this independent review of the health economic model of omalizumab in the treatment of urticaria.

Information shared by Novartis and iMTA

For the purpose of this independent review, the following information was shared by Novartis and iMTA:

- Health economic model, implemented in MS Excel using VBA. This is the international model developed by RTI Health Solutions with Dutch adaptations as integrated into the international model. The model version was 2.1., dated April 10th, 2015;
- "Addendum CEA model NL", a 3-page document describing changes made to the international model to accommodate Dutch health economic analyses;
- " Technical Appendix CEA model", an 86-pages document (dated January 31st, 2014), providing a technical description of the international (original) model;
- ASSURE study forms and CRF. These are the original forms used for patient surveys (a.o. patient costs and productivity losses associated with urticaria) and clinical data collection in the international ASSURE study. These data have not yet been published;
- SAS data files used for the analysis of Dutch data from the ASSURE study. The international ASSURE data have been analyzed by iMTA to generate Dutch input, e.g. for productivity losses and quality of life of patients in different severity stages of urticaria;
- 23 different Tables (Word format) showing results of the analysis of Dutch data from the ASSURE study, as analyzed by iMTA.
- PDF document "Resultaten samenvatting KEA model adaptatie Xolair in CSU 15042015", a 6-page document provided by Novartis showing the main outcomes on the cost-effectiveness of Xolair, as estimated by the adapted Dutch version of the international CEA model.

Process of independent review

The following steps were taken for this independent review:

1. Read background information on omalizumab and urticaria, along with the study of several guidelines, including NICE guidance and the draft guidelines for treatment of urticarial of NVDV. [4]
2. Study of the model structure:
    a. how is the model organized?
    b. which information is captured where?
    c. how are calculations performed?
    d. which parts of the model can be changed by users and what type of information is locked?
    e. are adaptations made for the Netherlands easily identifiable?
3. Check whether the input data used for the model calculations are similar to the input data as quoted in the international report and the Dutch adaptations of these input data.
4. Reproduction of results as described in the document "Resultaten samenvatting KEA model adaptatie Xolair in CSU 15042015".

[4] Richtlijn chronische spontane urticaria. Multidisciplinaire evidence-based richtlijn. Concept februari 2015

5. Check model outcomes by running different model calculations. Here, we checked whether model outcomes behave as expected by varying different input parameters, e.g. inclusion of direct health care costs only versus inclusion of all cost categories relevant for the Netherlands, e.g. direct health care costs, patient costs and productivity costs. Cost-effectiveness calculations were made and probabilistic sensitivity analyses were run to check the outcomes.

Update May 2017:

After we were informed that the data for Cyclosporin A that were included in the health economic model has no empirical basis, we decided that all comparisons involving Cyclosporin A were redundant. Hence, in this report, only the comparison between Xolair and Standard of Care is made.

General findings

The model reflects current Dutch standards for pharmacoeconomic evaluations.[5] This means that analysis was performed from a societal perspective, including direct health care costs, patient costs, and productivity losses. Discounting was applied using different discounting for costs (4%) and effects (1.5%). The model uses Dutch input data for:

- Drug costs; the price of omalizumab was communicated by Novartis and other drug costs were derived from www.medicijnkosten.nl
- Health care use of patients, based on the ASSURE study and valued according to standard cost prices for Dutch health economic studies;[6]
- Quality of life, based on the ASSURE study and valued according to the Dutch EQ-5D tariff;[7]
- Productivity losses, based on the ASSURE study and valued according to standard cost prices for Dutch health economic studies;
- Mortality, based on Statistics Netherlands data;
- Patient costs, based on the ASSURE study and valued according to standard cost prices for Dutch health economic studies.

One remark to be made is that the Dutch model results lean heavily on data from the ASSURE study, although only 99 patients (including 6 with missing data) were included in the Dutch part of ASSURE. It is unclear whether these 93 patients are representative of the larger urticaria patient group in the Netherlands. Here, it is important to consider whether Dutch hospitals participating in ASSURE are general hospitals or hospitals serving as a tertiary reference center. This information was not available to the reviewer.

The model assumes treatment only for more severe urticaria patients (UAS7≥16) and assumes a distribution of 30% of patients in the most severe UAS7 category (UAS7≥28) and 70% in the moderate disease severity category (UAS7≥16). Dutch model adaptations have not adapted these

[5] Zorginstituut Nederland. Richtlijnen voor farmaco-economisch onderzoek. Diemen, 2006.
[6] Hakkaart-van Roijen et al. Handleiding kostenonderzoek. Diemen, College voor Zorgverzekeringen, 2009.
[7] Lamers LM, McDonnell J, Stalmeier PFM, Krabbe PFM, Busschbach JJV. The Dutch tariff: results and arguments for an effective design for national EQ-5D valuation studies. Health Econ 2006;15(10):1121-1132.

figures, although the Dutch ASSURE study data revealed a somewhat different pattern of disease severity, i.e. 39% (15/38) in the most severe category and 61% (23/38) in the moderate disease category. Again, it is unknown whether this reflects true distribution of Dutch patients over the different urticaria severity classes.

In any health economic evaluation, it is important to consider whether the new intervention (here: Omalizumab) is compared to the correct comparator treatment. The international model accommodates two choices for the comparator treatment, namely Standard of Care (usual care, e.g. step 1 and 2 of the stepped-care model) and Cyclosporin A, but as mentioned before this report only uses the comparator treatment Standard of Care due to lack of clinical data on the effectiveness of Cyclosporin A. We recommend to change the default comparator in the model to Standard of Care instead of Cyclosporin A for the time being.

Estimating cost-effectiveness in different scenarios

To test the model and its outcomes, several scenarios were run through the implementation of the model in Excel. These scenarios were created by either changing the baseline settings in the sheet "Settings" or changing the input data in the sheet "Input Data". Note, that the comparison between omalizumab and Cyclosporin A is removed from the report and all comparisons are made using Standard of Care as the comparator. Comparing the model results with each other, all scenarios behaved as expected. The following scenarios were run:

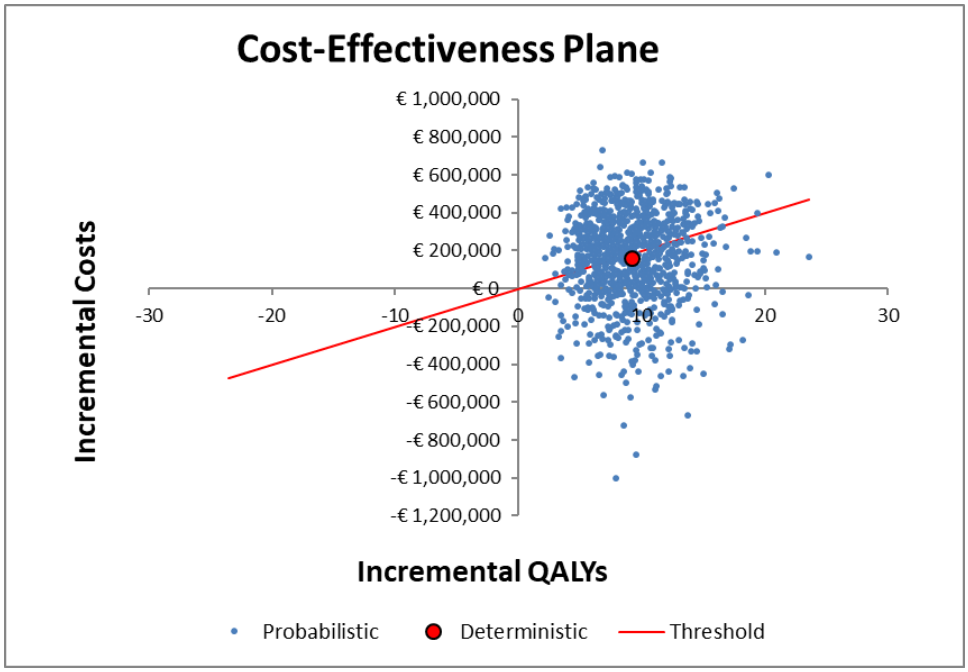
1. Base case scenario: all settings as default for the Dutch situation, (i.e. reproduction of Standard of Care scenario as documented in the Novartis report "Resultaten samenvatting KEA model adaptatie Xolair in CSU 15042015")
2. Scenario drug costs only: only costs of drugs are included in the analysis.
3. Scenario drug costs + direct health care costs: only costs of drugs and direct health care costs are included in the analysis
4. Scenario retired patients only (excluding productivity losses)
5. Scenario no treatment of severe patients, only moderate patients are included in the analysis

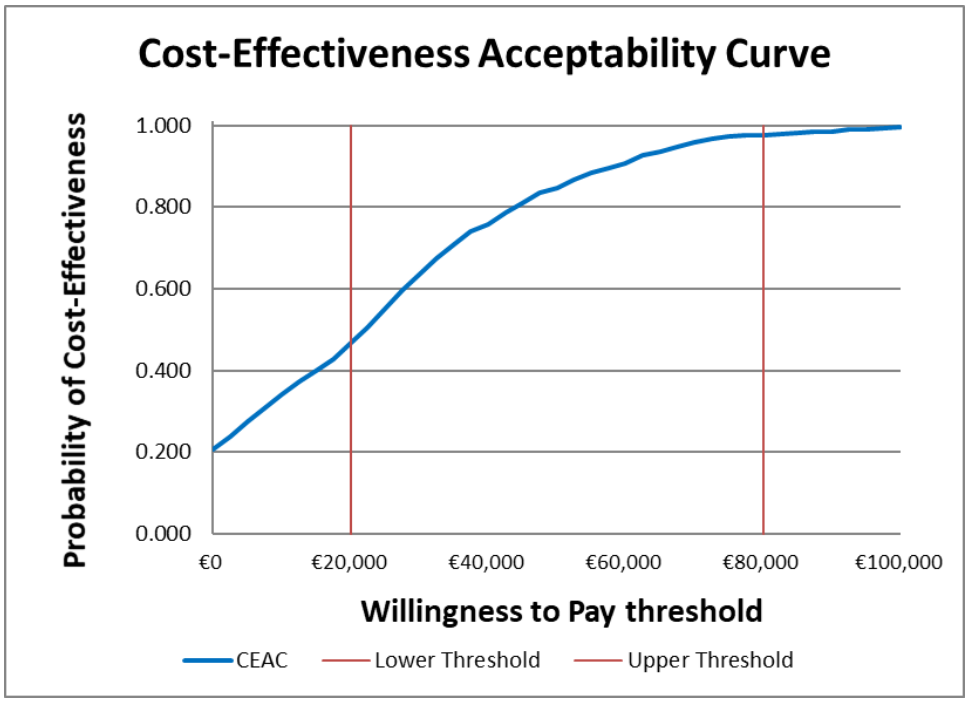
It is important to note that the remarks that are made below about omalizumab either or not being cost effective do not reflect the Dutch situation, but only model outcomes in certain hypothetical scenario's. The five scenarios above are only modeled to compare scenarios and to check whether outcomes adhere to expectations (validity), not to explore the actual cost-effectiveness of Xolair®.

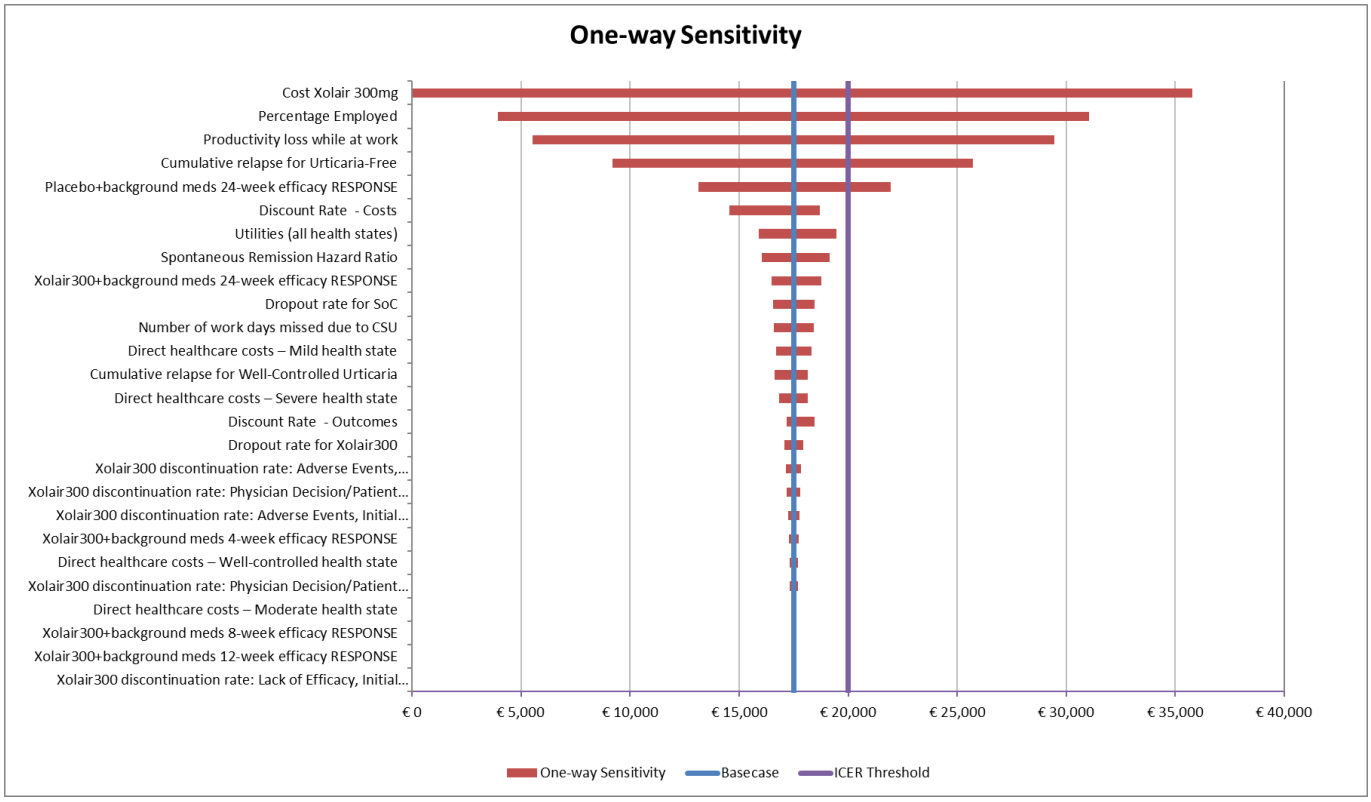
1. Base case scenario

In this scenario, the model was run using all default settings of the input data. From a societal perspective, the comparison of omalizumab to Standard of Care shows a low to high cost-effectiveness, depending on the threshold value used for the cost per QALY. At a lower threshold value, i.e. 20.000€/QALY, the probability of omalizumab to be cost-effective is about 47%, while it is about 98% at an 80.000€/QALY threshold value. These results are most sensitive to the cost of Xolair, to the percentage of patients employed and to assumptions on the productivity losses of these employed patients as a consequence of their health problems.

Settings for the Standard of Care Scenario	Value
Patient Number	100
Time Horizon	10 Years
Discounting – Costs	4.0 %
Discounting – Benefits	1.5 %
Age	36
Proportion of starting cohort with Severe urticaria symptoms	29 %
Include drug costs	Yes
Include direct healthcare costs (non-drug related)	Yes
Include indirect costs (lost productivity and absence)	Yes
Patient Sub-grouping	All Patients
Xolair Scenario	Base case 300mg (24-wk)
Comparator Definition	Standard of Care (as per trial protocol)





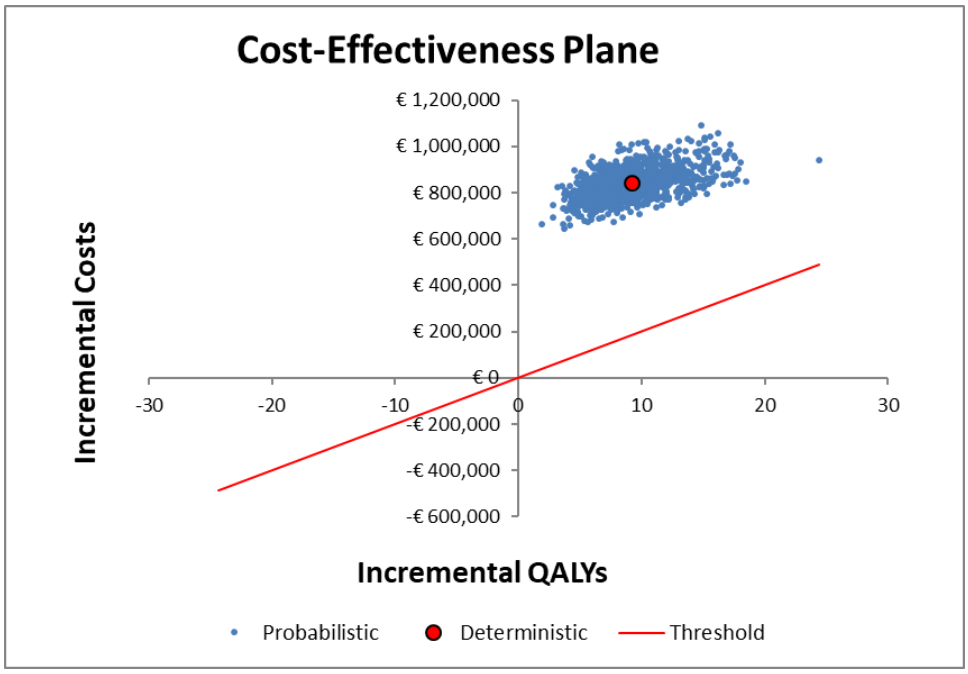


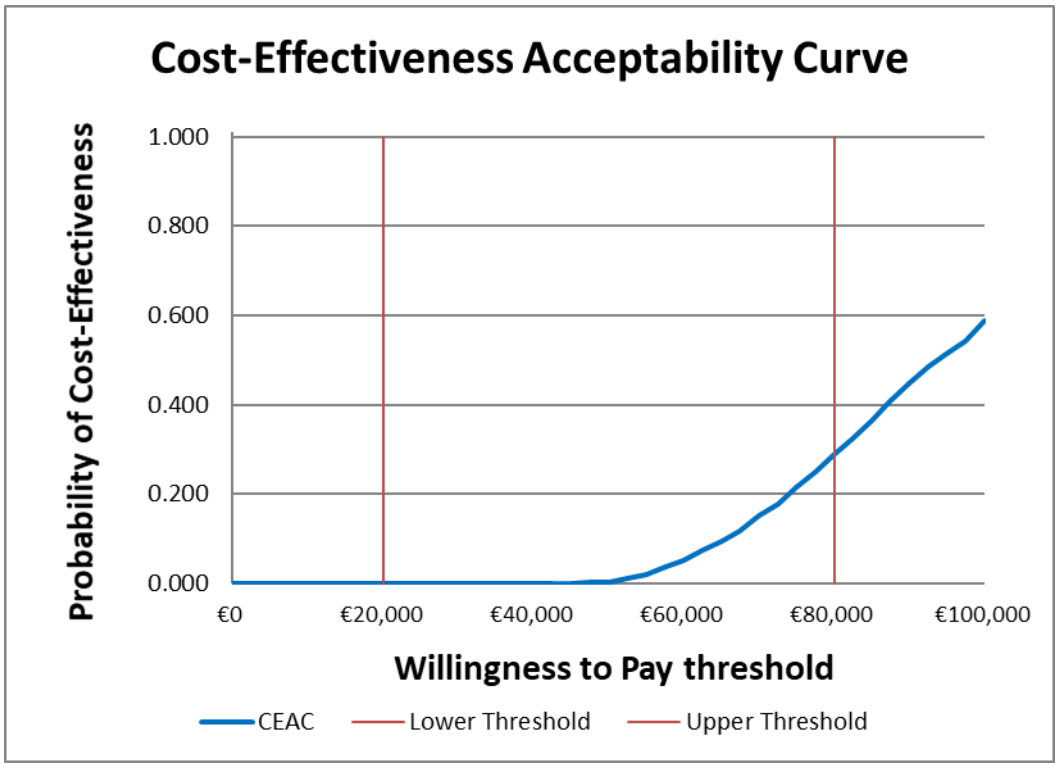
2. Scenario Only Drug Costs

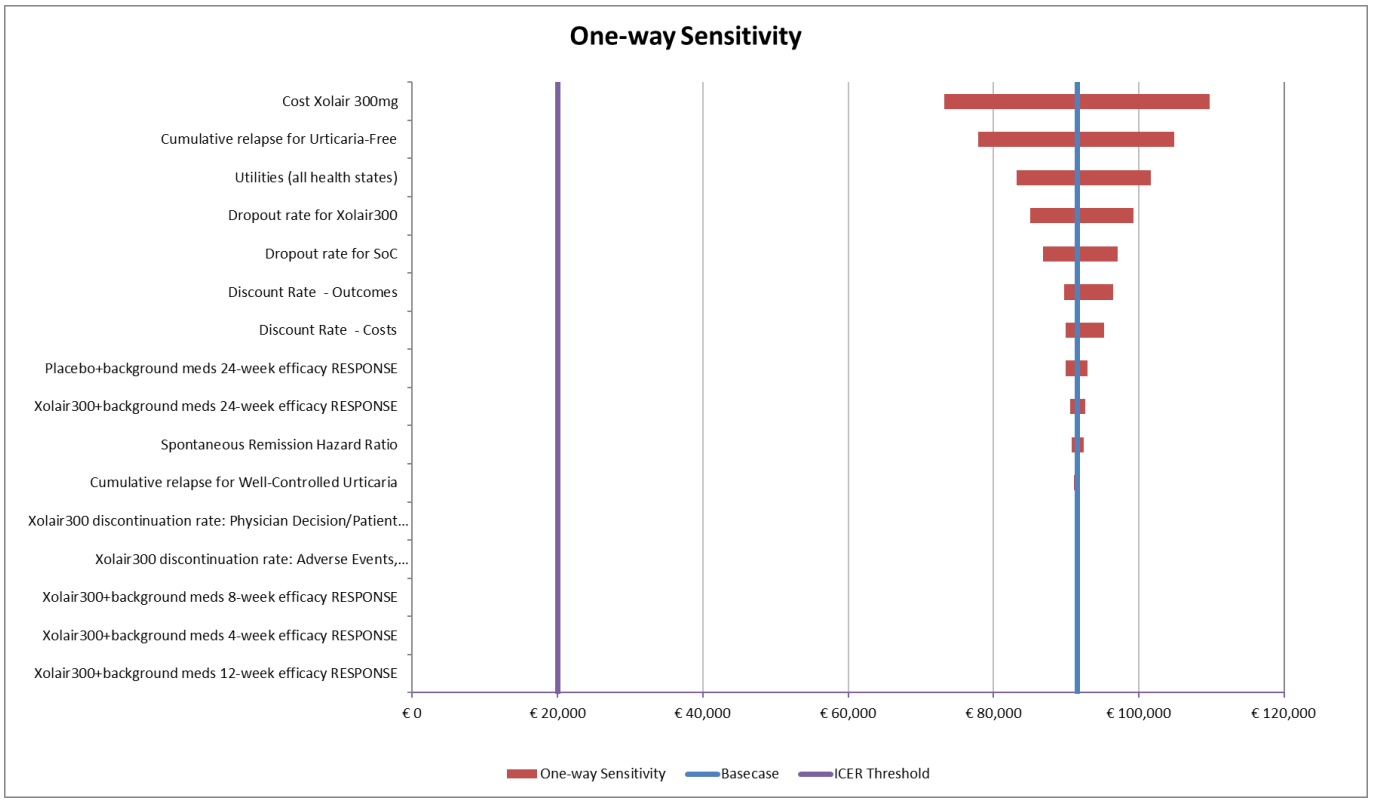
In this scenario, we check what the impact is of only using the drug costs as the costs of Xolair. In this scenario, the investment in omalizumab does not pay out by reductions in health care costs, patient costs or productivity costs, as these cost categories are not included in the analysis. Hence, we a priori expect omalizumab not to be cost-effective. Although this scenario obviously is not adhering to

guidelines for health economic analyses, we have run this scenario in order to compare outcomes to subsequent scenarios, in which we add other types of costs. This enables to compare scenarios among each other and to control whether cost-effectiveness is changing according to expectations. In this "drug costs only scenario" (see highlighted settings), we keep all other settings the same as the default settings. Here, we obviously changed the reference treatment from Cyclosporin A (previously) to Standard of Care (current analysis). When only looking at the drug costs we see that Xolair has a zero probability to be cost-effective at an ICER of 20.000 euro per QALY and that the probability rises to about 29% at a threshold level of 80.000€/QALY. This means that the model behaves as expected given this scenario.

Settings for the Drug Cost only scenario	*Value*
Patient Number	100
Time Horizon	10 Years
Discounting – Costs	4.0 %
Discounting – Benefits	1.5 %
Age	36
Proportion of starting cohort with Severe urticaria symptoms	29 %
Include drug costs	Yes
Include direct healthcare costs (non-drug related)	**No**
Include indirect costs (lost productivity and absence)	**No**
Patient Sub-grouping	All Patients
Xolair Scenario	Base case 300mg (24-wk)
Comparator Definition	Standard of Care (as per trial protocol)


Cost-Effectiveness Plane
€ 1,200,000
€ 1,000,000
€ 800,000
€ 600,000
€ 400,000
€ 200,000
€ 0
-€ 200,000
-€ 400,000
-€ 600,000
-30
-20
-10
0
10
20
30
Incremental Costs
Incremental QALYs
Probabilistic
Deterministic
Threshold


Cost-Effectiveness Acceptability Curve
1.000
0.800
0.600
0.400
0.200
0.000
€0
€20,000
€40,000
€60,000
€80,000
€100,000
Probability of Cost-Effectiveness
Willingness to Pay threshold
CEAC
Lower Threshold
Upper Threshold

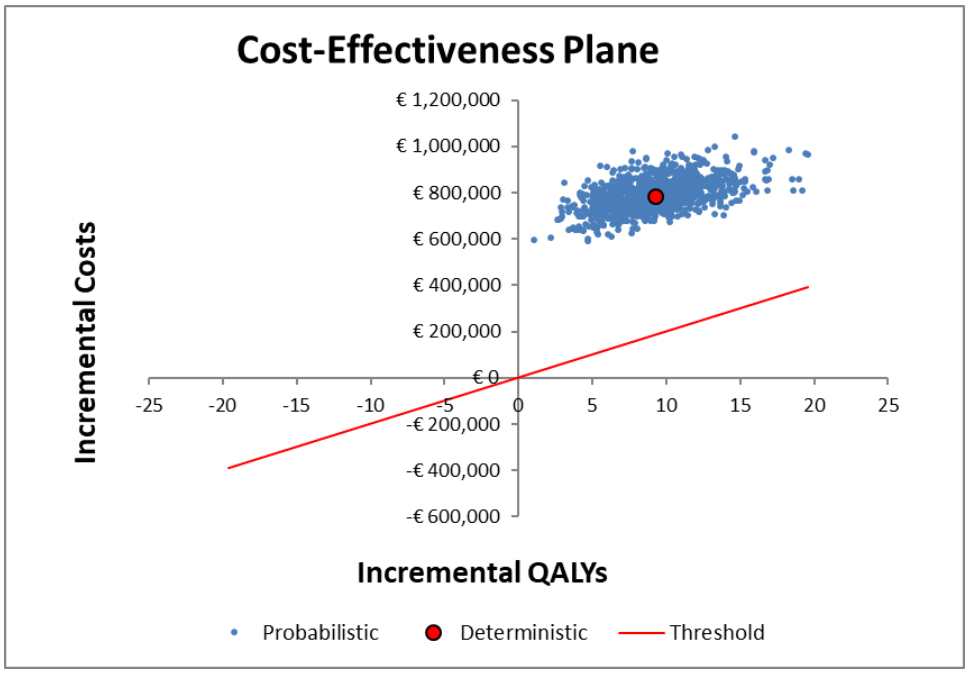


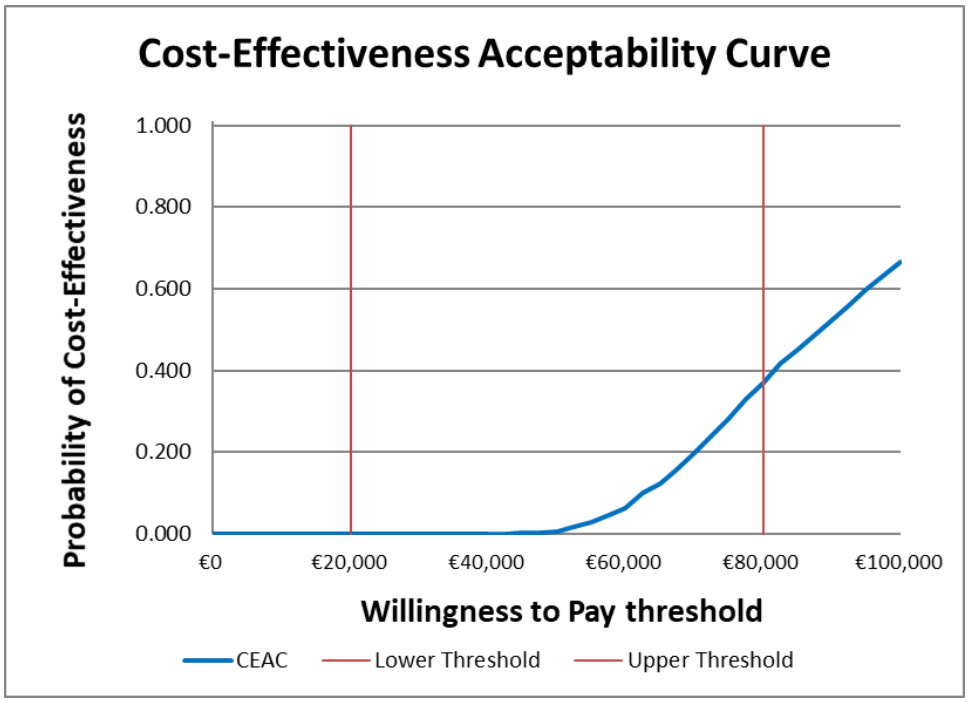
3. Scenario Drug costs and Direct Healthcare Costs

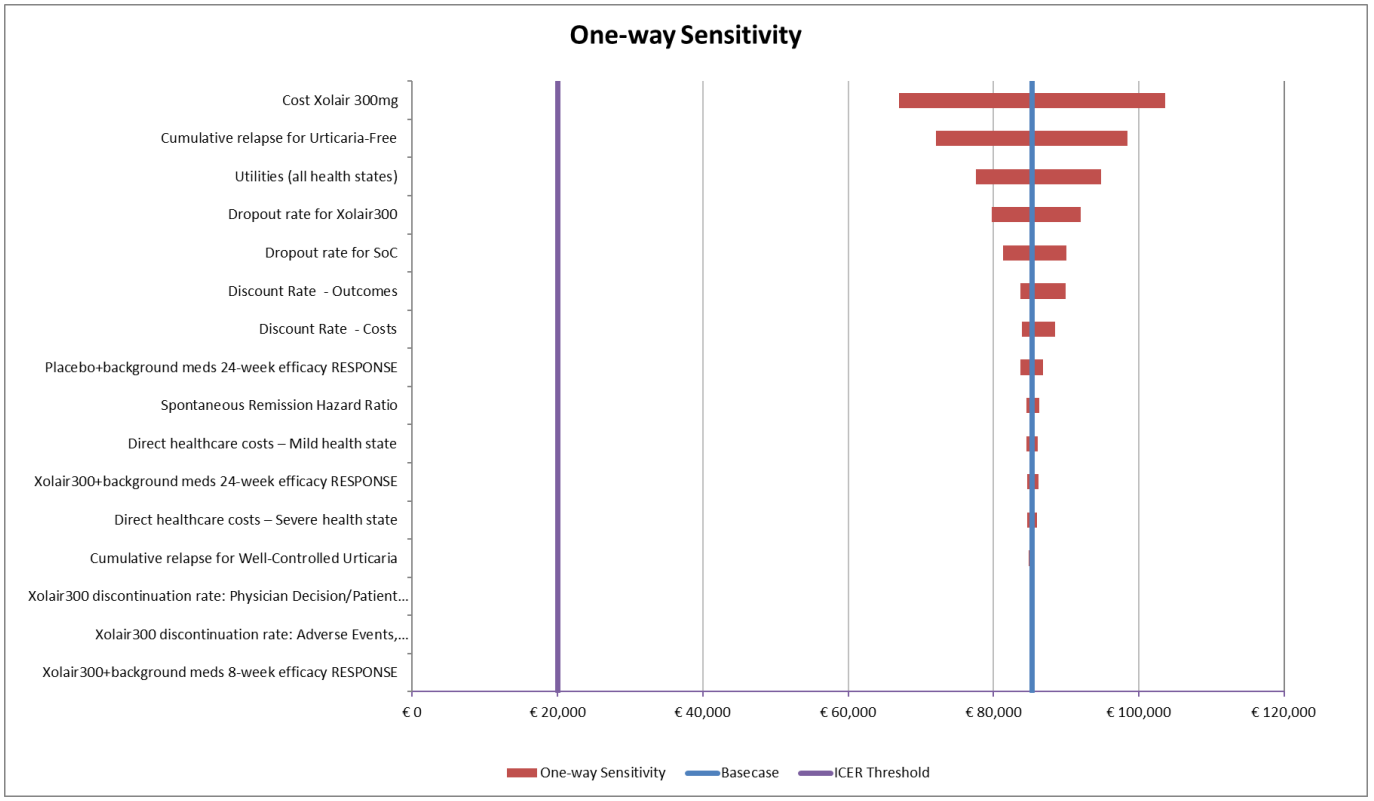
In this scenario, we check what the impact is of only using the drug costs and direct healthcare costs. This scenario is identical to an analysis taking a health care perspective, with wider societal costs such as patient cost and productivity costs not included in the calculations. The same conclusion can be drawn as in the previous scenario with only the drug costs included, i.e. that omalizumab is not cost effective. This is as expected given the change in input parameters in comparison to scenario 1, as above, and the importance of inclusion of productivity costs, as demonstrated by the tornado diagram under scenario 1.

Settings for the drug and direct health care cost scenario	*Value*
Patient Number	100
Time Horizon	10 Years
Discounting – Costs	4.0 %
Discounting – Benefits	1.5 %
Age	36
Proportion of starting cohort with Severe urticaria symptoms	29 %
Include drug costs	Yes

Settings for the drug and direct health care cost scenario	*Value*
Include direct healthcare costs (non-drug related)	Yes
Include indirect costs (lost productivity and absence)	**No**
Patient Sub-grouping	All Patients
Xolair Scenario	Base case 300mg (24-wk)
Comparator Definition	Standard of Care (as per trial protocol)



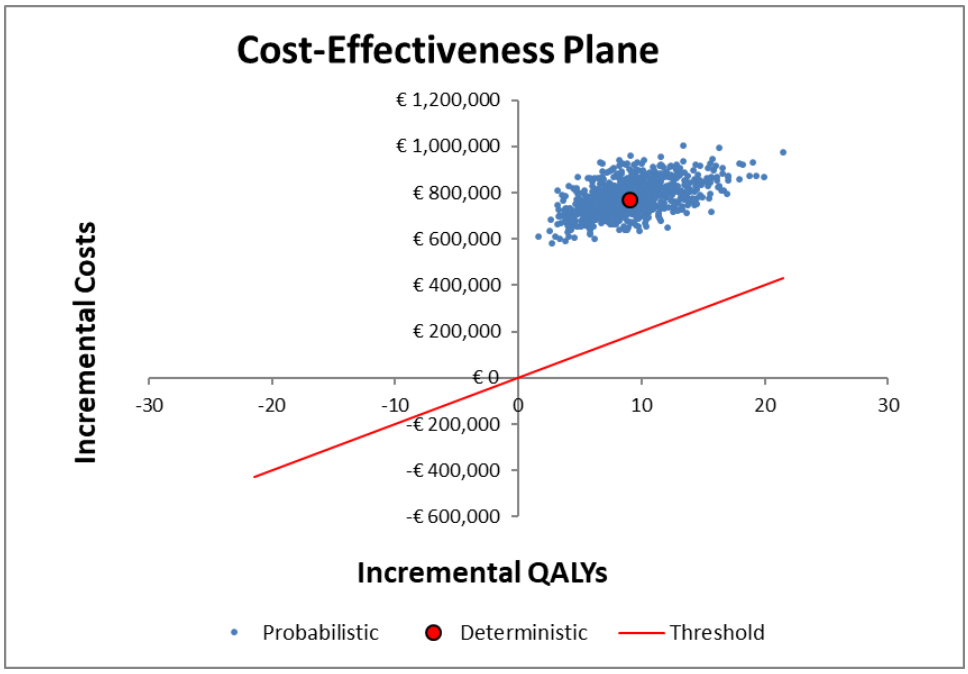


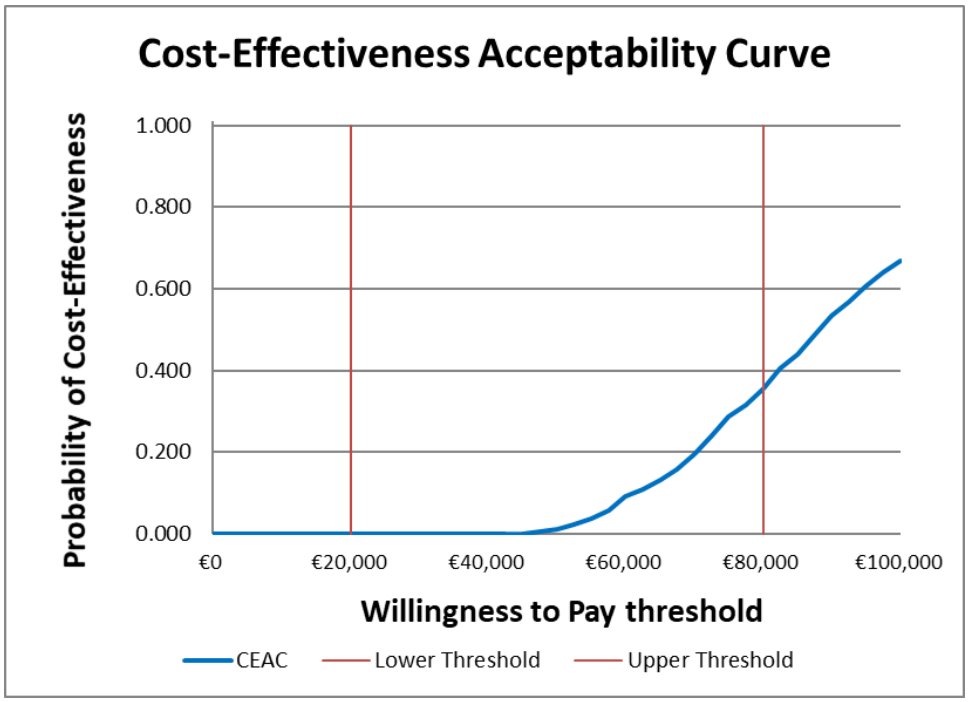


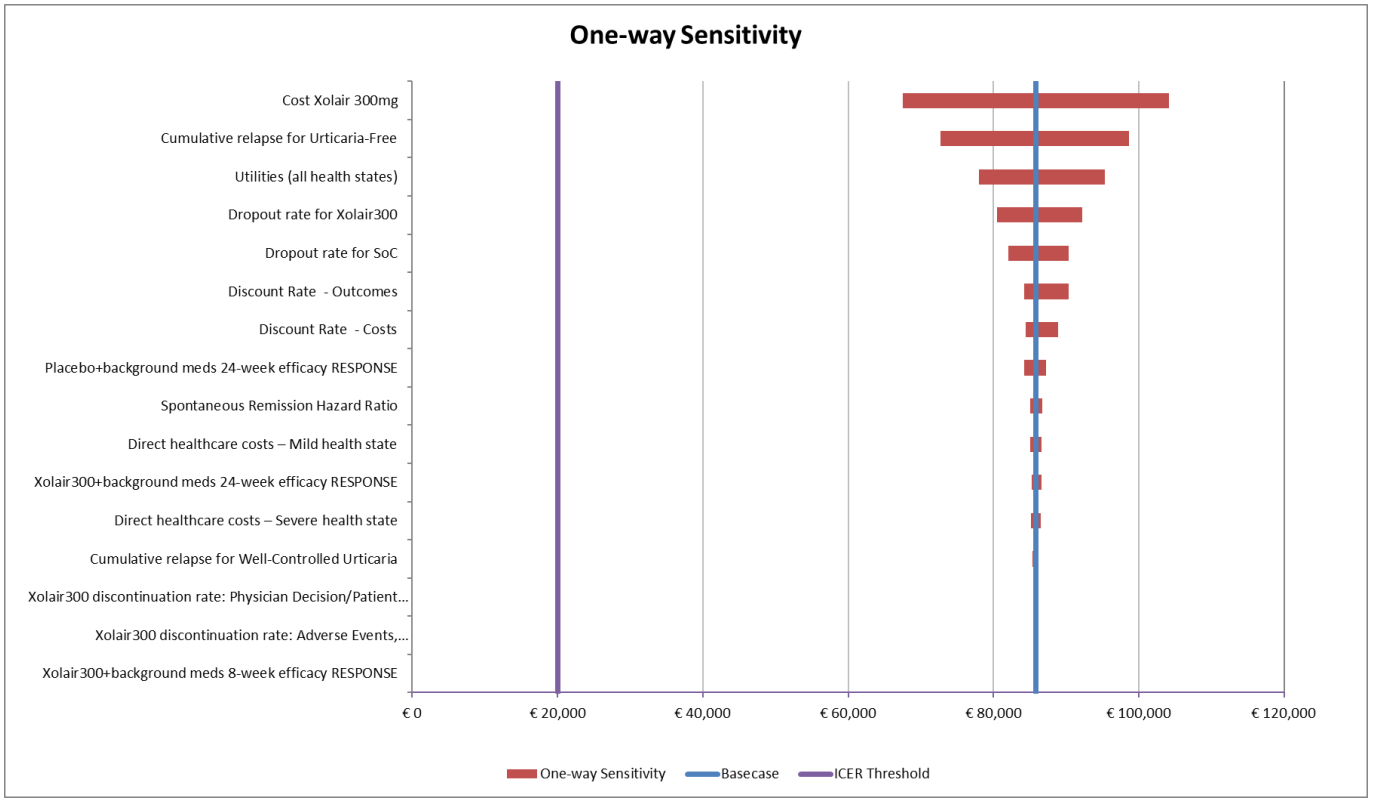
4. Scenario Only retired patients (exclusion of productivity losses)

Here, we changed the age to the retirement age to see if it affects the indirect non-healthcare costs, the costs of absenteeism. This scenario also leads to the conclusion that Xolair is not cost-effective, which is as expected, as changing the baseline inclusion age to 67 does lead to an exclusion of the costs (and possible savings) related to productivity losses. Again, the model behaves as expected given this scenario.

Settings	Value
Patient Number	100
Time Horizon	10 Years
Discounting – Costs	4.0 %
Discounting – Benefits	1.5 %
Age	**67**
Proportion of starting cohort with Severe urticaria symptoms	29 %
Include drug costs	Yes
Include direct healthcare costs (non-drug related)	Yes
Include indirect costs (lost productivity and absence)	Yes
Patient Sub-grouping	All Patients
Xolair Scenario	Base case 300mg (24-wk)
Comparator Definition	Standard of Care (as per trial protocol)



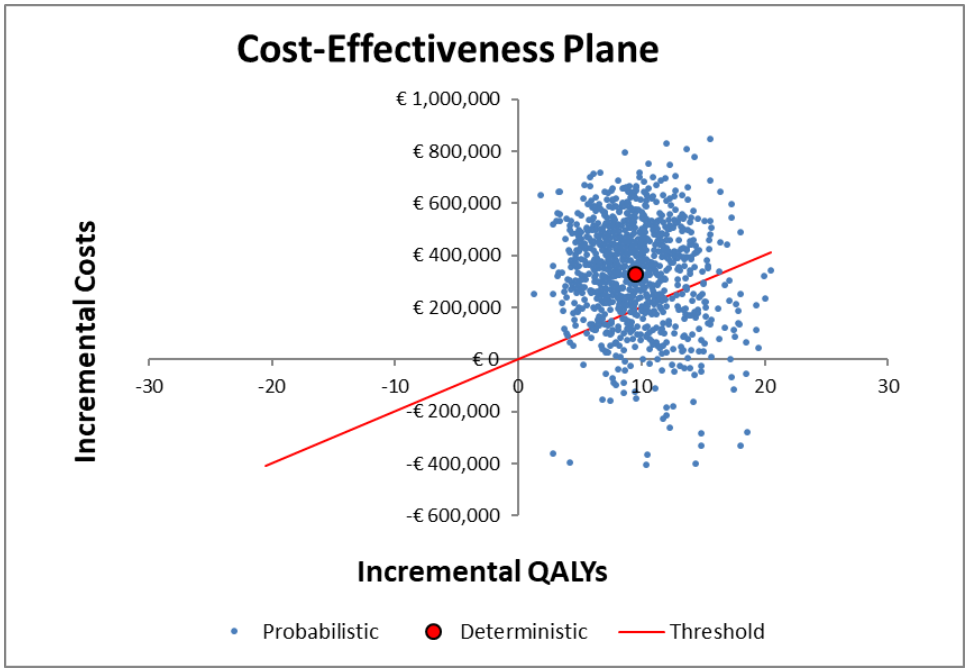


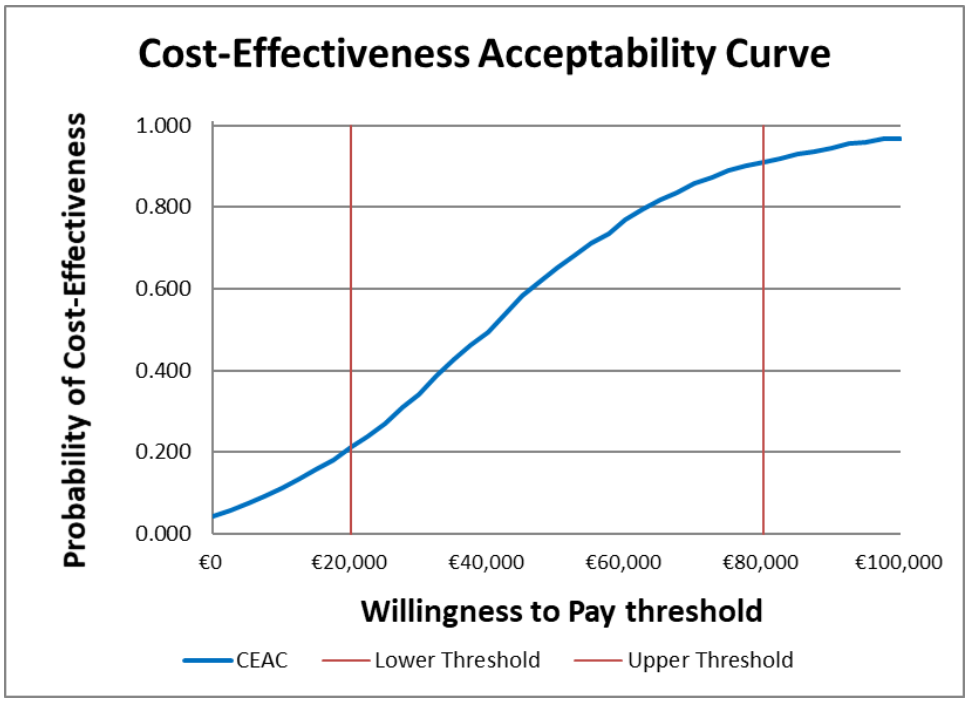


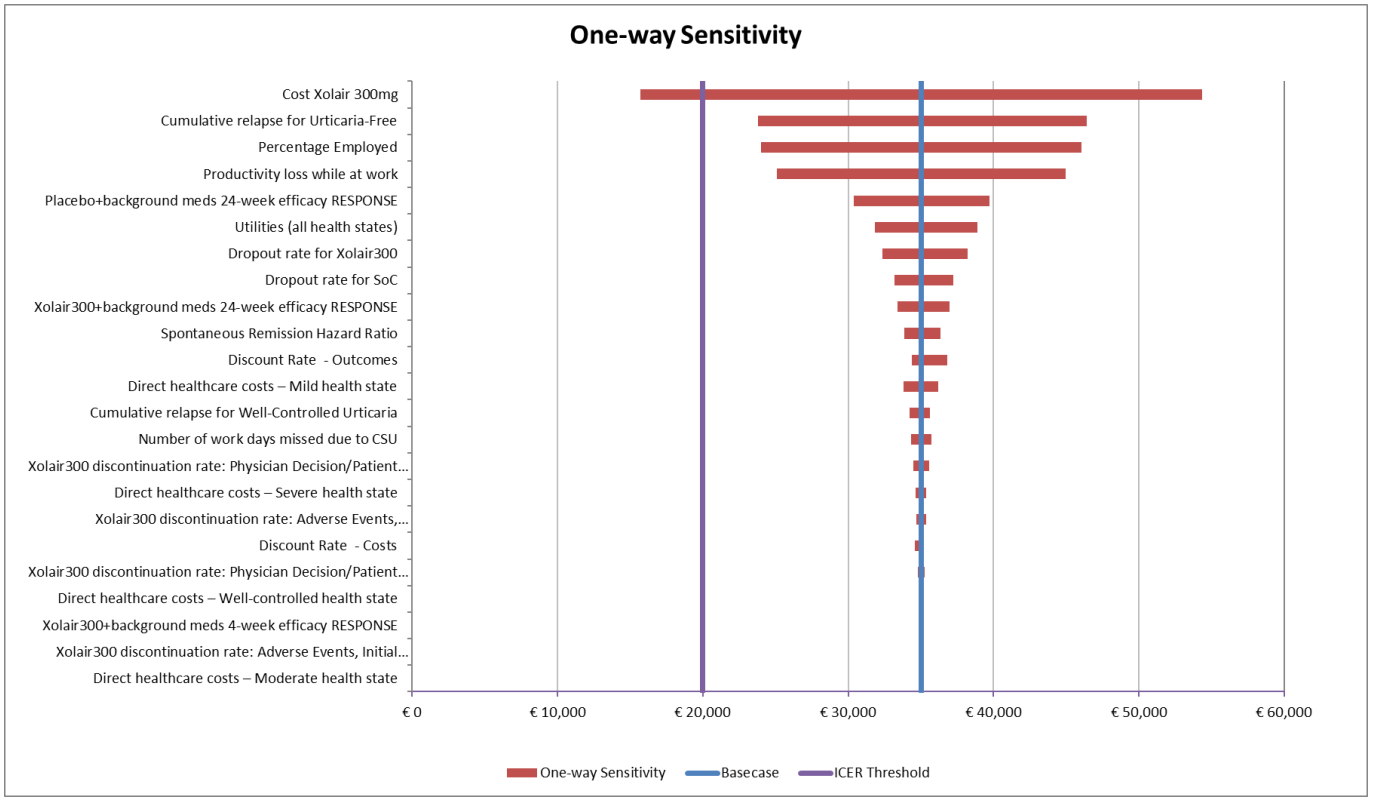
5. Scenario zero baseline severe cases

In this scenario, we want to see how the model behaves when putting the number of baseline severe cases to zero. All other settings are kept the same as with the default settings. From the CEAC we notice that the probability of cost-effectiveness is 21% at the lower threshold and 91% at the higher threshold value.

Settings	Value
Patient Number	100
Time Horizon	10 Years
Discounting – Costs	4.0 %
Discounting – Benefits	1.5 %
Age	36
Proportion of starting cohort with Severe urticaria symptoms	**0 %**
Include drug costs	Yes
Include direct healthcare costs (non-drug related)	Yes
Include indirect costs (lost productivity and absence)	Yes
Patient Sub-grouping	All Patients
Xolair Scenario	Base case 300mg (24-wk)
Comparator Definition	Standard of Care (as per trial protocol)




Cost-Effectiveness Acceptability Curve
Probability of Cost-Effectiveness
1.000
0.800
0.600
0.400
0.200
0.000
€0
€20,000
€40,000
€60,000
€80,000
€100,000
Willingness to Pay threshold
CEAC
Lower Threshold
Upper Threshold


One-way Sensitivity
Cost Xolair 300mg
Cumulative relapse for Urticaria-Free
Percentage Employed
Productivity loss while at work
Placebo+background meds 24-week efficacy RESPONSE
Utilities (all health states)
Dropout rate for Xolair300
Dropout rate for SoC
Xolair300+background meds 24-week efficacy RESPONSE
Spontaneous Remission Hazard Ratio
Discount Rate - Outcomes
Direct healthcare costs – Mild health state
Cumulative relapse for Well-Controlled Urticaria
Number of work days missed due to CSU
Xolair300 discontinuation rate: Physician Decision/Patient...
Direct healthcare costs – Severe health state
Xolair300 discontinuation rate: Adverse Events,...
Discount Rate - Costs
Xolair300 discontinuation rate: Physician Decision/Patient...
Direct healthcare costs – Well-controlled health state
Xolair300+background meds 4-week efficacy RESPONSE
Xolair300 discontinuation rate: Adverse Events, Initial...
Direct healthcare costs – Moderate health state
€ 0
€ 10,000
€ 20,000
€ 30,000
€ 40,000
€ 50,000
€ 60,000
One-way Sensitivity
Basecase
ICER Threshold

Conclusions

1. The model reflects current Dutch standards for pharmacoeconomic evaluations.
2. All input parameters of the model as described by iMTA were retrieved in the Excel model.
3. All model results as communicated by Novartis could be reproduced.
4. The model depends heavily on Dutch input data from the ASSURE study, with data from only 93 Dutch patients. These data show hardly any differentiation of less and more severe urticaria stages, both for the quality of life and for productivity losses. Whether this reflects the clinical situation of patients reliably is beyond the scope of this review.
5. Cost-effectiveness of omalizumab depends on the perspective: cost-effectiveness is more favorable in the societal perspective, the perspective of choice in the Netherlands, and not cost-effective when considered from the health care perspective. This means that the input data with regard to productivity losses should be checked with caution.