

Executive summary of the methods report for 'The EAACI/GA²LEN/EDF/WAO Guideline for the Definition, Classification, Diagnosis and Management of Urticaria. The 2017 Revision and Update'

To the Editor,

For the revision and update of the EAACI/GA²LEN/EDF/WAO guideline on urticaria¹, we defined and followed a structured process as recommended by national and international guideline development manuals² and took the Appraisal of Guidelines Research and Evaluation (AGREE II) Instrument³ into account. The full methods report can be found in the online Appendix S1.

Experts representing 44 international societies were nominated. The experts were responsible to define key questions and select relevant outcomes using an online survey tool.⁴ Secondly, a systematic review protocol was developed specifying the search strategy, three databases, the inclusion/exclusion criteria, the outcomes and study appraisal methods, data collection and synthesis procedures. The methods as recommended by Cochrane,⁵ and the Grading of Recommendations Assessment, Development and Evaluation (GRADE) working group were adhered to.⁶ Record screening, data extraction and study appraisal were carried out twice and independently by two methodologists. Risk ratios, mean difference and corresponding confidence intervals were calculated, and whenever appropriate, meta-analysis was performed using Review Manager.⁷ The Cochrane Risk of Bias Assessment tools was used, and we evaluated the certainty of the evidence as postulated by GRADE using GRADEpro GDT.⁸ A summary of the four possible GRADE rating can be seen in Table 1. Furthermore, we developed evidence-to-decision frameworks (EtD)⁹ providing a concise overview of the available evidence including other, relevant context factors.

The literature search took place on 1st June 2016. A total of 8090 records were identified and screened in two phases by two methodologists. A total of 65 studies could be included, and we created 31 GRADE evidence profiles. Recommendations were drafted using standardized wording (Table 2).

Additionally, the experts drafted recommendations for all remaining key questions and those for which no evidence could be identified. A preconsensus conference voting on the recommendation took place. Results and feedback were integrated. The draft recommendations and EtD frameworks were made available online to all conference participants ahead of time.

TABLE 1 Summary of the GRADE approach to assessing the quality of evidence by outcome by Balshem et al. 2011¹¹

High (++++)	We are very confident that the true effect lies close to that of the estimate of effect.
Moderate (+++)	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low (++)	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low (+)	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

On 1st December 2016, the consensus conference took place with over 250 participants. Each recommendation was voted on using a structured, nominal group technique process¹⁰: presentation of the available evidence/GRADE profile, presentation of the draft recommendation, open discussion, voting and/or generating alternative phrasing, final voting. Green and red cards were used to vote for or against a suggested recommendation. Consensus levels had been predefined as: >90% agreement - strong consensus, 70%-89% - consensus. Voting results were documented, and each recommendation passed (at least 75% agreement). An internal and an external review of the final guideline was conducted.

FUNDING INFORMATION

The Guideline was funded by the EAACI Dermatology Section, GA²LEN, EDF and WAO.

CONFLICTS OF INTEREST

None Declared.

TABLE 2 Standardized wording and symbols (GRADE)

Type of recommendation	Wording	Symbols	Implications
Strong recommendation for the intervention	"We recommend ..."	↑↑	We believe that all or almost all informed people would make that choice. Clinicians will have to spend less time on the process of decision-making and may devote that time to overcome barriers to implementation and adherence. In most clinical situations, the recommendation may be adopted as a policy.
Conditional recommendation for the intervention	"We suggest ..."	↑	We believe that most informed people would make that choice, but a substantial number would not. Clinicians and healthcare providers will need to devote more time on the process of shared decision-making. Policy makers will have to involve many stakeholders, and policy making requires substantial debate.
Conditional recommendation for either the intervention of the comparison	"We cannot make a recommendation with respect to ..."	0	At the moment, a recommendation in favour or against an intervention cannot be made due to certain reasons (e.g no evidence data available, conflicting outcomes, etc.)
Conditional recommendation against the intervention	"We suggest against ..."	↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.
Strong recommendation against the intervention	"We recommend against ..."	↓↓	We believe that all or almost all informed people would make a choice against that intervention. This recommendation can be adopted as a policy in most clinical situations.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.

Methods and evidence report for the evidence – and consensus- based (S3) Guideline for the definition, classification, diagnosis, and management of urticaria – revision and update 2017.

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1 Abbreviations

AEs	Adverse events
AH	antihistamines
BID	twice a day
CI	Confidence interval
CIndU	Chronic inducible urticaria
CU/CSU	Chronic urticaria, chronic spontaneous urticaria
GRADE	Grading of Recommendations Assessment, Development and Evaluation
EtD	Evidence-to-Decision frameworks
ITT	intention-to-treat analysis
MD	mean difference
PICO	Patient - Intervention - Comparison - Outcome
PP	per-protocol analyses
QD	Once a day
QW	once a week
RCT	randomized controlled trials
RR	Risk Ratio
SD	standard deviation
SoF	Summary of findings tables

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Begad	Wahba	Cairo	Egypt
Susan	Waserman	Hamilton	Canada
Bettina	Wedi	Carl-Neuberg-Str. 1	Hannover
Karsten	Weller	Belin	Germany
Vesarat	Wessagowit	Bangkok	Thailand
Paraskevi	Xepapadaki	Athens	Greece
Patrick	Yong	Frimley	United Kingdom
Zuotao	Zhao	Xicheng strict	Beijing
Martin	Zikeli	Wiener Neustadt	Austria
Torsten	Zuberbier	Berlin	Germany

4 Introduction

This report presents the methods and processes used to develop the evidence – and consensus-based (S3) Guideline for the definition, classification, diagnosis, and management of urticaria — revision and update 2016. The guideline should be referenced as:

[Editors, please to add the full reference of the guideline including the DOI here]

This report presents in chronological order the pursued steps: pre-voting of key questions, systematic literature search, assessment and GRADE, online pre-conference voting and consensus conference.

The Division of Evidence Based Medicine, Department of Dermatology, Venerology and Allergology, Charité – Universitätsmedizin Berlin, corporate member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, performed the evidence assessment, the preparation of the Evidence-to-Decision frameworks and facilitated the voting.

The Guideline was funded by the EAACI Dermatology Section, GA²LEN, EDF and WAO. In total. 44 expert from different fields received official nominations from their national societies to be involved in the development of the Urticaria GL. Additionally, the consensus conference was opened up to a wider range of participants including all relevant professional groups - those who treat patients with urticaria in different settings and those who conduct research in this area.

5 Method and Results

5.1 Voting for key questions and rating of outcomes

In the first step, twenty-two key questions had been suggested to be used for the development of the Urticaria Guideline 2016 Update. An online survey was created for expert panel members to vote on the inclusion/exclusion of the key question and to generate further key questions of interest.

Additionally, as recommended by Grading of Recommendations Assessment, Development and Evaluation (short GRADE) process (1), relevant outcomes were chosen a priori and their importance was also rated by the expert panel. Expert were asked to rate outcomes as either ‘not important’, ‘important but not critical for making a decision’, or ‘critical for making a decision’.

A survey on seven consensus- und 15 evidence-based key questions as well as seven outcomes was conducted using an online survey tool. Data was collected over 10 days (14.04.2016 – 24.04.2016). Off the 41 invited participants (expert panel) 30 completed the survey (response rate 73%).

A detailed overview of the content and results of the two voting rounds can be found in Table 1:
Voting results 1 – Consensus- and Evidence-based key questions.

Table 1: Voting results 1 – Consensus- and Evidence-based key questions

Consensus-based key questions				
	Agree		Disagree	
1. How should urticaria be classified?	29	96,67%	1	3,33%
2. Which instruments should be used to assess and monitor (chronic) urticaria patients?	29	96,67%	1	3,33%
3. Should routine diagnostic measures be performed in acute urticaria?	25	83,33%	5	16,67%
4. Should routine diagnostic measures be performed in chronic spontaneous urticaria?	26	86,67%	4	13,33%
5. Should extended diagnostic measures be performed in chronic spontaneous urticaria?	23	76,67%	7	23,33%
6. Should routine diagnostic measures be performed in inducible, non-spontaneous subtypes of urticaria?	27	90,00%	3	10,00%
7. Should treatment aim at complete symptom control in urticaria?	28	93,33%	2	6,67%
Evidence-based key questions				
	Agree		Disagree	
8. Should modern second generation H1-antihistamines be used as first-line treatment of urticaria?	29	96,67%	1	3,33%
9. Are modern second generation H1-antihistamines to be preferred over first generation H1-antihistamines for the treatment of urticaria?	28	93,33%	2	6,67%
10. Is an increase in the dose to fourfold of modern second generation H1-antihistamines useful and to be preferred over other treatments in urticaria (second-line treatment)?	28	93,33%	2	6,67%
11. Should modern second generation H1-antihistamines be taken regularly or as needed?	29	96,67%	1	3,33%
12. Should different second generation H1-antihistamines be used at the same time?	19	63,33%	11	36,67%
13. If there is no improvement, should higher than fourfold doses of second generation H1-antihistamines be used?	18	60,00%	12	40,00%
14. Is omalizumab useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines (third-line treatment of urticaria)?	30	100,00%	0	0,00%
15. Is cyclosporine A useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines (third-line treatment of urticaria)?	28	93,33%	2	6,67%
16. Are leukotriene antagonists useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines (third-line treatment of urticaria)?	24	80,00%	6	20,00%
17. Should oral corticosteroids be used as add-on treatment in the treatment of urticaria?	28	93,33%	2	6,67%
18. Are pseudoallergen-free diets useful in the treatment of chronic spontaneous urticaria?	18	60,00%	12	40,00%
19. Could any other treatment options be recommended as third-line treatment in urticaria?	25	83,33%	5	16,67%
20. Should the same treatment algorithm be used in all subtypes of chronic urticaria?	28	93,33%	2	6,67%
21. Should the same treatment algorithm be used in children?	28	93,33%	2	6,67%
22. Should the same treatment algorithm be used in pregnant women and during lactation?	26	86,67%	4	13,33%

Question with an agreement rate below 50% were omitted, and question above 75% agreement rate were included. Questions with an agreement rate between 50% and 75% were re-voted during a second round of voting in addition to new suggestions. Consequently, three questions were re-voted as well as one newly suggested key question (see table 2).

Data was collected over 8 days (12.05.2016 – 20.05.2016). 28 of the 41-invited expert panel members (68% response rate) voted on the 2nd round. As a result, one question was added. The other three remained part of the guideline (see Table 2: Voting results round 2).

Table 2: Voting results round 2

Evidence-based key questions											
	Agree			Disagree			Omit				
12. Should different second generation H1-antihistamines be used at the same time?	22	78.57%		2	7.14%		4	14.29%			
13. If there is no improvement, should higher than fourfold doses of second generation H1-antihistamines be used?	19	67.86%		3	10.71%		6	21.43%			
18. Are pseudoallergen-free diets useful in the treatment of chronic spontaneous urticaria?	22	78.57%		2	7.14%		4	14.29%			
New key question											
	Agree			Disagree			Omit				
23. Are H2-antihistamines useful as add-on treatment in patients unresponsive to low or high doses of H1-antihistamines?	21	77.78%		0	0.00%		6	22.22%			

Concerning the voting of the outcomes, five outcomes were voted as critical, a further two as important (see Table 3: Outcomes and rating of outcomes).

Table 3: Outcomes and rating of outcomes

	Rating of outcomes										
	not important			important, but not critical for making a decision			critical for making a decision			mean	
	1	2	3	4	5	6	7	8	9		
Proportion of participants with complete suppression of urticaria	0	0	0	0	0	3	9	8	10	8	critical
Proportion of participants with 'good' or 'excellent' response	0	0	0	0	1	1	7	8	13	8	critical
Proportion of participants with 50% or greater improvement in quality of life measurements	0	0	1	1	4	4	8	8	4	7	critical
Mean reduction in Weekly Urticaria Activity Score (UAS7)	0	1	0	1	3	0	4	12	9	8	critical
Serious adverse events (i.e. serious enough to require withdrawal of treatment)	0	1	0	0	1	2	3	10	13	8	critical
Minor participant-reported adverse events not requiring withdrawal of treatment, e.g. sedation	1	0	3	2	11	11	1	1	0	5	important
Proportion of participants who relapse within one month of stopping intervention	1	1	4	1	4	2	8	6	3	6	important

5.2 Systematic literature review and GRADE

First, each question selected by the expert panel (Table 1: Voting results 1 – Consensus- and Evidence-based key questions, questions 8 - 22) was transformed into structured questions, which specifies the target population, the intervention, the comparison and the outcome used to assess

efficacy and safety (**for PICO question, see GRADE evidence profiles**)(2). The PICO questions were the basis for the systematic literature search strategy. An internal protocol was prepared.

The Urticaria Guideline 2016 is an update; therefore, we did not search for other guidelines or systematic reviews. Systematic searches for randomized controlled trials and clinical, controlled trials were performed in MEDLINE(R) 1946 to March Week 4 2016 (Ovid), MEDLINE In-Process & Other Non-Indexed Citations March 31, 2016 (Ovid), EMBASE 1974 to 2016 Week 13 (Ovid) and CENTRAL (Cochrane Central Register of Controlled Trials - Issue 3 of 12, March 2016). The extended search strategy was drafted taking into consideration the search strategy used in the Cochrane review by Sharma et al. 2014 (3), see Appendix 1: Example search strategy). We did not search trials registries, grey literature sources, or contacted authors due to limited resources. EndNote™ was used to manage references.

5.2.1 Eligibility criteria

The pre-selected inclusion criteria for the title/ abstract and the full-text screening are stated in Box 1.

Patients:

- chronic spontaneous urticaria (CSU), chronic idiopathic/chronic urticaria
- chronic inducible urticaria (CIndU) [cold urticaria, pressure urticaria, heat urticaria, solar urticaria, symptomatic dermatographism (=urticaria factitia), vibratory angioedema, aquagenic urticaria, cholinergic urticaria, contact urticaria]
- angioedema without wheal

Interventions (stated with minimum standard dosage for adults where applicable):

- H1-antihistamines (H1-AH) 1st generation:
 - clemastine fumarate 1mg BID ($\pm$ 1,34mg clemastine fumarate), 20ml sirup BID ($\pm$ 1,34mg clemastinehydrogen fumarate = 1mg clemastine)
 - dimetindene maleate 0.05-0.1mg/kg BW QD ($\pm$ 1-2 dragees á 1mg dimetindene maleate), 1ml TID ($\pm$ 20 drops)
 - diphenhydramine
 - hydroxycine dihydrochlorid 37,5mg ($\pm$ 1,5 tablets; 25mg $\pm$ 20.93mg hydroxycine)
 - ketotifen fumarate (HC 20-511 Sandoz) 1.38mg ($\pm$ 1 capsule)
- H1-antihistamines 2nd generation:
 - acrivastin 8mg TID
 - bilastine 20mg QD ($\pm$ 1 tablet)
 - cetirizine dihydrochlorid 10mg QD ($\pm$ 1 tablet $\pm$ 8.42mg cetirizine)/ 10mg sirup QD (1ml sirup $\pm$ 1mg cetirizine-HCl)
 - desloratadine 5mg QD ($\pm$ 1 tablet)
 - ebastine 10mg QD ($\pm$ 1 tablet)
 - emedastine 2mg BID ($\pm$ 1 drop BID; 1ml solution $\pm$ 0.5mg emedastine [0.05%] as difumarate [0.884mg/1ml emedastine difumarate])
 - fexofenadine 180mg QD ($\pm$ 1 tablet)
 - levocetirizine dihydrochlorid 5mg QD ($\pm$ 1 tablet $\pm$ 4.2mg levocetirizine)
 - loratadine 10mg QD ($\pm$ 1 tablet)
 - mizolastine 10mg QD ($\pm$ 1 tablet)
 - rupatadine 10mg QD ($\pm$ 1 tablet $\pm$ 12.79mg rupatadine fumarate)
- doxepine 50mg QD ($\pm$ 5 tablets; 1 tablet $\pm$ 11.31mg rupatadine fumarate)
- omalizumab 150mg and 300mg per month (100mg omalizumab $\pm$ 1ml solution in syringe)
- TNF-alpha inhibitors: adalimumab, certolizumab pegol, etanercept, golimumab, infliximab
- anakinra (100mg) in 0.67ml (150 mg/ml) syringe
- rituximab (50ml contain 500mg rituximab [CHO-cells])
- intravenous immunoglobulins (IVIG)
- methotrexate
- phototherapy: UVB, narrow band-UVB, PUVA
- cyclosporine
- tacrolimus
- montelukast 10mg ($\pm$ 10.38mg montelukast natrium)
- dapsone
- sulfasalazine
- hydroxychloroquine
- colchicine
- autologous whole blood (AWB)/ autologous serum/ autohemotherapy
- heparin
- pseudoallergen-free diets (has to be defined as such in the trial)
- oral corticosteroids (prednisone, prednisolone, methylprednisolone, triamcinolone, betamethasone, dexamethasone)

Comparisons:

- 2nd generation H1-AH versus placebo or versus 1st generation H1-AH
- 2nd generation H1-AH low dose versus high dose (up to 4-fold)
- H1- AH versus other therapies or versus H1-AH combined with other therapies or other therapies versus each other (other therapies refers to those listed above)

Outcomes:

- at least one efficacy outcome had to be reported in a study for the study to be included
- for the comparison 1st gen AH vs 2nd gen AH details in regards to adverse events (AEs) will be extracted and no efficacy outcome is necessary as inclusion condition
- outcome of special interest in regards to sleep for the comparison 2nd generation H1-AH versus 2nd generation H1-AH regularly versus as needed and up dosing
- outcome assessment: 1-2 weeks or 3-12 weeks after the treatment was started

Study type:

- controlled clinical trial (defined as a clinical study that includes a comparison group) or randomized controlled trial

Box 1: Inclusion criteria

The exclusion criteria for the title/ abstract as well as for the full-text screening were as listed below (Box 2).

- healthy volunteers with induced wheals
- urticaria pigmentosa
- food-induced allergic reaction, for example, shrimp allergy
- hereditary angioneurotic edema/ hereditary angioedema (HAE)
- contact urticaria
- diets other than as defined as pseudoallergene diet
- studies reporting outcomes at a follow-up time of more than 12 weeks only
- outcome assessment after a treatment duration shorter than 1 week
- comparisons of same medication in different treatment regime (for example verum A updosing every week versus verum B updosing every week,) or different applications (for example, tablet versus capsule)
- if only an abstract was available and no numerical data for efficacy outcomes (only p –values or text) were reported, the abstract was excluded
- if in the full-text publication (including any supplementary materials) numerical outcome data was not provided in a format suitable for ReviewManager, the full-text was excluded (for details, see section 1.6 Statistical Analyses).

Box 2: Exclusion criteria

5.2.2 Screening and Data extraction

Two researchers (SR, CD) screened all hits independently. During the title/ abstract screening, in cases where no abstract was available we ordered the full-text unless the title indicated exclusion clearly. Articles in Polish, Chinese and Japanese were assessed by one person only and, if included, only one person extracted the data (see 11 Acknowledgment).

Independent double extraction was done within a team of three researchers (SR; CD, RNW) using a standardized data extraction form (MSEExcel), different opinions where resolved by discussion. The items listed in Table 4 were extracted if available in the pre-defined format. Data was transformed whenever appropriate (see below). We used Engauge Digitizer Version 9.8 to extract data points from images of graphs.

Table 4: Items for data extraction

Study characteristics and baseline data	
first author and year	First author and year of print publication
intervention	Latin abbreviation for treatment regime; duration of medication as stated in publication; PBO for matched placebo and 'nothing' for no medication
randomized or assigned patients	n (Number of patients per arm)
study design	Type of RCT or CCT, MC- multi-centre, SC - single center
Inclusion criteria disease	CIU, CSU, CU or CIndU type; extraction of full inclusion criteria from study
Inclusion criteria age	Years (as stated)
special patient population	No; children (age), pregnant or lactating women,
washout	Duration & medication
concomitant treatment	As stated in publication
age at baseline	M±SD, median (IQR), or range (as reported in publication)
Gender distribution at baseline (female)	% (rounded off to whole numbers)

Outcomes: efficacy and HRQL data are extracted for week 1-2 and week 3 - 12	
Follow-up point in time	As stated in publication
Definition of outcome (scoring)	As stated in publication - <i>must be investigator assessed</i>
matched outcome	State score that was matched with 'complete suppression'
Patients with complete suppression	n/N
matched outcome	State score that was matched with 'good' or 'excellent'
Patients with at least 'good' or 'excellent' response	n/N (includes n of complete suppression)
follow-up point in time	As stated in publication
Definition of efficacy score	As stated in publication
mean change (SD)	Mean±SD and n / <i>make note of who assessed</i>
follow-up point in time	As stated in publication
UAS or UAS7	state which one: UAS or UAS7 / <i>make note of who assessed it</i>
patients with ≤ 6 points	n/N
Follow-up point in time	As stated in publication
Definition of HRQL outcome	As stated in publication
mean change (SD)	Mean±SD and n
Patients with ≥50% improvement in QoL	n/N
Outcomes: Adverse events and Relapse	
Withdrawal/drop out due to AE	n/N
Point in time of AE	As stated in publication
Patients with at least 1 AE	n/N
Adverse Events	Number of patients with somnolence, fatigue, drowsiness, tiredness, dizziness for studies comparing 1st vs. 2nd gen AH only (preferable 'patient-assessed')
Definition of relapse	Definition of relapse at time x (up to max. 6 months)
Proportion of patients relapsing at time x	n/N

5.2.3 Risk of Bias Assessment

The data extraction sheet also contained the categories of the Cochrane Risk of Bias Assessment tool (4). We assessed *sequence generation*, *allocation concealment* and *other sources of bias* at the study level. For *blinding patients and personnel* and *blinding outcome assessment*, we assessed risk of bias on the outcome level. In case of an open trial comparing different active treatments the following rules were applied: for patient-reported outcomes the risk of bias was determined to be unclear; for physician-reported/evaluated outcomes the risk of bias was determined to be high, for adverse events the risk of bias was determined to be high. In case of placebo-controlled RCTs, both, patient- and physician-reported outcomes were determined to be at a high risk of bias. In the category *incomplete outcome data*, we assessed each outcome as follows: if for dichotomous efficacy outcomes, an intention-to-treat analysis (ITT) was published or we were able to calculate our own ITT the risk of bias was rated as low. If studies reported a modified ITT (mITT) or a per-protocol analysis (PP) – for example for continuous outcomes such as DLQI - we rated the risk of bias for this outcome as unclear. If in addition to a reported mITT or PP (or unknown - no information provided) the loss to follow-up was ≥ 10% the risk of bias for the corresponding outcome was rated as high. Concerning the safety outcomes, the risk of bias assessment was determined to be unclear if the number of patients assessed for adverse events (AE) was not reported. If adverse events were not reported per

arm, or no numerical data was available, the risk of bias was considered high. In all other cases, the risk of bias was deemed low unless there was a lack of reporting or other issues became apparent during the individual study assessments.

Controlled clinical studies were included but rated as high risk of bias overall.

5.2.4 Statistical analyses

We calculated risk ratios and mean differences with the corresponding 95 % confidence intervals using Review Manager 5.3.4 (5). For each key question, each comparison and outcome were entered into Review Manager separately and subgroups for each point in time of evaluation were created. We included several multi-arm studies where the comparator arm was split in case of multiple comparisons to avoid counting participants more than once (only when data was later pooled). On several occasions, no events in either arm were reported (for example, where no adverse events occurred). No effect measure can be calculated; we included this information for reference in the summary tables. The GRADE output displays these as 'not estimable'.

Decisions on appropriateness of pooling the data were made taking the PICO question into consideration. We choose the Mantel-Haentzel approach using a random-effects model because the difference between the studies suggested that no common effect was assessed (DerSimonian-Laird (6)). The decision was made to pool data if heterogeneity was $I^2 \leq 80\%$. In cases where $I^2 \geq 40\%$ we downgrade during the assessment of the quality of evidence (GRADE – inconsistency criteria).

We pooled data across time points: week 1 and 2, week 3 and 4 and across week 5 and 6. Data was not pooled across 8 and 12 weeks or when the dosage changed between two time points. If multiple time points had been reported, we preferred the earliest time point in each time bracket.

5.2.5 Data transformation

We performed a variety of data transformations because the data reported in the included publications was not always in a format suitable for meta-analysis.

$$SD_{E, \text{change}} = \sqrt{SD_{E, \text{baseline}}^2 + SD_{E, \text{final}}^2 - (2 \times \text{Corr} \times SD_{E, \text{baseline}} \times SD_{E, \text{final}})}$$

$$\text{Corr}_E = \frac{SD_{E, \text{baseline}}^2 + SD_{E, \text{final}}^2 - SD_{E, \text{change}}^2}{2 \times SD_{E, \text{baseline}} \times SD_{E, \text{final}}}$$

In order to calculate summary measures for continuous outcomes, a measure of dispersion, i.e. the standard error or the standard deviation (SD) had to be available. For continuous outcomes the

absolute mean change in a score from baseline could be calculated where baseline and final data was provided. The corresponding standard deviation could only be calculated using the formula below if we were able to use data from another publication and calculate a correlation coefficient assuming that the intervention did not change the variability of the outcome measures, as suggested by Cochrane (4).

Otherwise missing standard deviations for mean changes were calculated based on the confidence interval and the standard error (section 7.7.3.2; 4).

$$SE = (\text{upper limit CI} - \text{lower limit CI}) / 3.92$$

$$SD = SE \times \sqrt{N}$$

If only the baseline mean value $\pm$ SD and the end mean value w/o SD (read off chart) was available or the final mean $\pm$ SD but no SD for the mean change was reported or calculable, no effect measure could be calculated.

Concerning dichotomous efficacy outcomes, we calculated a non-responder-imputation-based ITT to harmonize the data pool.

5.3 Assessing the quality of evidence - GRADE

The GRADE (7) approach was used to grade the quality of evidence and develop evidence-to-decision frameworks (7). We used the GRADE pro GDT (8) – an online computer program – to create evidence profiles for each comparison. During this process, the following five criteria were used to rate each outcome as *not serious*, *serious* (downgraded by 1 level) or *very serious* (downgraded by 2 levels). Randomized, controlled trials (RCT) start with the highest rating (not serious). A summary of the criteria influencing the quality and the different quality levels are displayed in Table 5 (adapted from Bashem et al. 2001 (9)). Each criteria that may decrease the quality is described in detail below.

Table 5: Summary of the GRADE approach to assessing the quality of the evidence by outcome (9)

Study design	Initial quality of body of evidence	Criteria that may decrease the quality	Criteria that may increase the quality	Quality of body of evidence	
RCT	high	- Risk of bias	- Large effect	High (++++)	We are very confident that the true effect lies close to that of the estimate of effect.
		- Inconsistency	- Dose response	Moderate (+++)	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is
		- Indirectness	- Residual confounding		
		- Imprecision			
		- Publication bias			

substantially different.

Low (++)	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very low (+)	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

1. *Risk of bias*: The Cochrane Risk of Bias Assessment tool was used - as described in detail in section 5.2.3 Risk of Bias Assessment. We downgraded if several risk of bias items were deemed unclear and/or high. Where more than one study had been included in a meta-analysis, we looked at the weights assigned in the meta-analysis to help determine the overall risk of bias.

2. *Inconsistency*: If only one study was available, we could not assess inconsistency. No default option for this case is available; hence, we rated inconsistency as *not serious*. If more than one study was included, we downgraded to *serious* if statistical heterogeneity was detected as $I^2 \geq 40\%$ and to *very serious* if $I^2 \geq 70\%$.

3. *Indirectness*: Only if the population and/or intervention specified in the key question differed from the population and/or intervention in the studies included did we downgrade to *serious*. For example, if a study included non-responders to different doses of H1-AH but the PICO question had specified for the population to be non-responder to high doses of H1-AH did we downgrade.

4. *Imprecision*: Imprecision was rated as *serious* if the confidence interval was very wide (for example, 0.06 to 15.14 or 2.05 to 97.04). In addition, the boundaries of the calculated confidence intervals were assessed. The GRADE approach postulates for the minimal clinical important difference (MID) thresholds to be larger than 25% benefit (1.25) and 25% harm (0.75) (9). If the confidence interval crossed the MID threshold this represents uncertainty in regards to clinical importance. If one or both MID thresholds were crossed, we downgraded to *serious*. If only the line of no effect was crossed but no MID threshold, we did not downgrade because the result is precise.

For continuous outcomes, we based our assessment on MID thresholds that are anchor-based and available in the peer-reviewed literature. For the Dermatology Quality of Life Index with a possible range of scores from 0 to 30, the MID threshold used was 3 (Shikar et al. 2005 suggested 2.2 to 3.2; (10)). For the Urticaria Activity Score 7 (UAS7) Mathias et al. 2012 had suggested an MID range from

9.5 to 10.5, we used 10 (11). Where no anchor-based MIDs were available, we used distribution-based MIDs, namely $\frac{1}{2}$ the SD (12).

5. *Publication bias*: We planned to assess publication bias using a funnel plot. However, this analysis only becomes valid if more than seven studies are available. Publication bias could not be assessed and was rated ‘undetected’.

The final categories ‘large effect’, ‘plausible confounding’ and ‘dose response gradient’ were not applicable here.

5.4 Evidence-to-decision frameworks - GRADE

The evidence-to-decision (EtD) frameworks help guideline expert panel members decide and formulate recommendations. In addition to the GRADE evidence profiles, EtD frameworks give guideline developers the opportunity to make an *overall judgement of the size of the desirable and the undesirable effect*, the *balance* of the two, and to summarize the *overall quality* of the evidence.

A number of other points have been summarized here as they vary internationally: importance of the problem, resources required, costs, cost-effectiveness, equity, and acceptability. The criteria ‘feasibility’ remained part of the EtD with the standard sentence: ‘Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems’.

Standardized wording and symbols are used to formulate the recommendations, see Table 6.

Table 6: Standardized wording and symbols for recommendations

Type of recommendation	Wording	Symbols	Implications
Strong recommendation for the intervention	“We recommend ...”	↑↑	We believe that all or almost all informed people would make that choice. Clinicians will have to spend less time on the process of decision making, and may devote that time to overcome barriers to implementation and adherence. In most clinical situations, the recommendation may be adopted as a policy.
Conditional recommendation for the intervention	“We suggest ...”	↑	We believe that most informed people would make that choice, but a substantial number would not. Clinicians and health care providers will need to devote more time on the process of shared decision making. Policy makers will have to involve many stakeholders and policy making requires substantial debate.
Conditional recommendation for either the intervention or the comparison	“We cannot make a recommendation with respect to ...”	0	At the moment, a recommendation in favour or against an intervention cannot be made due to certain reasons (e. g. no evidence data available, conflicting outcomes, etc.)
Conditional recommendation	“We suggest	↓	We believe that most informed people would make a choice against that intervention, but a substantial number would not.

against the intervention	against ..."		
Strong recommendation against the intervention	"We recommend against ..."	↓↓	We believe that all or almost all informed people would make a choice against that intervention. This recommendation can be adopted as a policy in most clinical situations.

Each PICO question leads to a GRADE evidence profile, which in turn is the basis for the evidence-to-decision frameworks. This leads to the final preparation of the *type and strength of the recommendation, justification* and statements on *considerations for subgroups, implementations, and monitoring and evaluation* as well as *research priorities* that may have become apparent (see Box 3).

TYPE OF RECOMMENDATION	Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	Strong recommendation for the intervention
	○	○	○	○	○
RECOMMENDATION					
JUSTIFICATION					
SUBGROUP CONSIDERATIONS					
IMPLEMENTATION CONSIDERATIONS					
MONITORING AND EVALUATION					
RESEARCH PRIORITIES					

Box 3: Standardized format for recommendations (GRADE, (8))

5.5 Results

The literature was searched on 01.04.2016 and 8090 hits were identified. The removal of duplicates left 5627 records for the title/ abstract screening. Additionally, automatic updates for all databased were received monthly and screened in accordance with the inclusion/ exclusion criteria until 01.06.2016. Autoalerts lead to the inclusion of an additional 6 hits in the title/ abstract screening. We identified 3 publications through reference lists. A total of 65 records were included in the evidence-

based review. A list of excluded fulltext with reasons for exclusion can be found in Appendix 2: Excluded studies.

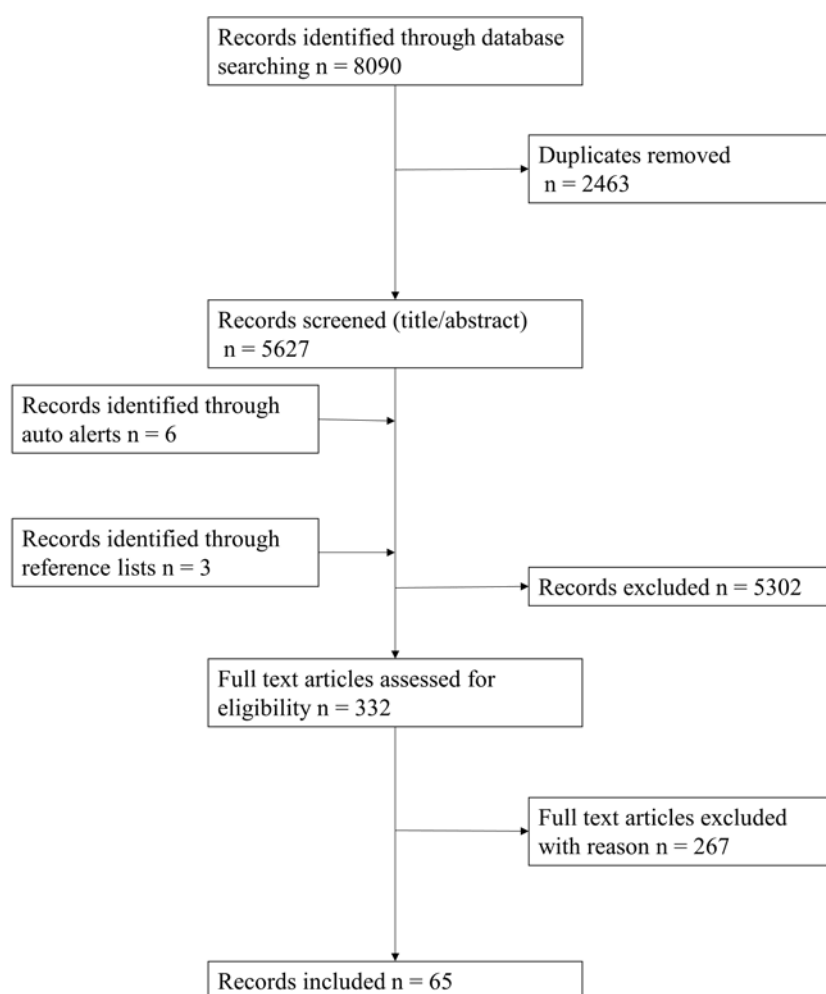


Figure 1: Study selection flow chart

A total of 31 GRADE evidence profiles were created. A summary of the evidence is displayed in Table 7. Additionally, there were 5 key questions for which no evidence could be identified, therefore these were answered consensus-based only in addition to the remaining 8 consensus-based questions (KQ 1-7 and 23, see Table 7: Summary of evidence with quality of the evidence by outcome).

Table 7: Summary of evidence with quality of the evidence by outcome

Key question & Evidence summary
8. H1-antihistamines versus placebo: 2nd generation H1-AH was superior to placebo based on 'complete suppression' (low/moderate quality), 'good or excellent response - w1-2; w3-4' (low/moderate quality), 'mean change in symptom score' (moderate quality), 'mean change in DLQI' (low/moderate quality) and 'mean difference (mean change in DLQI; moderate quality; but not clinically important). No difference was found for 'good or excellent response - w6' (very low quality), 'mean difference in symptom score' (moderate quality), 'mean change in SF-36' (low quality), 'withdrawal due to AE' (very low – moderate quality) and 'patients with at least 1 AE' (low/moderate quality).

9. second generation H1-antihistamines versus first generation H1-antihistamines:

No difference was found for 2nd gen H1-AH compared to 1st gen H1-AH based on 'good or excellent response' (low to high quality), 'withdrawal due to AE - w2' (low quality), 'patients with at least 1 AE' (very low), 'somnolence- w2' (very low quality), 'fatigue' (low quality) and 'relapse after one week of stopping treatment' (moderate quality).

2nd gen H1-AH were superior compared to 1st gen H1-AH based on 'withdrawal due to AE - w4' (low quality), 'somnolence- w4' (low quality) and 'tiredness' (low quality).

10. high versus low dose second generation H1-antihistamines

No difference was found for 2nd gen H1-AH 4-fold dose versus 1-fold dose based on 'mean change in UAS' (moderate quality) and 'withdrawal due to AE' (very low quality).

No difference was found for 4-fold dose vs. 2-fold dose of H1-AH based on 'mean change in UAS' (moderate quality) and 'withdrawal due to AE' (moderate quality).

No difference was found for 2-fold dose vs. 1-fold dose of H1-AH based on 'good or excellent response' (moderate quality), 'withdrawal due to AE' (moderate quality) and 'relapse' (low quality).

11. second generation H1-antihistamines regularly versus needed

Taking 2nd generation H1-AH regularly is marginally superior to taking 2nd generation H1-AH as needed based on 'complete suppression', however the quality of evidence is very low. No difference was found for 'withdrawal due to AE' (low quality) and 'patients with at least one AE' (very low quality).

Weller et al. 2013 found no difference in the reduction of wheal area size between taking H1-AH on-demand and no H1-AH.

14. omalizumab in patients unresponsive to high doses of H1-antihistamines

Omalizumab 150mg was superior to placebo based on 'complete suppression' (moderate quality), 'good or excellent response' (high quality), 'mean change in UAS7' (high quality) and 'mean change in DLQI' (moderate quality). No difference was found for 'withdrawal due to AE' (low quality) and for 'patients with at least one AE' (moderate quality).

Omalizumab 300mg was superior to placebo for 'complete suppression' (high quality), 'good or excellent response' (high quality), 'mean change in UAS7' (moderate quality), 'mean change in DLQI' (high quality) and 'mean difference in CU-Q2oL' (moderate/high quality). No difference was found for 'withdrawal due to AE' (high quality) and 'patients with at least one AE' (moderate/high quality).

15. cyclosporine in patients unresponsive to high doses of H1-antihistamines ?

No difference was found for 'complete suppression' (very low) and 'good or excellent response - w4' (low quality).

No difference was found for 'withdrawal due to AE' (high quality).

Add-on CSA was superior to no add-on treatment based on 'good or excellent response - w1-2' (low quality) and 'mean change UAS7' (moderate quality).

No evidence was found for CSA as add-on treatment versus other interventions as add-on treatment.

16. Are leukotriene antagonists useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines

No difference was found for montelukast as add-on treatment to H1-AH compared to placebo based on 'mean difference in total symptom score' (low quality) and 'good or excellent response' (very low quality) No safety data was available.

Montelukast as add-on treatment to H1-AH was superior to H1-AH alone based on 'excellent response' (low quality).

No difference was found for 'withdrawal due to AE' (moderate quality) and 'patients with at least one AE' (low quality).

19. Could any other treatment options be recommended as third-line treatment in urticaria?

No difference was found for 'good or excellent response' (moderate quality). No further evidence could be identified.[autologous whole blood vs. placebo]

No difference was found for 'mean change in TSS' (low quality), 'withdrawal due to AE' (moderate quality) and 'patients with at least one AE' (low quality).

No difference was found for 'complete suppression' (low quality), 'withdrawal due to AE' (high quality) and 'patients with at least one AE' (moderate quality) [dapsone as add-on to existing treatment vs. no add-on]

Hydroxychloroquine as add-on to H1-AH was superior to no add-on based on 'mean change in USS' (low quality) and 'mean change in DLQI' (very low quality) but no safety data was available.[hydroxychloroquine as add-on treatment to H1-AH vs. placebo]

Montelukast was inferior to montelukast plus desloratadine based on 'mean difference/mean change in total symptom score' (moderate quality). No further evidence could be identified.

Desloratadine 5mg QD was superior to montelukast 10mg QD based on 'mean difference/mean change in total symptom score' (moderate quality). No further evidence could be identified.

No difference was found for desloratadine versus desloratadine plus motelukast based on 'mean difference (mean change in TSS)' (moderate quality). No further evidence could be identified.

Mizolastine (1-fold) plus NB-UVB was superior to mizolastine (1-fold) alone based on 'mean change in total symptom score' (moderate quality) but no difference was found for 'withdrawal due to AE'.

Desloratadine 1-fold plus self-blood acupoint injections was superior to desloratadine alone based on 'change in mean total symptom score' (moderate quality). No difference was found for 'withdrawal due to AE' (moderate quality) and 'patients with at least one AE' (low quality).
Desloratadine plus daspone was superior to desloratadine alone based on 'mean change in UAS7' (moderate quality, but of uncertain clinical importance). No difference was found for 'complete suppression' (low quality) and 'withdrawal due to AE' (low quality).
Levocetirizine (2-fold) plus NB-UVB was superior to levocetirizine (2-fold) based on 'mean change in USS7' (moderate quality, but of uncertain clinical importance). No further evidence could be identified.
20. Should the same treatment algorithm be used in all subtypes of chronic urticaria?
<i>symptomatic dermographism</i> : No difference was found for 'complete remission' (very low), '≥ 90% relief' (very low) and 'withdrawal due to AE' (low). [cetirizine vs. cetirizine + betamethasone]
<i>Delayed pressure urticaria</i> : Montelukast plus loratadine was superior to loratadine alone based on 'total suppression of response after rechallenge' (low quality). No difference was found for 'withdrawal due to AE' (moderate quality).
<i>Cold urticaria</i> : 2nd generation H1-AH were superior to placebo based on 'symptom free' (moderate quality). No difference was found for 'patients with at least one AE' (low quality) and 'withdrawal due to AE' (moderate quality). No difference was found for any of the assessed outcomes (low quality) except for 'symptom free - 2nd gen AH 4-fold vs. 1-fold' (low quality). [H1-AH high vs. low dose]
No difference was found for 'symptom free' (very low), 'patients with at least one AE' (very low) and 'drowsiness' (very low). [2 nd gen. H1-AH vs. 1 st gen. H1-AH]
Doxepine was superior to placebo based on 'very effective' (low quality), however no safety data was available.
Hydroxyzine was superior to placebo based on 'very effective' (very low quality), however no safety data was available. No difference was found based on 'very effective' (very low quality) and no safety data was available. [hydroxyzine vs. doxepine]
21. Should the same treatment algorithm be used in children?
2nd generation H1-AH was superior to placebo based on 'good or excellent response' (low/moderate quality) and 'mean change in C-DLQI' (low quality). No difference was found for 'patients with at least one AE' (low quality).

The evidence found to support question 19- 22 were presented as separate evidence-to-decision frameworks but only one final recommendation for each question was drafted based on expert suggestions. Questions 19, 20 and 21 each are supported by systematically assessed scarce evidence (9 GRADE profiles, 8 GRADE profiles, 1 GRADE profile, respectively).

6 Pre-conference online voting

An online survey tool was used for the pre-conference online voting. Overall, 11 GRADE evidence profiles and 11 EtD were created to support the remaining 7 evidence-based questions. Experts could download each GRADE profile and framework and proceed to vote on the draft judgements (Figure 2):

1. Do you agree with judgements about the **magnitude** of desirable & undesirable effects?
2. Do you agree with the judgement about the **balance** of desirable & undesirable effects?
3. Do you have any comments about the other sections of the above presented EtD table?

Question

Are leukotriene antagonists useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines (third-line treatment of urticaria)?

PICO: Is montelukast as add-on treatment to H1-AH more effective and safer than H1-AH in patients with CSU unresponsive to H1-AH?

POPULATION: patients with CSU unresponsive to H1-AH

INTERVENTION: montelukast + H1-AH

COMPARISON: placebo + H1-AH

Assessment

1	JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS																																
DESIRABLE EFFECTS	How substantial are the desirable anticipated effects?	Is montelukast as add-on treatment to H1-AH more effective and safer than H1-AH in patients with CSU unresponsive to H1-AH? <table><tr><th rowspan="2">Outcomes</th><th rowspan="2">Nº of participants (studies) Follow-up</th><th rowspan="2">Quality of the evidence (GRADE)</th><th rowspan="2">Relative effect (95% CI)</th><th colspan="2">Anticipated absolute effects</th></tr><tr><th>Risk with placebo + H1-AH</th><th>Risk difference with montelukast + H1-AH</th></tr><tr><td>excellent response - w6</td><td>96 (2 RCTs)</td><td>⊕⊕⊕⊕ LOW 1,2</td><td>RR 4.77 (1.95 to 11.66)</td><td>83 per 1.000</td><td>314 more per 1.000 (79 more to 888 more)</td></tr><tr><td>mean difference (mean change in TSS)</td><td>80 (1 RCT)</td><td>⊕⊕⊕⊕ LOW 1,2</td><td>-</td><td>The mean mean difference (mean change in TSS) was 0</td><td>MD 0.01 higher (0.13 higher to 0.09 lower)</td></tr><tr><td>patients with at least 1 AE - w6</td><td>54 (1 RCT)</td><td>⊕⊕⊕⊕ LOW 1,2</td><td>not estimable</td><td>0 per 1.000</td><td>0 fewer per 1.000 (0 fewer to 0 fewer)</td></tr><tr><td>withdrawal due to AE - w6</td><td>42 (1 RCT)</td><td>⊕⊕⊕⊕ MODERATE 1</td><td>not estimable</td><td>0 per 1.000</td><td>0 fewer per 1.000 (0 fewer to 0 fewer)</td></tr></table>	Outcomes	Nº of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects		Risk with placebo + H1-AH	Risk difference with montelukast + H1-AH	excellent response - w6	96 (2 RCTs)	⊕⊕⊕⊕ LOW 1,2	RR 4.77 (1.95 to 11.66)	83 per 1.000	314 more per 1.000 (79 more to 888 more)	mean difference (mean change in TSS)	80 (1 RCT)	⊕⊕⊕⊕ LOW 1,2	-	The mean mean difference (mean change in TSS) was 0	MD 0.01 higher (0.13 higher to 0.09 lower)	patients with at least 1 AE - w6	54 (1 RCT)	⊕⊕⊕⊕ LOW 1,2	not estimable	0 per 1.000	0 fewer per 1.000 (0 fewer to 0 fewer)	withdrawal due to AE - w6	42 (1 RCT)	⊕⊕⊕⊕ MODERATE 1	not estimable	0 per 1.000	0 fewer per 1.000 (0 fewer to 0 fewer)	
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UNDESIRABLE EFFECTS	How substantial are the undesirable anticipated effects?	<table><tr><td>excellent response - w6</td><td>80 (1 RCT)</td><td>⊕⊕⊕⊕ LOW 1,2</td><td>-</td><td>The mean mean difference (mean change in TSS) was 0</td><td>MD 0.01 higher (0.13 higher to 0.09 lower)</td></tr><tr><td>patients with at least 1 AE - w6</td><td>54 (1 RCT)</td><td>⊕⊕⊕⊕ LOW 1,2</td><td>not estimable</td><td>0 per 1.000</td><td>0 fewer per 1.000 (0 fewer to 0 fewer)</td></tr><tr><td>withdrawal due to AE - w6</td><td>42 (1 RCT)</td><td>⊕⊕⊕⊕ MODERATE 1</td><td>not estimable</td><td>0 per 1.000</td><td>0 fewer per 1.000 (0 fewer to 0 fewer)</td></tr></table>	excellent response - w6	80 (1 RCT)	⊕⊕⊕⊕ LOW 1,2	-	The mean mean difference (mean change in TSS) was 0	MD 0.01 higher (0.13 higher to 0.09 lower)	patients with at least 1 AE - w6	54 (1 RCT)	⊕⊕⊕⊕ LOW 1,2	not estimable	0 per 1.000	0 fewer per 1.000 (0 fewer to 0 fewer)	withdrawal due to AE - w6	42 (1 RCT)	⊕⊕⊕⊕ MODERATE 1	not estimable	0 per 1.000	0 fewer per 1.000 (0 fewer to 0 fewer)															
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CERTAINTY OF EVIDENCE	What is the overall certainty of the evidence of effects?	The relative importance or values of the main outcomes of interest: <table><tr><th>Outcome</th><th>Relative importance</th><th>Certainty of the evidence (GRADE)</th></tr><tr><td>excellent response - w6</td><td>critical</td><td>⊕⊕⊕⊕ LOW</td></tr><tr><td>mean difference (mean change in TSS)</td><td>critical</td><td>⊕⊕⊕⊕ LOW</td></tr><tr><td>patients with at least 1 AE - w6</td><td>critical</td><td>⊕⊕⊕⊕ LOW</td></tr><tr><td>withdrawal due to AE - w6</td><td>critical</td><td>⊕⊕⊕⊕ MODERATE</td></tr></table>	Outcome	Relative importance	Certainty of the evidence (GRADE)	excellent response - w6	critical	⊕⊕⊕⊕ LOW	mean difference (mean change in TSS)	critical	⊕⊕⊕⊕ LOW	patients with at least 1 AE - w6	critical	⊕⊕⊕⊕ LOW	withdrawal due to AE - w6	critical	⊕⊕⊕⊕ MODERATE																		
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withdrawal due to AE - w6	critical	⊕⊕⊕⊕ MODERATE																																	
BALANCE OF EFFECTS	Does the balance between desirable and undesirable effects favor the intervention or the comparison?	Summary of findings: <table><tr><th>Outcome</th><th>With placebo + H1-AH</th><th>With montelukast + H1-AH</th><th>Difference (95% CI)</th><th>Relative effect (RR) (95% CI)</th></tr><tr><td>excellent response - w6</td><td>83 per 1.000</td><td>397 per 1.000 (162 to 972)</td><td>314 more per 1.000 (from 79 more to 888 more)</td><td>RR 4.77 (1.95 to 11.66)</td></tr><tr><td>mean difference (mean change in TSS)</td><td></td><td>The mean difference (mean change in TSS) in the intervention group was 0.01 higher (0.13 higher to 0.09 lower)</td><td>MD 0.01 higher (0.13 higher to 0.09 lower)</td><td>-</td></tr><tr><td>patients with at least 1 AE - w6</td><td>0 per 1.000</td><td>0 per 1.000 (0 to 0)</td><td></td><td>not estimable</td></tr><tr><td>withdrawal due to AE - w6</td><td>0 per 1.000</td><td>0 per 1.000 (0 to 0)</td><td></td><td>not estimable</td></tr></table>	Outcome	With placebo + H1-AH	With montelukast + H1-AH	Difference (95% CI)	Relative effect (RR) (95% CI)	excellent response - w6	83 per 1.000	397 per 1.000 (162 to 972)	314 more per 1.000 (from 79 more to 888 more)	RR 4.77 (1.95 to 11.66)	mean difference (mean change in TSS)		The mean difference (mean change in TSS) in the intervention group was 0.01 higher (0.13 higher to 0.09 lower)	MD 0.01 higher (0.13 higher to 0.09 lower)	-	patients with at least 1 AE - w6	0 per 1.000	0 per 1.000 (0 to 0)		not estimable	withdrawal due to AE - w6	0 per 1.000	0 per 1.000 (0 to 0)		not estimable								
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FEASIBILITY	Is the intervention feasible to implement?	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.																																	

Figure 2: Screenshot of an example evidence-to-decision framework

Expert then voted on the draft recommendation (Figure 3):

3. Do you agree with the **direction and strength** of the recommendation (for or against and strong or weak)?
4. Do you agree with the **wording** of the recommendation?
5. Do you have **any comments or suggestions for the justification** of the recommendation?

Summary of judgements

	JUDGEMENT							IMPLICATIONS
DESIRABLE EFFECTS	Trivial	Small	Moderate	Large		Varies	Don't know	Probably favors montelukast + H1-AH
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		Varies	Don't know	Probably favors montelukast + H1-AH
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	High			No included studies	Probably favors montelukast + H1-AH
BALANCE OF EFFECTS	Favors the comparison	Probably favors the comparison	Does not favor either the intervention or the comparison	Probably favors the intervention	Favors the intervention	Varies	Don't know	Probably favors montelukast + H1-AH
FEASIBILITY	No	Probably no	Probably yes	Yes		Varies	Don't know	

Conclusions

TYPE OF RECOMMENDATION 3	Strong recommendation against the intervention =	Conditional recommendation against the intervention =	Conditional recommendation for either the intervention or the comparison •	Conditional recommendation for the intervention =	Strong recommendation for the intervention =
RECOMMENDATION 4	We cannot make a recommendation with respect to montelukast as add-on treatment to H1-AH for patients with chronic urticaria unresponsive to H1-AH.				
JUSTIFICATION 5	Montelukast as add-on treatment to H1-AH was superior to H1-AH alone based on 'excellent response' (low quality). No difference was found for 'mean difference in TSS' (low quality), 'withdrawal due to AE' (moderate quality) and 'patients with at least one AE' (low quality).				
SUBGROUP CONSIDERATIONS	No evidence was available for children (< 18 years of age), pregnant or lactating women.				
IMPLEMENTATION CONSIDERATIONS	-				
MONITORING AND EVALUATION	-				
RESEARCH PRIORITIES	Further research investigating montelukast as add-on treatment is needed.				

Figure 3: Sample draft recommendation

For each of the 8 consensus-based questions and for 4 of the 5 questions, for which no evidence could be identified, the experts – as listed in 2 *Guideline Development group members*- drafted recommendations, resulting in 13 draft recommendations (KQ 17 was split into 2 parts).

The invitation to participate in the pre-conference online voting was sent to 43 experts. The survey was online for 4 weeks (20.09.2016 – 18.10.2010). Each week we sent out a reminder.

For each recommendation, the strength of consensus in terms of percentage of agreement was documented. Three levels of consensus were defined and distinguished: 'strong consensus' (agreement of > 90 % of the members of the expert group), 'fair consensus' (75 to 89 % agreement) 'weak consensus' (>50 to 74 % agreement).

6.1 Results of the pre-conference online voting

Of the 43 expert invited to participate, 36 participated fully and one replied partially. The pre-voting results were taken into account in preparation of the consensus conference.

Prior to the consensus conference, the expert panel unanimously decided to amend several key question as listed in Table 8: Amended list of consensus-based key questions.

Table 8: Amended list of consensus-based key questions

Original questions that remained unchanged:
How should urticaria be classified?
Should routine diagnostic measures be performed in acute urticaria?
Should routine diagnostic measures be performed in chronic spontaneous urticaria?
Should extended diagnostic measures be performed in chronic spontaneous urticaria?
Questions that were removed or rephrased:
2. Which instruments should be used to assess and monitor (chronic) urticaria patients?
6. Should routine diagnostic measures be performed in inducible, non-spontaneous subtypes of urticaria?
7. Should treatment aim at complete symptom control in urticaria?
New/amended questions:
Should we maintain the current classification of chronic urticaria?
Should differential diagnoses be considered in patients with chronic spontaneous urticaria?
Should patients with chronic urticaria be assessed for disease activity, impact, and control?
Which instruments should be used to assess and monitor disease activity in chronic spontaneous urticaria patients?
Which instruments should be used to assess and monitor quality of life impairment in chronic spontaneous urticaria patients?
Which instruments should be used to assess and monitor disease control in chronic spontaneous urticaria patients?
Should patients with chronic spontaneous urticaria be advised to discontinue medication that is suspected to worsen the disease?

7 Conference December 1st 2016

Prior to the consensus conference, the results of the online voting had been integrated into the evidence-to-decision frameworks as well as the consensus-based drafts and made available to all consensus conference participants (list of additional consensus conference members at the beginning of this document).

Consensus conference participants was a large group comprised of a) of the guideline panel members (all of which had official nominations from their national societies and had been involved in the preparatory work of the consensus conference including drafting of the recommendation and online voting) and b) an enlarged group of interested participant that qualified either by being regularly involved in treating patients with urticaria or by basic or clinical research in the field. The enlarged group shall help to ensure regional implementability and act as messenger to help implement the guidelines.

At the start of the consensus conference declarations of interest were collected from every participants. Employees of pharmaceutical companies were excluded from voting. Participants were asked to abstain from voting for those questions, where a potential conflict of interest may be perceived. Due to limited time and resources, an individual assessment of each member's individual COI declaration and respective documentation of abstentions was not feasible. The expert panel and the consensus conference participants agreed on this process. All declarations of interest are appended to this report (Appendix 4: Declarations of Interest).

The formal consensus methodology of the nominal group technique was used to come to an agreement on the different recommendations (13). The consensus conference followed a structure approach: a) presentation of the draft recommendation, b) initial open discussion, c) initial voting d) further discussion/ collection of alternative wording e) final voting if necessary.

All consensus conference participants received upon completion of the declaration of interest form two voting cards (green and red). At the initial and the final voting stage, a show of cards indication agreement (green) or disagreement (red) with the suggested draft recommendation. Each time, the number of red cards were counted and documented.

Based on the GRADE approach, one of five possible phrasings was chosen as shown in Table 5. Throughout the guideline, the consented passages are highlighted in grey, the strength of the consensus is reflected with symbols. It is clearly stated whether the recommendation is an evidence- and consensus-based recommendation or whether it is based on consensus. Strong consensus was defined as >90% agreement, 70-89% was documented as consensus. All recommendations passed with a least 75% agreement. One recommendation was voted to be eliminated (Should the same treatment algorithm be used in all subtypes of chronic urticaria). All others are part of the final guideline.

8 Peer Review

Markus Magerl, Marcus Maurer, Martin Metz and Torsten Zuberbier drafted the guideline text. The draft version was sent to the expert panel for commenting (15. June 2017). The amended guideline version was then sent out for external review (01. September 2017) . All relevant societies were involved. Details about the review process are available upon request.

9 Implementation, evaluation, updating

International guidelines should be adapted to national level. Evaluation strategies should then be adapted accordingly. In four years, an update of the guideline is planned.

10 Strength and Limitations

The strength of the body of evidence presented lies within the application of rigorous and systematic methods as recommended by Cochrane and the GRADE working group, which we describe in detail here. We also used Evidence to Decisions Frameworks to include the balance of potentially desirable and undesirable effects as well as to raise awareness about the feasibility, costs, equity and acceptability of the intervention. These barriers to implementation need to be considered within the national or local context.

The evidence identified regarding the treatment of urticaria is very diverse and many studies report different outcomes at different time points. The reader should be aware of the issue of multiplicity, although we specified outcomes and time points *a priori* in the protocol. There were no protocol amendments or deviations from the protocol.

Concerning statistical limitations, for different comparisons we did pool two trials although the detection of heterogeneity using the I^2 statistics is suboptimal. It is also worth mentioning that the UAS7 is scored in two different ways. When pooling data, we did not differentiate between these two systems. However, Karsten Weller (expert, Weller et al [unpublished data]) found that these two scoring systems are very similar. With regard to the assessment of various outcomes, some trials did not report whether the outcome was patient or physician-assessed. Each unclear case was debated within the review team and a pragmatic approach was chosen when handling the data.

Due to resource restrictions, neither did we include handsearching nor did we search grey literature repositories or trial registers for further evidence. However, a large number of experts were involved in the guideline development and no missing or ongoing trials became apparent in the process.

The review protocol specified that each primary study had to report the necessary data to be able to calculate effect measures. Reporting was often suboptimal and studies had to be excluded. We did not qualitatively report those studies, which may have introduced reporting bias.

During the guideline development process, no patient representative or patient organization was involved. Since this is an international guideline, which should be adapted to national or local context, it is crucial to involve patient representatives at that level.

11 Acknowledgment

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Appendix 1: Example search strategy

Database: Ovid MEDLINE(R) 1946 to March Week 4 2016

1. exp Urticaria/
2. "urticaria*".ab,kf,ti.
3. hives.ab,kf,ti.
4. w?eals.ab,kf,ti.
5. "dermatographi*".ab,kf,ti.
6. ("factiti*" adj3 urticaria*).ab,kf,ti.
7. ((cold or heat or pressure or solar) adj3 urticaria*).ab,kf,ti.
8. (vibratory adj3 angio?edema).ab,kf,ti.
9. ((cholinergic or contact) adj3 urticaria*).ab,kf,ti.
10. ((aquagenic or (water adj3 induc*)) adj3 urticaria*).ab,kf,ti.
11. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10
12. Randomized Controlled Trials as Topic/
13. randomized controlled trial/
14. Random Allocation/
15. Double-Blind Method/
16. Single Blind Method/
17. clinical trial/
18. clinical trial, phase I.pt.
19. clinical trial, phase II.pt.
20. clinical trial, phase III.pt.
21. clinical trial, phase IV.pt.
22. controlled clinical trial.pt.
23. randomized controlled trial.pt.
24. multicenter study.pt.
25. clinical trial.pt.
26. exp Clinical Trials as topic/
27. 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24 or 25 or 26
28. (clinical adj trial\$).tw.
29. ((singl\$ or doubl\$ or treb\$ or tribl\$) adj (blind\$3 or mask\$3)).tw.
30. Placebos/
31. placebo\$.tw.
32. randomly allocated.tw.
33. (allocated adj2 random\$).tw.
34. 28 or 29 or 30 or 31 or 32 or 33
35. 27 or 34
36. case report.tw.
37. letter/
38. historical article/
39. 36 or 37 or 38
40. 35 not 39
41. 11 and 40

Appendix 2: Excluded studies

Title	Year	Reason for exclusion
(Protocol PJPR0019)		Not available through inter library loan
(Urticaria)	1933	no CCT/RCT
(Urticaria)	1936	no CCT/RCT
(Chinese)	1989	no relevant comparison, combination of H1+H2
(Chinese)	1990	no relevant comparison, top. vs. sys.
Mayo Clinic	2001	no CCT/RCT
Manufacturing Chemist	2011	no CCT/RCT
EUCTR [www.clinicaltrialsregister.eu]	2012	ongoing trial - no results
(correction)	2014	no CCT/RCT (correction for Morgan 2014)
M. Abajian	2016	duplicate
D. Abeck	1999	no CCT/RCT
H. A. Abramson	1938	other patient population, no CSU
A. M. Abu Shareeah	1992	no PBO arm
A. M. Abu Shareeah	1997	no original data (Abstract Abu Shareeah 1998)
A. M. Abu Shareeah	1998	insufficient data for RevMan
A. a. Abushareeah	1997	no original data (Abstract Abu Shareeah 1998)
M. L. Agcaoili	2011	no data reported, no numerical outcome data
S. Aithal	1999	no RCT/CCT
W. A. Akers	1972	no study, no CCT/RCT
A. Alomar	1990	duplicate
A. Alomar	1990	duplicate
A. Alomar	1990	no efficacy or DLQI, , no numerical outcome data
B. S. Alper	2000	no CCT/RCT
B. S. Alper	2000	duplicate
A. M. Alsamarai	2012	interventions not included, no relevant comparison
S. Altrichter	2016	no relevant outcome data
S. M. Amar	2008	no CCT/RCT (Abstract only)
B. Amichai	2001	no CCT/RCT
Anonymous	1983	no CCT/RCT
Anonymous	1990	no CCT/RCT
Anonymous	1992	no CCT/RCT
Anonymous	1993	no CCT/RCT
Anonymous	1996	no CCT/RCT
Anonymous	1999	no original data
Anonymous	1999	no CCT/RCT
Anonymous	1999	no CCT/RCT
Anonymous	2002	no CCT/RCT
Anonymous	2002	no CCT/RCT
Anonymous	2003	no CCT/RCT

Anonymous	2005	no CCT/RCT
Anonymous	2007	no CCT/RCT
Anonymous	2009	abstract only - no separate evaluation of U, no CSU
Anonymous	2013	no CCT/RCT
Anonymous	2015	no CCT/RCT
Anonymous	2015	no CCT/RCT
J. Antonova	2014	no relevant outcome
S. Aractingi	2000	no CCT
R. Asero	2016	no CCT/RCT
R. E. Ashton	1983	not Urticaria, no CSU
F. Aubin	2016	no comparison group, no CCT
C. Bachert	2001	not urticaria, no CSU
S. E. Bagenstose	2004	no relevant comparison
A. Bajaj	2008	no comparator, no CCT
B. Balaraman	2009	no CCT/RCT
E. B. Baskan	2004	comparison of 2 group with identical intervention but at 1 month vs 3 months follow up
C. Beauchamp	1985	no CCT/RCT
D. Bernstein	2001	no relevant outcome (abstract only)
J. A. Bernstein	2014	no additional relevant data
M. Billardon	1989	no CCT/RCT
C. Bindslev-Jensen	1998	no CCT/RCT
M. Blanca Gómez	1984	no relevant comparison
M. Bloom	2004	no separate evaluation of AR and U, no CSU
H. F. Blum	1935	no CCT/RCT
R. Borici-Mazi	1999	no relevant comparison group
G. W. Bray	1942	no CCT/RCT
E. Bronsky	2001	insufficient data for RevMan
N. Burgess	1939	no CCT/RCT
C. F. Cao	1999	no relevant comparison
T. Casale	2013	no additional data to Maurer 2013, Asteria II
T. Casale	2014	Asteria I, II und Glacial
T. B. Casale	2014	no CCT/RCT
T. B. Casale	2015	no original data
Z. Y. Chen	1996	no translation available
A. Chopra	1995	no CCT/RCT
M. M. U. Chowdhury	2015	no CCT/RCT
D. Church	2009	no n per group reported, otherwise xfold
M. K. Church	2010	no CCT/RCT
J. Cook	1979	intervention not included
L. J. Cook	1981	health volunteers, no CSU
A. J. Cooke	2013	no outcome data for PBO group
N. H. Cox	1983	no CCT/RCT
R. F. Criado	2008	<80% of pts. with CSU, no CSU
B. a. Czarnetzk	1995	insufficient information for RevMan

N. Daher	2010	no CCT/RCT
P. Dave	2000	no relevant comparison
A. de Dios-Velazquez	2016	no RCT/CCT
A. De Luca	1999	no CCT/RCT
P. Debbarman	2013	no new data
P. Debbarman	2014	insufficient data for RevMan
M. Degonda	2002	no relevant outcomes (not reported separately for f group in phase ii)
M. Di Gioacchino	2003	no relevant outcomes
E. Di Leo	2009	no control group/ cross-over RCT, no CCT
G. Diller	1983	no relevant intervention
M. S. Doutre	2008	no CCT/RCT
J. S. Dover	1988	no CCT/RCT
S. C. Dreskin	2004	no CCT/RCT
L. Dubertret	1999	insufficient data for RevMan
C. Eberhartinger	1969	no relevant comparison
M. H. Ellis	1998	no CCT/RCT
L. F. Ensina	2015	no CCT/RCT
Z. Erbagci	2002	no numerical data, no numerical outcome data
EUCTR2009-012013-22-DE	2009	no relevant outcome data
X. Z. Fan	2000	unobtainable
S. Y. Fang	2010	no comparison, no CCT
M. Farshchain	2002	no relevant comparison
J. C. Feng	2001	no relevant comparison
A. Finn	1999	unobtainable
A. F. Finn, Jr.	1999	no relevant dose
A. E. Gale	1989	no relevant outcome data, insufficient data for RevMan
M. Garavaglia	1995	no relevant outcome data
M. Garavaglia	1995	no relevant outcome data
M. Geller	2016	no CCT
A. Gimenez-Arnau	2009	change SD missing, no relevant numerical outcome data
M. Go	1989	insufficient data for RevMan
L. M. Gober	2008	no numerical outcome data
K. Godse	2014	acute urticaria, no CSU
K. V. Godse	2006	no numerical outcome data
K. V. Godse	2011	no comparison group, no CCT
K. V. Godse	2010	no CCT/RCT
C. L. Goh	1991	no numerical outcome data for control groups
A. A. Goldfarb	1963	No CSU
A. B. Goldsobel	1986	no relevant outcome data
C. Göring	2000	No CCT/RCT
J. A. Grant	1999	no CSU
C. Grattan	2014	no original data
M. W. Greaves	2015	no CCT/RCT
S. L. Greene	1985	no relevant comparison

J. J. Grob	2004	no numerical outcome data, no numerical outcome data
A. Groffik	2011	no RCT/CCT
J. Gu	2002	no relevant comparison
W. T. Gu	1990	no relevant comparison, combination H1+H2
X. L. Guo	2013	no relevant numerical outcome data (primary outcome)
Z. P. Guo	2003	
F. Hampel	2010	mixed population, no CSU
S. Handa	2004	no relevant comparison
F. Hao	2003	no relevant comparison
R. P. Harvey	1981	no relevant comparator
R. Hein	2000	n per group unclear, no numerical outcome data, table 1 wrong
B. Hellwig	2008	no CCT/RCT
L. Hendeles	1996	no CCT/RCT
J. B. Hong	2010	no relevant outcomes reported
H. Jia	1998	no relevant comparison
M. Johnson	2015	insufficient data for RevMan
D. S. Jolliffe	1985	no CCT/RCT
L. Juhlin	1987	no relevant outcome data (efficacy) data, phase 2
L. Juhlin	1991	no relevant outcome data (efficacy) phase 2
L. Juhlin	2004	no CCT/RCT
L. Juhlin	1987	no relevant outcome data; no relevant time point (d5)
C. H. Jyothi	2011	< 50% patients with relevant CIndU, no CSU
B. Kalis	1996	mixed population, no CSU
B. Kalis	1985	no relevant comparison
Y. Kameyoshi	2007	insufficient data for RevMan
Kanga	1994	no CCT/RCT
A. Kaplan	2014	no original data, pooled A I & II
A. P. Kaplan	2010	no comparison group, no CCT
A. P. Kaplan	2011	no CCT/RCT
A. P. Kaplan	2015	no original data
C. H. Katelaris	2014	no new data
S. Khan	2013	no CCT/RCT
A. Kobza Black	1988	no relevant time point (d5)
E. Kocaturk	2012	unclear time of assessment (w10 or 16), no numerical outcome data
H. D. Komarow	2015	no CCT/RCT
K. Kontou-Fili	1991	no relevant primary numerical outcome data
K. Kontou-Fili	1990	no control group, no CCT
M. Kosnik	2011	no relevant numerical outcome
N. G. Kounis	2016	no CCT/RCT
A. Kukita	1990	no relevant comparison
D. Lambert	1993	no relevant comparison
D. M. Lang	2014	no CCT/RCT
F. Lawlor	2004	no CCT/RCT
F. Lawlor	1989	no relevant primary numerical outcome data

F. Levnadier	1997	no numerical outcome data
F. Leyh	1989	no relevant time point (d5)
F. Leynadier	1994	no CSU, healthy volunteers
H. J. Li	1993	no relevant comparison, combination with H2
W. L. Li	1991	unobtainable
X. Y. Lin	2001	no relevant comparison
J. Lipozencic	2007	no CCT/RCT
L. L. Liu	2002	no relevant comparison
L. L. Liu	2003	no relevant comparison
R. A. Logan	1989	no comparison group, no CCT
G. Lorette	2000	no outcomes for relevant time points
M. P. Loria	2001	no numerical efficacy results, no numerical outcome data
J. C. Lv	1994	no relevant comparison, loratadine vs terfenadine
E. Magen	2012	no relevant comparison
M. Magerl	2009	no relevant time point of evaluation
M. Magerl	2007	medication only 1 time 10h before test/ not 1-2 weeks after
D. Mahawar	2014	no relevant comparison
R. Maiti	2011	no relevant comparison
W. Marsch	1992	no CCT/RCT
U. P. Masche	2001	no CCT/RCT
M. Maurer	2011	no relevant outcome data - 24w data
M. Maurer	2013	no additional data to Kaplan 2013 GLACIA
E. O. Meltzer	2007	not urticaria, no CSU
Y. C. Minocha	1995	no comparison group, no CCT
E. Monroe	2003	no efficacy outcome data, no numerical outcome data
E. Monroe	1989	no numerical outcome data, abstract only
E. W. Monroe	1988	n per group not stated, therefore not calculable
P. M. Mora	2005	no relevant outcome data
E. Morita	2005	not Urticaria, no CSU
A. Mukhopadhyay	1995	no relevant comparator
S. Muller	2016	no CCT/RCT
NCT00619801	2008	duplicate
NCT00628108	2008	no original data
H. Neittaanmaki	1988	no relevant outcome data; no numerical data; insufficient data for RevMan
H. S. Nelson	2000	no relevant dose
E. Nettis	2001	no numerical outcome data
S. M. Nsouli	2013	no numerical outcome data
Y. Okubo	2013	no relevant comparator
J. H. Olafsson	1986	no numerical data for MSS, no numerical outcome data
J. Ortonne	1998	no numerical outcome data
J. P. Ortonne	2004	no numerical outcome data
M. L. Pacor	1993	not CIU (but food allergy), no CSU
M. L. Pacor	2001	no Urticaria (ASA or food allergy), no CSU
L. Paradis	1996	insufficient data for RevMan; background KQ19

E. Paul	1989	no numerical outcome data
J. Peyri	1991	no relevant outcome data
P. Potter	2014	no numerical outcome data
P. Potter	2016	duplicate
S. Pradhan	2014	mean + sd but no change scores, n unclear, no numerical outcome data
N. Rajan	2010	no n , no control group data, no numerical outcome data
R. C. Raval	1995	no relevant comparison no relevant numerical outcome data; mean change data unclear (positive or negative); unclear CIs
G. E. Reeves	2004	
J. Ring	2002	no CCT/RCT
J. Ring	2001	no numerical outcome data for relevant outcomes/control group
K. Rosen	2015	only absolute and % score (no change or SD/CI), no relevant outcome data
M. Saenz	2012	no outcome data (abstract only)
S. Saini	2011	no additional data
S. S. Saini	2013	no additional data
O. P. Salo	1989	no relevant time point (5d)
J. Sanchez	2015	no relevant numerical outcome data
M. Sanchez-Borges	2014	no RCT/CCT
A. Sanofi	2008	no CSU
K. Sasada	1971	no relevant intervention/comparison
E. Seropian	1984	1st vs 1st gen AH - no relevant comparison
V. K. Sharma	2014	no relevant outcome
G. R. Sharpe	1993	no relevant outcome
A. Sheikh	2014	no CCT/RCT
M. Staevska	2014	time point of evaluation 5d; no relevant numerical outcome data (i.e. mean change; only median and IQR provided)
M. Staevska	2014	duplicate
M. Staevska	2010	dose increase in two 2nd gen AH, no relevant comparison
M. T. Staevska	2013	no numerical outcome data
S. A. Steinweg	2015	no RCT/CCT
J. P. St-Pierre	1985	1st vs PBO - no relevant comparison
H. Tanizaki	2013	dose not relevant
H. Tanizaki	2013	no urticaria, no CSU
A. K. Thompson	2000	dose not relevant
UCB Pharma	2008	no separate evaluation for CSU
T. van Joost	1989	no relevant time point (5d)
G. Vena	2002	unobtainable
G. A. Vena	2006	no numerical outcome data
K. Verma	1999	mixed population (physical and idiopathic urticaria), no CSU
K. S. Wan	2014	no relevant comparison
H. J. Wang	2012	no relevant comparison
E. Y. Wu	2015	no RCT/CCT
G. Q. Wu	2001	no relevant comparison, 2nd gen single dose vs. 2nd gen single dose
R. Yin	2003	no relevant dosage
H.-S. You	2015	no relevant comparison

H. Y. Zhang	2001	Not available through inter library loan
G. Zhao	1994	no relevant comparison, loratadine vs astemizol
Y. Zhi	2004	no relevant comparison
X. Zhou	2003	no relevant comparison
T. J. Zhu	1994	no relevant comparison, loratadine vs. AH
Y. Zou	2003	no relevant comparison
T. Zuberbier	1995	no relevant numerical outcome
T. Zuberbier	1995	no comparison group, no CCT
T. Zuberbier	1996	no numerical primary outcome

Appendix 3: Grade evidence profiles

Appendix 4: Declarations of Interest of panel members

Appendix 5: Declarations of Interest of all voting participants
(available upon request)

Key Question: 8. Should second generation H1-antihistamines be used as first-line treatment of urticaria?

PICO Question: Are 2nd gen H1-AH 1-fold dose more effective and safer than placebo in patients with CSU?

Bibliography: Belaich 1990, Breneman 1995, Bristoff 1996, Camarasa 2001, Di Lorenzo 2004, Dubertret 2007, Gimenez-Arnau 2007, Grob 2008/Ortonne 2007, Guerra 1994, Hoxha 2011, Juhlin 1988, Kaplan 2005/Spector 2007, Kapp 2006, Monroe 1992, Nettis 2004, Nettis 2006, Ollert 1999, Paul 1998, Potter 2016, Siergiejko 1994, Zuberbier 2010

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2nd gen H1-AH 1-fold	placebo	Relative (95% CI)	Absolute (95% CI)		
complete suppression - w1												
2	randomised trials	serious ¹	not serious	not serious	not serious	none	28/132 (21.2%)	4/98 (4.1%)	RR 4.33 (1.71 to 10.92)	136 more per 1.000 (from 29 more to 405 more)	⊕⊕⊕⊖ MODERATE	
complete suppression - w3-w4												
5	randomised trials	serious ¹	not serious	not serious	not serious	none	127/439 (28.9%)	25/291 (8.6%)	RR 3.06 (1.93 to 4.84)	177 more per 1.000 (from 80 more to 330 more)	⊕⊕⊕⊖ MODERATE	
complete suppression - w6												
1	randomised trials	serious ¹	not serious	not serious	serious ²	none	27/51 (52.9%)	0/49 (0.0%)	RR 52.88 (3.31 to 843.81)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕⊕⊖⊖ LOW	
good or excellent response (by investigator) - w1-2												
4	randomised trials	serious ¹	serious ³	not serious	not serious	none	154/270 (57.0%)	52/273 (19.0%)	RR 3.31 (1.85 to 5.90)	440 more per 1.000 (from 162 more to 933 more)	⊕⊕⊖⊖ LOW	
good or excellent response (by investigator) - w3-4												
7	randomised trials	serious ¹	not serious	not serious	not serious	none	256/486 (52.7%)	107/411 (26.0%)	RR 2.04 (1.70 to 2.44)	271 more per 1.000 (from 182 more to 375 more)	⊕⊕⊕⊖ MODERATE	
good or excellent response (by investigator) - w6												
2	randomised trials	serious ⁴	serious ⁵	not serious	serious ⁶	none	115/177 (65.0%)	84/190 (44.2%)	RR 1.54 (0.97 to 2.43)	239 more per 1.000 (from 13 fewer to 632 more)	⊕⊖⊖⊖ VERY LOW	
good or excellent response (by patient) - w1												

1	randomised trials	serious ¹	not serious	not serious	not serious	none	42/67 (62.7%)	15/68 (22.1%)	RR 2.84 (1.75 to 4.61)	406 more per 1.000 (from 165 more to 796 more)	⊕⊕⊕○ MODERATE	
good or excellent response (by patient) - w4												
2	randomised trials	serious ¹	not serious	not serious	not serious	none	86/148 (58.1%)	45/153 (29.4%)	RR 1.98 (1.49 to 2.61)	288 more per 1.000 (from 144 more to 474 more)	⊕⊕⊕○ MODERATE	
good or excellent response (by patient) - w6												
1	randomised trials	serious ⁴	not serious	not serious	serious ⁷	none	30/47 (63.8%)	19/46 (41.3%)	RR 1.55 (1.03 to 2.32)	227 more per 1.000 (from 12 more to 545 more)	⊕⊕○○ LOW	
mean change in symptom score - w1												
3	randomised trials	not serious	not serious	not serious	serious ⁷	none	379	227	-	MD 1.29 lower (1.74 lower to 0.84 lower)	⊕⊕⊕○ MODERATE	
mean change in symptom score - w3-4												
3	randomised trials	not serious	not serious	not serious	serious ⁷	none	379	227	-	MD 1.35 lower (1.92 lower to 0.77 lower)	⊕⊕⊕○ MODERATE	
mean difference (mean change in TSS) - w6												
1	randomised trials	serious ⁸	not serious	not serious	not serious	none	40	40	-	1.77 higher (1.89 lower to 1.66 higher)	⊕⊕⊕○ MODERATE	
mean change in SF-36 - w1												
1	randomised trials	serious ⁹	not serious	not serious	serious ⁶	none	18	18	-	MD 1.41 higher (1.07 lower to 3.89 higher)	⊕⊕○○ LOW	
mean change in SF-36 - w3												

1	randomised trials	serious ⁹	not serious	not serious	serious ⁶	none	17	18	-	MD 1.95 higher (0.88 lower to 4.78 higher)	⊕⊕○○ LOW	
mean change in DLQI - w4												
2	randomised trials	not serious	not serious	not serious	serious ⁷	none	427	269	-	MD 3.82 lower (4.94 lower to 2.71 lower)	⊕⊕⊕○ MODERATE	
mean change in DLQI - w6												
1	randomised trials	serious ⁴	not serious	not serious	serious ⁷	none	65	72	-	MD 3.8 lower (5.71 lower to 1.89 lower)	⊕⊕○○ LOW	
mean difference (mean change in DLQI) - w4												
1	randomised trials	serious ¹	not serious	not serious	not serious	none	167	91	-	1.5 higher (0.2 higher to 2.9 higher)	⊕⊕⊕○ MODERATE	
withdrawal due to AE - w2												
1	randomised trials	serious ¹	not serious	not serious	not serious	none	0/30 (0.0%)	0/30 (0.0%)	not estimable		⊕⊕⊕○ MODERATE	
withdrawal due to AE - w3-4												
7	randomised trials	serious ¹	not serious	not serious	serious ⁶	none	9/629 (1.4%)	6/435 (1.4%)	RR 1.01 (0.36 to 2.82)	0 fewer per 1.000 (from 9 fewer to 25 more)	⊕⊕○○ LOW	
withdrawal due to AE - w6												
2	randomised trials	serious ⁴	not serious	not serious	very serious ^{2,6}	none	1/177 (0.6%)	1/185 (0.5%)	RR 1.06 (0.11 to 10.08)	0 fewer per 1.000 (from 5 fewer to 49 more)	⊕○○○ VERY LOW	
patients with at least 1 AE - w2												
1	randomised trials	serious ¹	not serious	not serious	serious ⁶	none	5/28 (17.9%)	2/13 (15.4%)	RR 1.16 (0.26 to 5.21)	25 more per 1.000 (from 114 fewer to 648 more)	⊕⊕○○ LOW	

patients with at least 1 AE - w4											
3	randomised trials	not serious	not serious	not serious	serious ⁶	none	146/443 (33.0%)	65/250 (26.0%)	RR 1.24 (0.97 to 1.59)	62 more per 1.000 (from 8 fewer to 153 more)	⊕⊕⊕○ MODERATE
patients with at least 1 AE - w6											
2	randomised trials	serious ¹	not serious	not serious	not serious	none	0/78 (0.0%)	0/49 (0.0%)	not pooled	see comment	⊕⊕⊕○ MODERATE

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

1. unclear method of randomization and allocation concealment; selective reporting
2. wide CI
3. statistical heterogeneity ($I^2 = 69\%$) maybe due to methodological differences
4. unclear allocation concealment, blinding, selective reporting
5. statistical heterogeneity ($I^2 = 79\%$) maybe due to methodological differences
6. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
7. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
8. unclear method of randomization and allocation concealment
9. unclear allocation concealment, blinding, selective reporting

Key Questions: 9. Are modern second generation H1-antihistamines to be preferred over first generation H1-antihistamines for the treatment of urticaria?

PICO Question: Are 2nd gen H1-AH more effective and safer than 1st gen H1-AH in patients with CSU?

Bibliography: Monroe 1992, Monroe 1992a, Ishibashi 1990, Kukita 194, Mensing 1991, Breneman 1996, Kalivas 1990

Quality assessment							N _o of patients		Effect		Quality	Importance
N _o of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2nd gen H1-AH	1st gen H1-AH	Relative (95% CI)	Absolute (95% CI)		
good or excellent response (by investigator and patient) - w1												
2	randomised trials	serious ¹	not serious	not serious	serious ²	none	45/73 (61.6%)	44/74 (59.5%)	RR 1.04 (0.80 to 1.35)	24 more per 1.000 (from 119 fewer to 208 more)	⊕⊕○○ LOW	
good or excellent response (by investigator and patient) - w4												
1	randomised trials	serious ¹	not serious	not serious	serious ²	none	44/67 (65.7%)	44/68 (64.7%)	RR 1.01 (0.79 to 1.30)	6 more per 1.000 (from 136 fewer to 194 more)	⊕⊕○○ LOW	
good or excellent response (by investiagtor) - w1-2												
4	randomised trials	not serious	not serious	not serious	not serious	none	276/447 (61.7%)	191/319 (59.9%)	RR 1.04 (0.93 to 1.17)	24 more per 1.000 (from 42 fewer to 102 more)	⊕⊕⊕⊕ HIGH	
good or excellent response (by investiagtor) - w4												
2	randomised trials	serious ¹	not serious	not serious	serious ²	none	62/99 (62.6%)	56/98 (57.1%)	RR 1.09 (0.87 to 1.37)	51 more per 1.000 (from 74 fewer to 211 more)	⊕⊕○○ LOW	
withdrawal due to AE - w2												
2	randomised trials	not serious	not serious	not serious	very serious ^{2,3}	none	0/382 (0.0%)	3/255 (1.2%)	RR 0.14 (0.01 to 2.76)	10 fewer per 1.000 (from 12 fewer to 21 more)	⊕⊕○○ LOW	
withdrawal due to AE - w4												

3	randomised trials	serious ⁴	not serious	not serious	serious ⁵	none	2/196 (1.0%)	13/203 (6.4%)	RR 0.22 (0.06 to 0.87)	50 fewer per 1.000 (from 8 fewer to 60 fewer)	 LOW	
patients with at least 1 AE (w2)												
2	randomised trials	not serious	very serious ⁶	not serious	serious ²	none	66/382 (17.3%)	76/255 (29.8%)	RR 0.55 (0.23 to 1.33)	134 fewer per 1.000 (from 98 more to 229 fewer)	 VERY LOW	
AE: sedation (w4)												
2	randomised trials	serious ⁷	serious ⁸	not serious	very serious ^{2,3}	none	18/127 (14.2%)	52/131 (39.7%)	RR 0.34 (0.07 to 1.64)	262 fewer per 1.000 (from 254 more to 369 fewer)	 VERY LOW	
AE: somnolence - w2												
2	randomised trials	not serious	very serious ⁹	not serious	serious ²	none	53/382 (13.9%)	66/255 (25.9%)	RR 0.49 (0.20 to 1.19)	132 fewer per 1.000 (from 49 more to 207 fewer)	 VERY LOW	
AE: somnolence - w4												
2	randomised trials	serious ⁷	not serious	not serious	serious ⁵	none	23/129 (17.8%)	40/135 (29.6%)	RR 0.60 (0.38 to 0.94)	119 fewer per 1.000 (from 18 fewer to 184 fewer)	 LOW	
AE: tiredness (w2)												
2	randomised trials	not serious	not serious	not serious	very serious ^{3,5}	none	4/382 (1.0%)	10/254 (3.9%)	RR 0.29 (0.08 to 0.97)	28 fewer per 1.000 (from 1 fewer to 36 fewer)	 LOW	
AE: fatigue (w4)												

1	randomised trials	serious ⁴	not serious	not serious	serious ²	none	4/69 (5.8%)	4/72 (5.6%)	RR 1.04 (0.27 to 4.01)	2 more per 1.000 (from 41 fewer to 167 more)	⊕⊕○○ LOW	
patients with relapse after 1w of stopping treatment												
1	randomised trials	not serious	not serious	not serious	serious ²	none	18/44 (40.9%)	15/24 (62.5%)	RR 0.66 (0.41 to 1.06)	212 fewer per 1.000 (from 38 more to 369 fewer)	⊕⊕⊕○ MODERATE	

CI: Confidence interval; **RR:** Risk ratio

1. unclear randomization method and allocation concealment, selective reporting
2. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
3. wide CI
4. unclear/high risk of bias assessment
5. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
6. statistical heterogeneity ($I^2 = 86\%$) maybe due to methodological differences
7. unclear risk of bias assessment
8. statistical heterogeneity ($I^2 = 88\%$) maybe due to methodological differences
9. statistical heterogeneity ($I^2 = 82\%$) maybe due to methodological differences

Key question: 10. Is an increase in the dose to fourfold of second generation H1-antihistamines useful and to be preferred over other treatments in urticaria (second-line treatment)?

PICO Question: Are 2nd gen H1-AH 2-fold dose more effective and safer than 2nd gen H1-AH 1-fold dose in patients with CSU unresponsive to H1-AH? PART 1 OF 3

Bibliography: Gimenez-Arnau 2007, Ishibashi 1989, Ishibashi 1990, Kukita 1994, Niimura 1990, NCT00536389,

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2nd gen H1-AH 2-fold	2nd gen H1-AH 1-fold	Relative (95% CI)	Absolute (95% CI)		
good or excellent response - w1-2												
5	randomised trials	not serious	not serious	serious ¹	not serious	none	225/354 (63.6%)	212/346 (61.3%)	RR 1.02 (0.92 to 1.14)	12 more per 1.000 (from 49 fewer to 86 more)	⊕⊕⊕⊖ MODERATE	
good or excellent response - w6												
1	randomised trials	not serious	not serious	serious ¹	serious ²	none	81/109 (74.3%)	70/112 (62.5%)	RR 1.19 (0.99 to 1.42)	119 more per 1.000 (from 6 fewer to 262 more)	⊕⊕⊖⊖ LOW	
mean change in UAS - w4												
1	randomised trials	serious ³	not serious	not serious	not serious	none	104	104	-	MD 0.1 lower (0.43 lower to 0.23 higher)	⊕⊕⊕⊖ MODERATE	
withdrawal due to AE - w1-2												
4	randomised trials	not serious	not serious	serious ¹	not serious	none	0/261 (0.0%)	0/256 (0.0%)	not pooled	see comment	⊕⊕⊕⊖ MODERATE	
withdrawal due to AE - w4												
1	randomised trials	serious ³	not serious	not serious	very serious ^{2,4}	none	2/104 (1.9%)	0/106 (0.0%)	RR 5.10 (0.25 to 104.87)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕⊖⊖⊖ VERY LOW	
withdrawal due to AE - w6												
1	randomised trials	not serious	not serious	serious ¹	not serious	none	0/109 (0.0%)	0/112 (0.0%)	not estimable		⊕⊕⊕⊖ MODERATE	
patients with at least 1 AE -w1 - w2												
4	randomised trials	not serious	not serious	serious ¹	serious ²	none	58/261 (22.2%)	52/252 (20.6%)	RR 1.06 (0.76 to 1.48)	12 more per 1.000 (from 50 fewer to 99 more)	⊕⊕⊖⊖ LOW	
patients with relapse after 1w of stopping treatment												

1	randomised trials	not serious	not serious	serious ¹	serious ²	none	7/20 (35.0%)	11/24 (45.8%)	RR 0.76 (0.36 to 1.60)	110 fewer per 1.000 (from 275 more to 293 fewer)	⊕⊕○○ LOW	
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CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

1. unclear if patients were nonresponders
2. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
3. unclear risk of bias assessment
4. wide CI

Key question: 10. Is an increase in the dose to fourfold of second generation H1-antihistamines useful and to be preferred over other treatments in urticaria (second-line treatment)?

PICO **Question:** Are 2nd gen H1-AH 4-fold dose more effective and safer than 2nd gen H1-AH 2-fold dose in patients with CSU unresponsive to H1-AH? PART 2 OF 3

Bibliography: NCT00536389

Quality assessment							Nº of patients		Effect		Quality	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2nd gen H1-AH 4-fold	2nd gen H1-AH 2-fold	Relative (95% CI)	Absolute (95% CI)		
mean change in UAS - w4												
1	randomised trials	serious ¹	not serious	not serious	not serious	none	100	104	-	MD 0.1 higher (0.23 lower to 0.43 higher)	⊕⊕⊕⊖ MODERATE	
withdrawal due to AE- w4												
1	randomised trials	serious ¹	not serious	not serious	not serious	none	2/104 (1.9%)	2/104 (1.9%)	RR 1.00 (0.14 to 6.97)	0 fewer per 1.000 (from 17 fewer to 115 more)	⊕⊕⊕⊖ MODERATE	

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

1. unclear method of randomization and allocation concealment, selective reporting

Key question: 10. Is an increase in the dose to fourfold of second generation H1-antihistamines useful and to be preferred over other treatments in urticaria (second-line treatment)?

PICO Question: Are 2nd gen H1-AH 4-fold dose more effective and safer than 2nd gen H1-AH 1-fold dose in patients with CSU unresponsive to H1-AH?

Bibliography: NCT00536389

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2nd gen H1-AH 4-fold	2nd gen H1-AH 1-fold	Relative (95% CI)	Absolute (95% CI)		
mean change in UAS - w4												
1	randomised trials	serious ¹	not serious	not serious	not serious	none	100	104	-	MD 0 (0.33 lower to 0.33 higher)	⊕⊕⊕○ MODERATE	
withdrawal due to AE - w4												
1	randomised trials	serious ¹	not serious	not serious	very serious ^{2,3}	none	2/104 (1.9%)	0/106 (0.0%)	RR 5.10 (0.25 to 104.87)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕○○○ VERY LOW	

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

1. unclear method of randomization and allocation concealment, selective reporting
2. wide CI
3. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Key Question: . Should modern second generation H1-antihistamines be taken regularly or as needed?

Question: Are 2nd gen H1-AH taken regularly more effective and safer than 2nd gen H1-AH taken as needed in patients with CSU?

Bibliography: Grob 2008

Quality assessment							Nº of patients		Effect		Quality	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2nd gen AH taken regularly	2nd gen AH taken as needed	Relative (95% CI)	Absolute (95% CI)		
complete suppression - w8												
1	randomised trials	serious ¹	not serious	serious ²	serious ³	none	21/46 (45.7%)	16/60 (26.7%)	RR 1.71 (1.01 to 2.89)	189 more per 1.000 (from 3 more to 504 more)	⊕○○○ VERY LOW	
withdrawal due to AE - w8												
1	randomised trials	serious ¹	not serious	serious ²	not serious	none	0/46 (0.0%)	0/60 (0.0%)	not estimable		⊕⊕○○ LOW	
patients with at least 1 AE - w8												
1	randomised trials	serious ¹	not serious	serious ²	serious ⁴	none	19/46 (41.3%)	16/60 (26.7%)	RR 1.55 (0.90 to 2.67)	147 more per 1.000 (from 27 fewer to 445 more)	⊕○○○ VERY LOW	

CI: Confidence interval; **RR:** Risk ratio

1. unclear allocation concealment; unclear blinding of outcome assessment; >10% loss to follow-up
2. only patients responding to previous treatment with desloratadine 5mg QD for 4w included
3. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
4. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Key Question: 14. Is omalizumab useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines (third-line treatment of urticaria)?
PICO Question: Is omalizumab 150mg as add-on treatment more effective and safer than placebo in patients with CSU unresponsive to 2nd gen H1-AH?

Bibliography: Maurer 2013, Saini 2015/Kaplan 2016

Quality assessment							N _o of patients		Effect		Quality	Importance
N _o of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	add-on omalizumab 150mg every 4w	placebo	Relative (95% CI)	Absolute (95% CI)		
complete suppression - w4												
2	randomised trials	not serious	not serious	not serious	serious ¹	none	10/163 (6.1%)	1/159 (0.6%)	RR 6.49 (1.17 to 35.86)	35 more per 1.000 (from 1 more to 219 more)	⊕⊕⊕○ MODERATE	
complete suppression - w8												
2	randomised trials	not serious	not serious	not serious	serious ¹	none	27/163 (16.6%)	12/159 (7.5%)	RR 2.20 (1.15 to 4.18)	91 more per 1.000 (from 11 more to 240 more)	⊕⊕⊕○ MODERATE	
complete suppression - w12												
2	randomised trials	not serious	not serious	not serious	serious ¹	none	30/163 (18.4%)	11/159 (6.9%)	RR 2.60 (1.05 to 6.39)	111 more per 1.000 (from 3 more to 373 more)	⊕⊕⊕○ MODERATE	
good or excellent response - w4												
2	randomised trials	not serious	not serious	not serious	not serious	none	40/163 (24.5%)	14/159 (8.8%)	RR 2.70 (1.47 to 4.96)	150 more per 1.000 (from 41 more to 349 more)	⊕⊕⊕⊕ HIGH	
good or excellent response - w8												
2	randomised trials	not serious	not serious	not serious	not serious	none	59/163 (36.2%)	23/159 (14.5%)	RR 2.48 (1.39 to 4.44)	214 more per 1.000 (from 56 more to 498 more)	⊕⊕⊕⊕ HIGH	
good or excellent response - w12												

2	randomised trials	not serious	not serious	not serious	not serious	none	67/163 (41.1%)	24/159 (15.1%)	RR 2.68 (1.70 to 4.21)	254 more per 1.000 (from 106 more to 485 more)	⊕⊕⊕⊕ HIGH	
mean change in UAS7 - w12												
2	randomised trials	not serious	not serious	not serious	not serious	none	162	159	-	MD 6.96 lower (9.65 lower to 4.26 lower)	⊕⊕⊕⊕ HIGH	
mean change in DLQI - w12												
2	randomised trials	not serious	not serious	not serious	serious ¹	none	145	141	-	MD 2.05 lower (3.64 lower to 0.46 lower)	⊕⊕⊕○ MODERATE	
withdrawal due to AE - w12												
1	randomised trials	not serious	not serious	not serious	very serious ^{2,3}	none	1/82 (1.2%)	1/79 (1.3%)	RR 0.96 (0.06 to 15.14)	1 fewer per 1.000 (from 12 fewer to 179 more)	⊕⊕○○ LOW	
patients with at least 1 AE - w12												
1	randomised trials	not serious	not serious	not serious	serious ²	none	59/88 (67.0%)	48/79 (60.8%)	RR 1.10 (0.88 to 1.39)	61 more per 1.000 (from 73 fewer to 237 more)	⊕⊕⊕○ MODERATE	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

1. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
2. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
3. wide CI

Key Questions: 14. Is omalizumab useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines (third-line treatment of urticaria)?
PICO Question: Is omalizumab 300mg as add-on treatment more effective and safer than placebo in patients with CSU unresponsive to 2nd generation of H1-AH?

Bibliography: Kaplan 2013/Kaplan 2016, Maurer 2013, Saini 2011, Saini 2015/Kaplan 2016, Staubach 2016

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	add-on omalizumab 300mg every 4w	placebo	Relative (95% CI)	Absolute (95% CI)		
complete suppression - w4												
4	randomised trials	not serious	not serious	not serious	not serious	none	81/437 (18.5%)	1/264 (0.4%)	RR 20.51 (5.86 to 71.82)	74 more per 1.000 (from 18 more to 268 more)	⊕⊕⊕⊕ HIGH	
complete suppression - w8												
3	randomised trials	not serious	not serious	not serious	not serious	none	129/412 (31.3%)	14/243 (5.8%)	RR 5.36 (3.13 to 9.18)	251 more per 1.000 (from 123 more to 471 more)	⊕⊕⊕⊕ HIGH	
complete suppression - w12												
4	randomised trials	not serious	not serious	not serious	not serious	none	167/456 (36.6%)	18/290 (6.2%)	RR 5.95 (3.72 to 9.51)	307 more per 1.000 (from 169 more to 528 more)	⊕⊕⊕⊕ HIGH	
good or excellent response - w4												
4	randomised trials	not serious	not serious	not serious	not serious	none	176/437 (40.3%)	18/264 (6.8%)	RR 6.10 (3.40 to 10.92)	348 more per 1.000 (from 164 more to 676 more)	⊕⊕⊕⊕ HIGH	
good or excellent response - w8												

3	randomised trials	not serious	not serious	not serious	not serious	none	199/412 (48.3%)	28/243 (11.5%)	RR 4.29 (2.65 to 6.94)	379 more per 1.000 (from 190 more to 684 more)	++++ HIGH	
good or excellent response - w12												
3	randomised trials	not serious	not serious	not serious	not serious	none	226/412 (54.9%)	34/243 (14.0%)	RR 4.00 (2.89 to 5.53)	420 more per 1.000 (from 264 more to 634 more)	++++ HIGH	
mean change in UAS7 - w4												
1	randomised trials	not serious	not serious	not serious	serious ¹	none	25	21	-	MD 13 lower (19.42 lower to 6.58 lower)	+++ MODERATE	
mean change in UAS7 - w12												
3	randomised trials	not serious	not serious	not serious	serious ¹	none	412	243	-	MD 11.39 lower (13.38 lower to 9.39 lower)	+++ MODERATE	
mean change in DLQI - w12												
3	randomised trials	not serious	not serious	not serious	not serious	none	372	204	-	MD 4.3 lower (5.57 lower to 3.03 lower)	++++ HIGH	
mean difference CU-Q2oL - w4												
1	randomised trials	not serious	not serious	not serious	not serious	none	44	47	-	MD 20.7 lower (29 lower to 12.5 lower)	++++ HIGH	
mean change in CU-Q2oL - w12												

1	randomised trials	not serious	not serious	not serious	serious ¹	none	252	84	-	MD 13 lower (18.44 lower to 7.56 lower)	⊕⊕⊕⊖ MODERATE	
withdrawal due to AE - w4												
1	randomised trials	not serious	not serious	not serious	not serious	none	0/25 (0.0%)	0/21 (0.0%)	not estimable		⊕⊕⊕⊕ HIGH	
patients with at least 1 AE - w4												
1	randomised trials	not serious	not serious	not serious	serious ²	none	12/25 (48.0%)	10/21 (47.6%)	RR 1.01 (0.55 to 1.85)	5 more per 1.000 (from 214 fewer to 405 more)	⊕⊕⊕⊖ MODERATE	
patients with at least 1 AE - w12												
2	randomised trials	not serious	not serious	not serious	not serious	none	81/123 (65.9%)	82/126 (65.1%)	RR 1.01 (0.84 to 1.20)	7 more per 1.000 (from 104 fewer to 130 more)	⊕⊕⊕⊕ HIGH	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

1. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
2. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Key Question: 15. Is cyclosporine A useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines (third-line treatment of urticaria)?

PICO Question: Is CSA as add-on treatment more effective and safer than placebo or no intervention in patients with CSU unresponsive to H1-AH?

Bibliography: Grattan 2000, Toubi 1997

Quality assessment							Nº of patients		Effect		Quality	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	add-on CSA	no add-on intervention	Relative (95% CI)	Absolute (95% CI)		
complete suppression - w1												
1	randomised trials	serious ¹	not serious	not serious	very serious ^{2,3}	none	13/25 (52.0%)	0/10 (0.0%)	RR 11.42 (0.74 to 175.71)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕○○○ VERY LOW	
complete suppression - w4												
1	randomised trials	serious ¹	not serious	not serious	very serious ^{2,3}	none	10/25 (40.0%)	0/10 (0.0%)	RR 8.88 (0.57 to 138.71)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕○○○ VERY LOW	
complete suppression - w12												
1	randomised trials	serious ¹	not serious	not serious	very serious ^{2,3}	none	13/25 (52.0%)	0/10 (0.0%)	RR 11.42 (0.74 to 175.71)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕○○○ VERY LOW	
good or excellent response - w1-2												
2	randomised trials	serious ¹	not serious	not serious	serious ³	none	30/45 (66.7%)	0/20 (0.0%)	RR 14.11 (2.05 to 97.04)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	
good or excellent response - w4												
1	randomised trials	not serious	not serious	not serious	very serious ^{2,3}	none	8/20 (40.0%)	0/10 (0.0%)	RR 8.90 (0.57 to 140.31)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	
mean change in UAS7 - w4												
1	randomised trials	not serious	not serious	not serious	serious ⁴	none	19	10	-	MD 10.4 lower (18.68 lower to 2.12 lower)	⊕⊕⊕○ MODERATE	
withdrawal due to AE - w4												

1	randomised trials	not serious	not serious	not serious	not serious	none	0/19 (0.0%)	0/10 (0.0%)	not estimable		⊕⊕⊕⊕ HIGH	
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CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

1. unclear method of randomization and allocation concealment; no blinding; > 10% loss to follow-up
2. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
3. wide CI
4. CI crosses MID threshold: statistically significant difference of uncertain clinical importance

Key Question: 16. Are leukotriene antagonists useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines (third-line treatment of urticaria)

PICO Question: Is montelukast as add-on treatment to H1-AH more effective and safer than H1-AH in patients with CSU unresponsive to H1-AH? PART 1 OF 2

Bibliography: Erbagci 2002, Nettis 2004

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	montelukast + H1-AH	placebo + H1-AH	Relative (95% CI)	Absolute (95% CI)		
excellent response - w6												
2	randomised trials	serious ¹	not serious	serious ²	not serious	none	21/48 (43.8%)	4/48 (8.3%)	RR 4.77 (1.95 to 11.66)	314 more per 1.000 (from 79 more to 888 more)	⊕⊕○○ LOW	
patients with at least 1 AE - w6												
1	randomised trials	serious ¹	not serious	serious ²	not serious	none	0/27 (0.0%)	0/27 (0.0%)	not estimable		⊕⊕○○ LOW	
withdrawal due to AE - w6												
1	randomised trials	serious ¹	not serious	not serious	not serious	none	0/21 (0.0%)	0/21 (0.0%)	not estimable		⊕⊕⊕○ MODERATE	

CI: Confidence interval; **RR:** Risk ratio

1. unclear method of randomization and allocation concealment
2. all patients with CSU were included (not only non-responders)

Key Question: 16. Are leukotriene antagonists useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines (third-line treatment of urticaria)

PICO Question: Is montelukast as add-on treatment to H1-AH more effective and safer than placebo in patients with CSU unresponsive to H1-AH? PART 2 OF 2

Bibliography: Di Lorenzo 2004, Wan 2009

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	montelukast + H1-AH	placebo	Relative (95% CI)	Absolute (95% CI)		
mean difference (mean change in TSS) - montelukast 10mg QD + desloratadine 5mg QD vs placebo - w6												
1	randomised trials	serious ¹	not serious	serious ²	not serious	none	40	40	-	MD 1.76 lower (1.87 lower to 1.64 higher)	⊕⊕○○ LOW	
good or excellent response - montelukast 5mg BID + hydroxyzine 25mg BID vs placebo - w4												
1	randomised trials	serious ¹	not serious	serious ²	serious ^{3,4}	none	8/30 (26.7%)	0/30 (0.0%)	RR 17.00 (1.03 to 281.91)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕○○○ VERY LOW	

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

1. unclear method of randomization and allocation concealment

2. all patients with CU were included (not only non-responders to H1-AH)

3. CI crosses MID threshold: statistically significant difference of uncertain clinical importance

4. wide CI

Key question: 19. Could any other treatment options be recommended as third-line treatment in urticaria?

PICO Question: Levocetirizine + NB-UVB compared to levocetirizine for urticaria

Bibliography: Engine 2008b

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	levocetirizine + NB-UVB	levocetirizine	Relative (95% CI)	Absolute (95% CI)		
mean change in UAS7 - levocetirizine 10mg QD + NB-UVB TIWvs levocetirizine 10mg QD - 10 sessions = w3												
1	randomised trials	serious ¹	not serious	not serious	not serious	none	45	33	-	MD 5.49 lower (8.03 lower to 2.95 lower)	 MODERATE	
mean change in UAS7 - levocetirizine 10mg QD + NB-UVB TIWvs levocetirizine 10mg QD - 10 sessions = w7												
1	randomised trials	serious ¹	not serious	not serious	not serious	none	45	33	-	MD 4.02 lower (7.22 lower to 0.82 lower)	 MODERATE	

CI: Confidence interval; **MD:** Mean difference

1. unclear/high risk of bias

Key question: 19. Could any other treatment options be recommended as third-line treatment in urticaria?

PICO Question: Desloratadine + dapsone compared to desloratadine for urticaria

Bibliography: Engin 2008a

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	desloratadine + dapsone	desloratadine	Relative (95% CI)	Absolute (95% CI)		
complete suppression - desloratadine 10mg + dapsone 50mg QD vs desloratadine 10mg QD - w4												
1	randomised trials	serious ¹	not serious	not serious	very serious ^{2,3}	none	4/38 (10.5%)	0/27 (0.0%)	RR 6.46 (0.36 to 115.24)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕○○○ VERY LOW	
mean change in UAS7 - desloratadine 10mg + dapsone 50mg QD vs desloratadine 10mg QD - w4												
1	randomised trials	serious ¹	not serious	not serious	not serious	none	36	26	-	MD 1.23 lower (1.54 lower to 0.92 lower)	⊕⊕⊕○ MODERATE	
withdrawal due to AE - desloratadine 10mg + dapsone 50mg QD vs desloratadine 10mg QD - w4												
1	randomised trials	serious ¹	not serious	not serious	very serious ^{2,3}	none	2/38 (5.3%)	0/27 (0.0%)	RR 3.59 (0.18 to 71.91)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕○○○ VERY LOW	

CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

1. unclear/high risk of bias

2. wide CI

3. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Key question: 19. Could any other treatment options be recommended as third-line treatment in urticaria?
PICO Question: Desloratadine + self-blood acupoint injections compared to desloratadine alone for urticaria

Bibliography: Zhou 2008

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	desloratadine + self-blood acupoint injections	desloratadine alone	Relative (95% CI)	Absolute (95% CI)		
change in mean total symptom score (MTSS) - desloratadine 5mg QD + self-blood acupoint injection vs desloratadine 5m QD - w4												
1	randomised trials	serious ¹	not serious	not serious	not serious	none	93	85	-	MD 5 lower (5.57 lower to 4.43 lower)	⊕⊕⊕○ MODERATE	
withdrawal due to AE - desloratadine 5mg QD + self-blood acupoint injection vs desloratadine 5mg QD - w4												
1	randomised trials	serious ¹	not serious	not serious	not serious	none	0/93 (0.0%)	0/85 (0.0%)	not estimable		⊕⊕⊕○ MODERATE	
patients with at least 1 AE - desloratadine 5mg QD + self-blood acupoint injection vs desloratadine 5mg QD - w4												
1	randomised trials	serious ¹	not serious	not serious	serious ²	none	13/93 (14.0%)	8/85 (9.4%)	RR 1.49 (0.65 to 3.41)	46 more per 1.000 (from 33 fewer to 227 more)	⊕⊕○○ LOW	

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

1. unclear risk of bias
2. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Key question: 19. Could any other treatment options be recommended as third-line treatment in urticaria?

PICO Question: Mizolastine + NB-UVB compared to minolastine alone for urticaria

Bibliography: Zuo 2011

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	mizolastine + NB-UVB	minolastine alone	Relative (95% CI)	Absolute (95% CI)		
change in mean total symptom score (MTSS) - mizolastine 10mg QD + NB-UVB TIWvs mizolastine 10mg QD - w4												
1	randomised trials	serious ¹	not serious	not serious	not serious	none	42	39	-	MD 3.46 lower (4.14 lower to 2.78 lower)	⊕⊕⊕⊖ MODERATE	
change in mean total symptom score (MTSS) - mizolastine 10mg QD + NB-UVB TIWvs mizolastine 10mg QD - w8												
1	randomised trials	serious ¹	not serious	not serious	not serious	none	42	39	-	MD 3.73 lower (4.23 lower to 3.23 lower)	⊕⊕⊕⊖ MODERATE	
withdrawal due to AE - mizolastine 10mg QD + NB-UVB TIWvs mizolastine 10mg QD - w8												
1	randomised trials	serious ¹	not serious	not serious	not serious	none	0/39 (0.0%)	0/42 (0.0%)	not estimable		⊕⊕⊕⊖ MODERATE	

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

1. unclear risk of bias

Key question: 19. Could any other treatment options be recommended as third-line treatment in urticaria?

PICO Question: Is desloratadine more effective and safer than montelukast in patients with CSU?

Bibliography: Di Lorenzo 2004

Quality assessment							Nº of patients		Effect		Quality	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	desloratadine	montelukast	Relative (95% CI)	Absolute (95% CI)		
mean difference (mean change in TSS) - w6												
1	randomised trials	serious ¹	not serious	not serious	not serious	none	40	40	-	MD 1.66 points lower (1.28 lower to 1.05 lower)	⊕⊕⊕⊖ MODERATE	

CI: Confidence interval; **MD:** Mean difference

1. unclear method of randomization and allocation concealment

Key question: 19. Could any other treatment options be recommended as third-line treatment in urticaria?
PICO Question: Is montelukast more effective and safer than montelukast plus desloratadine in patients with CSU?

Bibliography: Di Lorenzo 2004

Quality assessment							Nº of patients		Effect		Quality	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	placebo + montelukast 10mg QD	desloratadine 5mg QD + montelukast 10mg QD	Relative (95% CI)	Absolute (95% CI)		
mean difference (mean change in TSS)												
1	randomised trials	serious ¹	not serious	not serious	not serious	none	40	40	-	MD 1.14 points higher (1.03 higher to 1.26 higher)	⊕⊕⊕○ MODERATE	

CI: Confidence interval; **MD:** Mean difference

1. unclear method of randomization and allocation concealment

Key question: 19. Could any other treatment options be recommended as third-line treatment in urticaria?

PICO Question: Is hydroxychloroquine as add-on treatment to H1-AH more effective and safer than placebo in patients with CSU unresponsive to H1-AH?

Bibliography: Boonpiyathad 2013

Quality assessment							N _o of patients		Effect		Quality	Importance
N _o of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydroxychloroquine + H1-AH	placebo + H1-AH	Relative (95% CI)	Absolute (95% CI)		
mean change in USS (w12)												
1	randomised trials	very serious ¹	not serious	not serious	not serious	none	19	20	-	MD 24.57 lower (33.85 lower to 15.29 lower)	⊕⊕○○ LOW	
mean change in DLQI (w12)												
1	randomised trials	very serious ¹	not serious	not serious	serious ²	none	19	20	-	MD 5.83 lower (9.31 lower to 2.35 lower)	⊕○○○ VERY LOW	

CI: Confidence interval; **MD:** Mean difference

1. unclear risk of bias (abstract only)

2. CI crosses MID threshold: statistically significant difference of uncertain clinical importance

Key question: 19. Could any other treatment options be recommended as third-line treatment in urticaria?
PICO Question: Is dapstone as add-on to existing treatment more effective and safer than placebo in patients with CSU?

Bibliography: Morgan 2014

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	dapsone 100mg QD + existing therapy	placebo QD + existing therapy	Relative (95% CI)	Absolute (95% CI)		
complete suppression (w6)												
1	randomised trials	not serious	not serious	not serious	very serious ^{1,2}	none	3/10 (30.0%)	0/12 (0.0%)	RR 8.27 (0.48 to 143.35)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	
withdrawal due to AE (w6)												
1	randomised trials	not serious	not serious	not serious	not serious	none	0/10 (0.0%)	0/12 (0.0%)	not estimable		⊕⊕⊕⊕ HIGH	
patients with at least 1 AE (w6)												
1	randomised trials	not serious	not serious	not serious	serious ¹	none	4/10 (40.0%)	3/11 (27.3%)	RR 1.47 (0.43 to 5.01)	128 more per 1.000 (from 155 fewer to 1.000 more)	⊕⊕⊕○ MODERATE	

CI: Confidence interval; **RR:** Risk ratio

1. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
2. wide CI

Key question: 19. Could any other treatment options be recommended as third-line treatment in urticaria?
PICO Question: Is NB-UVB more effective and safer than PUVA in patients with CSU?

Bibliography: Khafagy 2013

Quality assessment							N _e of patients		Effect		Quality	Importance
N _e of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	NB-UVB	PUVA	Relative (95% CI)	Absolute (95% CI)		
mean change in TSS - w3												
1	randomised trials	serious ¹	not serious	not serious	serious ²	none	12	12	-	MD 0.75 points lower (5.09 lower to 3.59 higher)	⊕⊕○○ LOW	
withdrawal due to AE - w3												
1	randomised trials	serious ¹	not serious	not serious	not serious	none	0/12 (0.0%)	0/12 (0.0%)	not estimable		⊕⊕⊕○ MODERATE	
patients with at least 1 AE - w3												
1	randomised trials	serious ¹	not serious	not serious	serious ²	none	8/12 (66.7%)	3/12 (25.0%)	RR 2.67 (0.93 to 7.69)	418 more per 1.000 (from 17 fewer to 1.000 more)	⊕⊕○○ LOW	

CI: Confidence interval; **MD:** Mean difference; **RR:** Risk ratio

1. unclear/high risk of bias
2. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Key question: 19. Could any other treatment options be recommended as third-line treatment in urticaria?
PICO Question: Are autologous whole blood injections more effective and safer than placebo in patients with CSU?

Bibliography: Staubach 2006

Quality assessment							N _e of patients		Effect		Quality	Importance
N _e of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	AWB injection	placebo	Relative (95% CI)	Absolute (95% CI)		
good or excellent response - w12												
1	randomised trials	not serious	not serious	not serious	serious ¹	none	9/28 (32.1%)	14/28 (50.0%)	RR 0.64 (0.33 to 1.24)	180 fewer per 1.000 (from 120 more to 335 fewer)	 MODERATE	

CI: Confidence interval; **RR:** Risk ratio

1. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Key Question: 20. Should the same treatment algorithm be used in all subtypes of chronic urticaria?
Question: Is hydroxyzine more effective and safer than doxepine in patients with cold urticaria?

Bibliography: Neittaanmäki 1984

Quality assessment							N ₂ of patients		Effect		Quality	Importance
N ₂ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydroxyzine	doxepine	Relative (95% CI)	Absolute (95% CI)		
very effective												
1	randomised trials	serious ¹	not serious	not serious	very serious ^{2,3}	none	2/12 (16.7%)	6/12 (50.0%)	RR 0.33 (0.08 to 1.33)	335 fewer per 1.000 (from 165 more to 460 fewer)	⊕○○○ VERY LOW	

CI: Confidence interval; **RR:** Risk ratio

1. unclear risk of bias
2. wide CI
3. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Key Question: 20. Should the same treatment algorithm be used in all subtypes of chronic urticaria?
PICO Question: Is hydroxyzine more effective and safer than placebo in patients with cold urticaria?

Bibliography: Neittaanmäki 1984

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	hydroxyzine	placebo	Relative (95% CI)	Absolute (95% CI)		
very effective												
1	randomised trials	serious ¹	not serious	not serious	very serious ^{2,3}	none	2/12 (16.7%)	0/12 (0.0%)	RR 5.00 (0.27 to 94.34)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	 VERY LOW	

CI: Confidence interval; **RR:** Risk ratio

1. unclear risk of bias
2. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
3. wide CI

Key Question: 20. Should the same treatment algorithm be used in all subtypes of chronic urticaria?
PICO Question: Is doxepine more effective and safer than placebo in patients with cold urticaria?

Bibliography: Neittaanmäki 1984, Neittaanmäki 1984

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	doxepine	placebo	Relative (95% CI)	Absolute (95% CI)		
very effective(1w)												
2	randomised trials	serious ¹	not serious	not serious	serious ²	none	14/22 (63.6%)	0/22 (0.0%)	RR 14.90 (2.13 to 104.08)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	 LOW	

CI: Confidence interval; **RR:** Risk ratio

1. unclear risk of bias
2. wide CI

Key Question: 20. Should the same treatment algorithm be used in all subtypes of chronic urticaria?

PICO Question: Are 2nd gen H1-AH more effective and safer than 1st gen H1-AH in patients with cold urticaria?

Bibliography: Villas Martinez 1992

Quality assessment							Nº of patients		Effect		Quality	Importance
Nº of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2nd gen H1-AH	1st gen H1-AH	Relative (95% CI)	Absolute (95% CI)		
symptom free (2w)												
1	randomised trials	serious ¹	serious ²	not serious	serious ³	none	8/14 (57.1%)	4/6 (66.7%)	RR 0.86 (0.30 to 2.49)	93 fewer per 1.000 (from 467 fewer to 993 more)	⊕○○○ VERY LOW	
patients with at least one AE (time unclear)												
1	randomised trials	serious ¹	not serious	not serious	very serious ⁴	none	3/14 (21.4%)	3/5 (60.0%)	RR 0.37 (0.10 to 1.39)	378 fewer per 1.000 (from 234 more to 540 fewer)	⊕○○○ VERY LOW	
drowsiness (time unclear)												
1	randomised trials	serious ¹	not serious	not serious	very serious ^{3,4}	none	2/14 (14.3%)	3/5 (60.0%)	RR 0.32 (0.06 to 1.80)	408 fewer per 1.000 (from 480 more to 564 fewer)	⊕○○○ VERY LOW	

CI: Confidence interval; **RR:** Risk ratio

1. unclear risk of bias

2. statistical heterogeneity ($I^2 = 40\%$) maybe due to methodological differences

3. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

4. wide CI

Key Question: 20. Should the same treatment algorithm be used in all subtypes of chronic urticaria?

PICO Question: Are 2nd gen H1-AH (high dose) more effective and safer than 2nd gen H1-AH (low dose) in patients with cold urticaria?

Bibliography: Krause 2013, Magerl 2012, Kaplan 2010/Siebenhaar 2009, Abajian 2016

Quality assessment							N _e of patients		Effect		Quality	Importance
N _e of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2nd gen H1-AH (high dose)	2nd gen H1-AH (low dose)	Relative (95% CI)	Absolute (95% CI)		
symptom free - 2nd gen AH 2-fold vs. 1-fold (1w)												
1	randomised trials	serious ¹	not serious	not serious	serious ²	none	11/20 (55.0%)	7/20 (35.0%)	RR 1.57 (0.77 to 3.22)	200 more per 1.000 (from 80 fewer to 777 more)	⊕⊕○○ LOW	
symptom free - 2nd gen AH 1 to 2-fold increase vs. 1-fold (4w)												
1	randomised trials	not serious	not serious	not serious	very serious ^{2,3}	none	2/15 (13.3%)	0/12 (0.0%)	RR 4.06 (0.21 to 77.37)	0 fewer per 1.000 (from 0 fewer to 0 fewer)	⊕⊕○○ LOW	
symptom free - 2nd gen AH 4-fold vs. 1-fold (1w)												
2	randomised trials	serious ¹	not serious	not serious	serious ⁴	none	27/50 (54.0%)	14/50 (28.0%)	RR 1.90 (1.15 to 3.16)	252 more per 1.000 (from 42 more to 605 more)	⊕⊕○○ LOW	
symptom free - 2nd gen AH 4-fold vs. 2-fold (1w)												
2	randomised trials	serious ¹	not serious	not serious	serious ⁴	none	23/42 (54.8%)	20/43 (46.5%)	RR 1.16 (0.77 to 1.76)	74 more per 1.000 (from 107 fewer to 353 more)	⊕⊕○○ LOW	
withdrawal due to AE - 2nd gen AH 1 to 4-fold increase vs. 2-fold (6w)												
1	randomised trials	not serious	not serious	not serious	not serious	none	0/15 (0.0%)	0/13 (0.0%)	not estimable		⊕⊕⊕⊕ HIGH	
patients with at least 1 AE - 2nd gen AH 2-fold vs. 1-fold (w1)												

1	randomised trials	serious ¹	not serious	not serious	serious ²	none	7/20 (35.0%)	5/20 (25.0%)	RR 1.40 (0.53 to 3.68)	100 more per 1.000 (from 118 fewer to 670 more)	 LOW	
patients with at least 1 AE - 2nd gen AH 4-fold vs. 1-fold (1w)												
1	randomised trials	serious ¹	not serious	not serious	serious ²	none	4/20 (20.0%)	5/20 (25.0%)	RR 0.80 (0.25 to 2.55)	50 fewer per 1.000 (from 188 fewer to 387 more)	 LOW	
patients with at least 1 AE - 2nd gen AH 4-fold vs. 2-fold (1w)												
2	randomised trials	serious ¹	not serious	not serious	serious ²	none	15/43 (34.9%)	14/43 (32.6%)	RR 1.02 (0.38 to 2.73)	7 more per 1.000 (from 202 fewer to 563 more)	 LOW	

CI: Confidence interval; **RR:** Risk ratio

1. unclear risk of bias
2. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
3. wide CI
4. CI crosses MID threshold: statistically significant difference of uncertain clinical importance

Key Question: 20. Should the same treatment algorithm be used in all subtypes of chronic urticaria?

PICO Question: Are 2nd gen H1-AH 1-4 fold more effective and safer than placebo in patients with cold urticaria?

Bibliography: Krause 2013, Dubertret 2003, Kaplan 2010/Siebenhaar 2009, Metz 2010, Abajian 2016

Quality assessment							№ of patients		Effect		Quality	Importance
№ of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	2nd gen H1-AH 1-4 fold	placebo	Relative (95% CI)	Absolute (95% CI)		
symptom free												
4	randomised trials	serious ¹	not serious	not serious	not serious	none	72/169 (42.6%)	6/99 (6.1%)	RR 4.33 (2.11 to 8.85)	202 more per 1.000 (from 67 more to 476 more)	⊕⊕⊕○ MODERATE	
withdrawal due to AE												
2	randomised trials	serious ¹	not serious	not serious	not serious	none	0/48 (0.0%)	0/48 (0.0%)	not pooled	see comment	⊕⊕⊕○ MODERATE	
patients with at least 1AE												
3	randomised trials	serious ¹	not serious	not serious	serious ²	none	41/131 (31.3%)	11/68 (16.2%)	RR 1.63 (0.92 to 2.89)	102 more per 1.000 (from 13 fewer to 306 more)	⊕⊕○○ LOW	

CI: Confidence interval; **RR:** Risk ratio

1. unclear risk of bias

2. "CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Key Question: 21. Should the same treatment algorithm be used in children?
PICO Question: Which evidence is available for the treatment of children with CSU?

Bibliography: Potter 2016

Quality assessment							N _e of patients		Effect		Quality	Importance
N _e of studies	Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	included treatment	included treatment/placebo	Relative (95% CI)	Absolute (95% CI)		
good or excellent response (by patient) - rupatadine 2.5/5mg QD vs placebo (w6)												
1	randomised trials	serious ¹	not serious	not serious	not serious	none	25/66 (37.9%)	11/69 (15.9%)	RR 2.38 (1.27 to 4.43)	220 more per 1.000 (from 43 more to 547 more)	⊕⊕⊕○ MODERATE	
good or excellent response (by patient) - desloratadine 0.5mg/ml QD vs placebo (w6)												
1	randomised trials	serious ¹	not serious	not serious	serious ²	none	23/71 (32.4%)	11/69 (15.9%)	RR 2.03 (1.07 to 3.84)	164 more per 1.000 (from 11 more to 453 more)	⊕⊕○○ LOW	
mean change in C-DLQI - desloratadine 0.5mg QD vs placebo (w6)												
1	randomised trials	serious ¹	not serious	not serious	serious ²	none	69	67	-	MD 2.9 lower (4.62 lower to 1.18 lower)	⊕⊕○○ LOW	
mean change in C-DLQI - rupatadine 2.5/5mg QD vs placebo (w6)												
1	randomised trials	serious ¹	not serious	not serious	serious ²	none	63	67	-	MD 3.6 lower (5.49 lower to 1.71 lower)	⊕⊕○○ LOW	
patients with at least 1 AE - rupatadine 2.5/5mg QD vs placebo (w6)												
1	randomised trials	serious ¹	not serious	not serious	serious ³	none	40/63 (63.5%)	37/67 (55.2%)	RR 1.15 (0.86 to 1.53)	83 more per 1.000 (from 77 fewer to 293 more)	⊕⊕○○ LOW	
patients with at least 1 AE - desloratadine 0.5mg/ml QD vs placebo (w6)												

1	randomised trials	serious ¹	not serious	not serious	serious ³	none	46/69 (66.7%)	37/67 (55.2%)	RR 1.21 (0.92 to 1.59)	116 more per 1.000 (from 44 fewer to 326 more)	⊕⊕○○ LOW	
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CI: Confidence interval; **RR:** Risk ratio; **MD:** Mean difference

1. unclear method of randomization and allocation concealment
2. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
3. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

CONFLICT OF INTEREST DECLARATION (WHO)		1. EMPLOYMENT AND CONSULTING			2. RESEARCH SUPPORT				3. INVESTMENT INTERESTS			4. INTELLECTUAL PROPERTY		
		Within the past 4 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of this guideline work?			Within the past 4 years, have you or has your research unit received support from a commercial entity or other organization with an interest related to the subject of this guideline work?				Do you have current investments (valued at more than US \$10 000 overall) in a commercial entity with an interest related to the subject of this guideline work? Please also include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds or similar investments that are broadly diversified and on which you exercise no control.			Do you have any intellectual property rights that might be enhanced or diminished by the outcome of this guideline work?		
LAST NAME	FIRST NAME	Employment	Consulting	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased	a) Research support, including grants, collaborations, sponsorships, and other funding	b) Non-monetary support valued at more than US \$1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc.)	c) Support (including honoraria) for being on a speakers bureau, giving speeches or training for a commercial entity or other organization with an interest related to the subject of this guideline work?	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	a) Stocks, bonds, stock options, other securities (e.g., short sales)	b) Commercial business interests (e.g., proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company)	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	a) Patents, trademarks, or copyrights (including pending applications)	b) Proprietary know-how in a substance, technology or process	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.
Alexander	Kapp	no	no		no	no	no		yes	no	Novartis Aktien	no	no	
Asero	Riccardo	no	no		no	no	no		no	no		no	no	
Maurer	Marcus	no	yes	b 1) Advisor / Speaker, 2) Uriach, 3) me, 4)	yes	yes	no	yes) research support, 2) Uriach, 3) Charité, 4)	no	yes	1) Ownership of company, 2) MOXIE (Products: AAS, UCT, AE-QoL, FricTest), 3) wife, 4)	no	no	
Sanchez-Borges	Mario	no	no		no	no	yes	Speaker fees from Novartis.	no	no		no	no	
ENSINA	LUIS FELIPE	no	no		yes	no	yes	a) I've participated as principal investigator in clinical research projects sponsored from Novartis (currently involved in one) with annual incomes under US\$10.000c) I've participated in Advisory Boards and as a speaker of Novartis, and also as a speaker of Takeda and Sanofi. I'm currently a speaker of Novartis and Takeda, with an annual incomes under US\$10.000,00 from each one.	no	no		no	no	
Metz	Martin	no	no		no	no	yes	c) (1) honoraria for lectures, (2) Bayer Pharma; Dr. R. Pflieger; Moxie; Novartis; UCB, (3) to me, (4) ~1200€ per lecture, ~1 lecture/month, (5) only honorarium for lectures given	no	no		no	no	
Aberer	Werner	no	yes	1 advisory board 2 Novartis3 myself4 not your Business; but if you ask me ...5 2015, 2016	no	no	yes	c) 1Speakers bureau2 Novartis3 myself4 again, like above5 2015,2016	no	no		no	no	
Vestergaard	Christian	no	yes	b, I served on an advisory board for Novartis on omlizumab and it use. this ceased in 2015.	no	no	yes	c) Speaker for Novartis, abbvie, and GSK.	no	no		no	no	

		5. PUBLIC STATEMENTS AND POSITIONS (during the past 3 years)			6. ADDITIONAL INFORMATION						7. TOBACCO OR TOBACCO PRODUCTS (answer without regard to relevance to the subject of this guideline work)		8. DECLARATION
		a) As part of a regulatory, legislative or judicial process, have you provided an expert opinion or testimony, related to the subject of this guideline work, for a commercial entity or other organization?	b) Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of this guideline work?	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	a) If not already disclosed above, have you worked for the competitor of a product that is the subject of this guideline work?	b) If not yet disclosed, will your participation in this guideline work enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial or business competitive advantage?	c) To your knowledge, would the outcome of this guideline work benefit or adversely affect interests of others with whom you have substantial common personal interests (such as your adult children or siblings)?	d) To your knowledge, would the outcome of this guideline work benefit or adversely affect interests of others with whom you have substantial common professional, financial or business interests (such as your close colleagues or department)?	e) Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence?	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	a) Within the past 4 years, have you had employment or received research support or other funding from, or had any other professional relationship with, an entity directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity?	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	
Alexander	Kapp	no	no		no	no	no	no	no		no		AK
Asero	Riccardo	no	no		no	no	no	no	no		no		RA
Maurer	Marcus	no	no		no	no	no	no	no		no		MM
Sanchez-Borges	Mario	no	no		no	no	no	no	no		no		MSB
ENSINA	LUIS FELIPE	no	no		no	no	no	no	no		no		LFE
Metz	Martin	no	no		no	no	no	no	no		no		mm
Aberer	Werner	no	no		no	no	no	no	no		no		WA
Vestergaard	Christian	no	no		no	no	no	no	no		no		CV

CONFLICT OF INTEREST DECLARATION (WHO)		1. EMPLOYMENT AND CONSULTING			2. RESEARCH SUPPORT				3. INVESTMENT INTERESTS			4. INTELLECTUAL PROPERTY		
		Within the past 4 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of this guideline work?			Within the past 4 years, have you or has your research unit received support from a commercial entity or other organization with an interest related to the subject of this guideline work?				Do you have current investments (valued at more than US \$10 000 overall) in a commercial entity with an interest related to the subject of this guideline work? Please also include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds or similar investments that are broadly diversified and on which you exercise no control.			Do you have any intellectual property rights that might be enhanced or diminished by the outcome of this guideline work?		
LAST NAME	FIRST NAME	Employment	Consulting	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased	a) Research support, including grants, collaborations, sponsorships, and other funding	b) Non-monetary support valued at more than US \$1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc.)	c) Support (including honoraria) for being on a speakers bureau, giving speeches or training for a commercial entity or other organization with an interest related to the subject of this guideline work?	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	a) Stocks, bonds, stock options, other securities (e.g., short sales)	b) Commercial business interests (e.g., proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company)	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	a) Patents, trademarks, or copyrights (including pending applications)	b) Proprietary know-how in a substance, technology or process	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.
Wedi	Bettina	no	yes	Category b) advisory board honorary, company: Novartis GmbH, belongs to me, last three years (for 1 or 2 advisory board meetings per year)	yes	no	yes	Category a) research grant, company: Novartis GmbH, belongs to The research unit, year 2014. Category c) honorary for speeches and trainings, current interest	no	no		no	no	
Abdul Latif	Amir Hamzah	no	no		no	no	no		no	no		no	no	
Brzoza	Zenon	no	no		no	no	no		no	no		no	no	
Vena	Gino	no	no		no	no	yes	Within the last 4 yrs, I have been a speaker for Novartis with a total honorarium of 2,000 Euros. I have no conflict of interest of any type during the current year.	no	no		no	no	
GODSE	KIRAN	no	no		yes	no	yes	ADVISORY BOARD NOVARTIS , SUN PHARMA , SANOFI AVENTIS	no	no		no	no	
Katellaris	Constance	yes	yes	Advisory Board member and Chair Novartis Omalizumab Board -paid for professional services approx \$2,000 - 2015	yes	no	yes	a) my institution is a site for a study in chronic urticaria sponsored by Sanofi - no monies paid personally but to institution to run the trial.	no	no		no	no	
Leslie	Tabi	no	yes	(b) Novartis, speaker and research involvement unpaid. Engagement with Novartis without payment.	yes	yes	yes	(a, b and c) Research funding paid to my assistant, but not myself. Engagements on training programme by Novartis, advisory and lectures. Unpaid but events funded by Novartis.	no	no		no	no	
Gonçalo	Margarida	no	yes	Novartis. During 2014-16, participation in 3 meetings of advisory boards on the use of omalizumab in CSU and in educational activities on urticaria. Amount received in total approximately 5,000,00 euros.	yes	no	no	Novartis paid a 1500,00 euros grant to the department for validation of the UCT and AAS7 in Portuguese.	no	no		no	no	
Meshkova	Raisa	no	no		no	yes	no	paid travel to meetings, Novartis	no	no		no	no	

continued

		5. PUBLIC STATEMENTS AND POSITIONS (during the past 3 years)			6. ADDITIONAL INFORMATION							7. TOBACCO OR TOBACCO PRODUCTS (answer without regard to relevance to the subject of this guideline work)		8. DECLARATION	
		a) As part of a regulatory, legislative or judicial process, have you provided an expert opinion or testimony, related to the subject of this guideline work, for a commercial entity or other organization?	b) Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of this guideline work?	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	a) If not already disclosed above, have you worked for the competitor of a product that is the subject of this guideline work?	b) If not yet disclosed, will your participation in this guideline work enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial or business competitive advantage?	c) To your knowledge, would the outcome of this guideline work benefit or adversely affect interests of others with whom you have substantial common personal interests (such as your adult children or siblings)?	d) To your knowledge, would the outcome of this guideline work benefit or adversely affect interests of others with whom you have substantial common professional, financial or business interests (such as your close colleagues or department)?	e) Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence?	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	a) Within the past 4 years, have you had employment or received research support or other funding from, or had any other professional relationship with, an entity directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity?	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	I hereby declare on my honour that the disclosed information is true and complete to the best of my knowledge. Should there be any change to the above information, I will promptly notify the responsible guideline project staff and complete a new declaration of interest form that describes the changes. This includes any change that occurs before or during the guideline work itself and through the period up to the publication of the final results or completion of the activity concerned. INITIALS		
										E) principle investigator in company sponsored clinical trials (rdhpc) company Novartis Pharma GmbH, last three years and ongoing					
Wedi	Bettina	no	no		no	no	no	no	yes		no		BW		
Abdul Latiff	Amir Hamzah	no	no		no	no	no	no	no		no		AHAL		
Brzoza	Zenon	no	no		no	no	no	no	no		no		ZB		
Vena	Gino	no	no		no	no	no	no	no		no		GAV		
GODSE	KIRAN	no	no		no	no	no	no	no		no		KG		
Katellaris	Constance	yes	yes	I am the Chair of the urticaria guideline working party of the Australasian Society of Clinical Immunology and Allergy. I am an author of the urticaria Guideline (ASCA)	no	no	no	no	no		no		CHK		
Leslie	Tabi	yes	yes	Multiple lectures and representations regarding the guidelines. No financial interest with Novartis	no	no	no	no	no		no		TAL		
Gonçalo	Margarida	no	no		no	no	no	no	no		no		MG		
Meshkova	Raisa	no	no		no	no	no	no	no		no		R.Y.M.		

CONFLICT OF INTEREST DECLARATION (WHO)		1. EMPLOYMENT AND CONSULTING			2. RESEARCH SUPPORT				3. INVESTMENT INTERESTS			4. INTELLECTUAL PROPERTY	
		Within the past 4 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of this guideline work?			Within the past 4 years, have you or has your research unit received support from a commercial entity or other organization with an interest related to the subject of this guideline work?				Do you have current investments (valued at more than US \$10 000 overall) in a commercial entity with an interest related to the subject of this guideline work? Please also include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds or similar investments that are broadly diversified and on which you exercise no control.			Do you have any intellectual property rights that might be enhanced or diminished by the outcome of this guideline work?	
LAST NAME	FIRST NAME	Employment	Consulting	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased	a) Research support, including grants, collaborations, sponsorships, and other funding	b) Non-monetary support valued at more than US \$1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc.)	c) Support (including honoraria) for being on a speakers bureau, giving speeches or training for a commercial entity or other organization with an interest related to the subject of this guideline work?	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	a) Stocks, bonds, stock options, other securities (e.g., short sales)	b) Commercial business interests (e.g., proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company)	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	a) Patents, trademarks, or copyrights (including pending applications)	b) Proprietary know-how in a substance, technology or process
Magerl	Markus	no	yes	Advisory boards for Novartis, approx. 2000€ per year, personally, ongoing.	no	no	yes	Lectures, supported by Novartis, personally, approx 4000€ per year, ongoing	no	no		no	no
Giménez-Arnau	Ana M	no	yes	Medical Advisor for Uriach Pharma, Genentech, Novartis, FAES, GSK	yes	yes	yes	Clinical trials and Research grant for observational studies and basic research studies Uriach Pharma, Novartis, Intendis Medical Advisor for Uriach Pharma, Genentech, Novartis, FAES, GSKResearch Grants supported by Uriach Pharma, NovartisEducational activities sponsored by Uriach Pharma, Novartis, Genentech, Menarini, LEO- PHARMA , GSK, MSD, Almirall	no	no		no	no
Hide	Michihiro	no	yes	1. b)(1) Advisory fee, lecture honorarium, (2) TAIHO Pharmaceutical Co., (3) the interest belongs to myself, (4) approximately 10,000 US dollars, (5) Sum of current interest and the year it was ceased.2. b) (1) Advisory fee, lecture honorarium, (2) Uriach and Teikoku Seiyaku, (3) the interest belongs to myself, (4) approximately 60,000 US dollars, (5) Sum of current interest and the year it was ceased.3. b)(1) Advisory fee, lecture honorarium, (2)MSD, (3) the interest belongs to myself, (4) approximately 60,000 US dollars, (5) Sum of current interest and the year it was ceased.4. b)(1) Advisory fee, lecture honorarium, (2)Novartis, (3) the interest belongs to myself, (4) approximately 80,000 US dollars, (5) Sum of current interest and the year it was ceased.	yes	no	yes	1. a.c)(1) lecture honorarium and grant, (2) Mitsubishi Tanabe Pharma Co., (3) the interest belongs to myself, (4) approximately 60,000 US dollars, (5) Sum of current interest and the year it was ceased.2. a.c)(1) lecture honorarium and grant, (2) Kyowahakko-Kirin Co., (3) the interest belongs to myself, (4) approximately 28,000 US dollars, (5) Sum of current interest and the year it was ceased.3. b)(1) lecture honorarium and sponsorship, (2) Shionogi Seiyaku Co., (3) the interest belongs to myself, (4) approximately 4,000 US dollars, (5) Sum of current interest and the year it was ceased.4. a.b)(1) lecture honorarium, (2) TAIHO Pharmaceutical Co., (3) the interest belongs to myself, (4) approximately 9,000 US dollars, (5) a current interest.5. b)(1) lecture honorarium, (2) Kaken Pharmaceutical Co., (3) the interest belongs to myself, (4) approximately 4,000 US dollars, (5) a current interest.6. b)(1) lecture honorarium, (2) Sanofi, (3) the interest belongs to myself, (4) approximately 3,000 US dollars, (5) a current interest.7. b)(1) lecture honorarium, (2) GSK, (3) the interest belongs to myself, (4) approximately 4,000 US dollars, (5) the year it was ceased	no	no		no	yes
													1. b)(1) Reward of providing a patent, 2) Shionogi Seiyaku Co, (3) the interest belongs to myself, (4) approximately 2,000 US dollars, (5) Sum of current interest and the year it was ceased.

		5. PUBLIC STATEMENTS AND POSITIONS (during the past 3 years)			6. ADDITIONAL INFORMATION						7. TOBACCO OR TOBACCO PRODUCTS (answer without regard to relevance to the subject of this guideline work)		8. DECLARATION
		a) As part of a regulatory, legislative or judicial process, have you provided an expert opinion or testimony, related to the subject of this guideline work, for a commercial entity or other organization?	b) Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of this guideline work?	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	a) If not already disclosed above, have you worked for the competitor of a product that is the subject of this guideline work?	b) If not yet disclosed, will your participation in this guideline work enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial or business competitive advantage?	c) To your knowledge, would the outcome of this guideline work benefit or adversely affect interests of others with whom you have substantial common personal interests (such as your adult children or siblings)?	d) To your knowledge, would the outcome of this guideline work benefit or adversely affect interests of others with whom you have substantial common professional, financial or business interests (such as your close colleagues or department)?	e) Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence?	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	a) Within the past 4 years, have you had employment or received research support or other funding from, or had any other professional relationship with, an entity directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity?	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	I hereby declare on my honour that the disclosed information is true and complete to the best of my knowledge. Should there be any change to the above information, I will promptly notify the responsible guideline project staff and complete a new declaration of interest form that describes the changes. This includes any change that occurs before or during the guideline work itself and through the period up to the publication of the final results or completion of the activity concerned. INITIALS
Magerl	Markus	no	no		no	no	no	no	no		no		MM
Giménez-Arnau	Ana M	yes	no	Expert opinion for regulation of a drug , URIACH PHARMA and FAES	no	no	no	no	no		no		AGA , Ana Giménez-Arnau
Hide	Michihiro	no	no		no	no	no	no	no		no		MH

CONFLICT OF INTEREST DECLARATION (WHO)		1. EMPLOYMENT AND CONSULTING			2. RESEARCH SUPPORT			3. INVESTMENT INTERESTS			4. INTELLECTUAL PROPERTY		
		Within the past 4 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of this guideline work?			Within the past 4 years, have you or has your research unit received support from a commercial entity or other organization with an interest related to the subject of this guideline work?			Do you have current investments (valued at more than US \$10 000 overall) in a commercial entity with an interest related to the subject of this guideline work? Please also include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds or similar investments that are broadly diversified and on which you exercise no control.			Do you have any intellectual property rights that might be enhanced or diminished by the outcome of this guideline work?		
LAST NAME	FIRST NAME	Employment	Consulting					a) Stocks, bonds, stock options, other securities (e.g., short sales)	b) Commercial business interests (e.g., proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company)		a) Patents, trademarks, or copyrights (including pending applications)	b) Proprietary know-how in a substance, technology or process	
Kocatürk	Emek	no	yes	I (myself) got consultancy fees from Novartis one week ago. 1200 USD per advisory board.	yes	no	yes	no	no		no	no	
Zhao	Zuotao	no	no		no	no	no	no	no		no	no	
Bindslev-Jensen	Carsten	no	no		yes	no	yes	no	no		no	no	
bedrikow	roberta buense	no	yes	b) Guest speaker, participate in events and advisory board: Novartis - It's a current interest and belong to me.	no	yes	yes	no	no		no	no	
Zuberbier	Torsten	no	yes	see separete sheet provided	no	no	no	no	no		no	no	
Bernstein	Jonathan	no	yes	I have been a consultant for Novartis and Genentech	yes	yes	yes	no	no		no	no	
Schmid-Grendelmeier	Peter	no	no		yes	no	yes	no	no		no	no	
Ballmer-Weber	Barbara	no	yes	Honoraria for talks and advisory boards by Novartis	no	no	no	no	no		no	no	
Toubi	Elias	no	yes	I served as consultant to Novartis	no	no	yes	no	no		no	no	
Saini	Sarbjit	no	yes	Consultant to Genentech, < \$5,000 Consultant to Medimmune< \$5,000, active Consultant to Novartis< \$5,000, active Consultant to Ono< \$5,000, active Consultant to Regeneron< \$5,000, active Consultant to Teva< \$5,000, active Consultant to Astra Zeneca < \$5,000, active	yes	no	no	1-Research Grant- Astra-Zeneca> \$100,000, current 2- Research Grant-Novartis> \$100,000, current	no	no	no	no	

5. PUBLIC STATEMENTS AND POSITIONS (during the past 3 years)				6. ADDITIONAL INFORMATION						7. TOBACCO OR TOBACCO PRODUCTS (answer without regard to relevance to the subject of this guideline work)		8. DECLARATION
a) As part of a regulatory, legislative or judicial process, have you provided an expert opinion or testimony, related to the subject of this guideline work, for a commercial entity or other organization?	b) Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of this guideline work?	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	a) If not already disclosed above, have you worked for the competitor of a product that is the subject of this guideline work?	b) If not yet disclosed, will your participation in this guideline work enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial or business competitive advantage?	c) To your knowledge, would the outcome of this guideline work benefit or adversely affect interests of others with whom you have substantial common personal interests (such as your adult children or siblings)?	d) To your knowledge, would the outcome of this guideline work benefit or adversely affect interests of others with whom you have substantial common professional, financial or business interests (such as your close colleagues or department)?	e) Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence?	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	a) Within the past 4 years, have you had employment or received research support or other funding from, or had any other professional relationship with, an entity directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity?	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	INITIALS	
Kocatürk	Emek	no	no	no	no	no	no	no	no			EK
Zhao	Zuotao	no	no	no	no	no	no	no	no			Zhao Z
Bindsløv-Jensen	Carsten	no	no	no	no	no	no	no	no			CBJ
bedrikow	roberta buense	no	no	no	no	no	no	no	no			RBB
Zuberbier	Torsten	no	no	no	no	no	no	no	no			TZ
Bernstein	Jonathan	no	no	no	no	no	no	no	no			JAB
Schmid-Grendelmeier	Peter	no	no	no	no	no	no	no	no			PSG
Ballmer-Weber	Barbara	no	no	no	no	no	no	no	no			ba
Toubi	Elias	no	no	no	no	no	no	no	no			E.T
Saini	Sarbjit	no	no	no	no	no	no	no	no			SSS

CONFLICT OF INTEREST DECLARATION (WHO)		1. EMPLOYMENT AND CONSULTING			2. RESEARCH SUPPORT				3. INVESTMENT INTERESTS			4. INTELLECTUAL PROPERTY		
		Within the past 4 years, have you received remuneration from a commercial entity or other organization with an interest related to the subject of this guideline work?			Within the past 4 years, have you or has your research unit received support from a commercial entity or other organization with an interest related to the subject of this guideline work?				Do you have current investments (valued at more than US \$10 000 overall) in a commercial entity with an interest related to the subject of this guideline work? Please also include indirect investments such as a trust or holding company. You may exclude mutual funds, pension funds or similar investments that are broadly diversified and on which you exercise no control.			Do you have any intellectual property rights that might be enhanced or diminished by the outcome of this guideline work?		
LAST NAME	FIRST NAME	Employment	Consulting		a) Research support, including grants, collaborations, sponsorships, and other funding	b) Non-monetary support valued at more than US \$1000 overall (include equipment, facilities, research assistants, paid travel to meetings, etc.)	c) Support (including honoraria) for being on a speakers bureau, giving speeches or training for a commercial entity or other organization with an interest related to the subject of this guideline work?		a) Stocks, bonds, stock options, other securities (e.g., short sales)	b) Commercial business interests (e.g., proprietorships, partnerships, joint ventures, board memberships, controlling interest in a company)		a) Patents, trademarks, or copyrights (including pending applications)	b) Proprietary know-how in a substance, technology or process	
Danilycheva staubach	Inna petra	no no	no no		no yes	no yes	yes yes	personal fees from Novartis Russia, Abbott Russia outside submitted work Novartis GmbH	no no	no no		no no	no no	
Craig	Timothy	no	yes	I do research for Genentech (CA, USA), CSL Behring (King of Prussia, USA), Shire (Boston USA), but do not benefit directly and the money goes to my institute.	yes	yes	yes	I do research for Genentech (CA, USA), CSL Behring (King of Prussia, USA), Shire (Boston USA), but do not benefit directly and the money goes to my institute.	no	no		no	no	
Larenas Linnemann	Désirée	no	yes	b) 1. advisory board2. for Novartis/ UCB / MSD /MitPharma on urticaria treatment, antihistamines-LTRA-Omalizumab . 3. I am the one involved.4. fee per session lecture: 600-1000 EUR. 5. this was 2015 and 2016.	yes	yes	yes	a) We made Mexican Urticaria Guidelines. Many pharma partners supported this effort. The prime authors finally received 2500 EUR fee. All the rest was used for the 2 face-to-face meetings with the whole team (35 persons) and the dissemination of the GL -printing etc., website for guidelines etc.2. UCB, MSD, Pfizer, Novartis, Carnot, TEVA, Sanofi3. Me4. 250.000 - 100.000 pesos per partner (12500-5000 EUR)5. This was 2014-2015b) Assistance for travel to international congresses (travel, hotel, registration)2. MSD, Pfizer, Novartis, Sanofi) 1. lecturing 2. for UCB / MSD /Pfizer /MitPharma on urticaria guidelines and urticaria Dx and treatment. 3. I am the one involved.4. speaker's fee per lecture: 400-700 EUR. 5. this was 2015 and 2016, several lectures.	no	no		no	no	
Sussman	Gordon	no	yes	Consulting on advisory boards for Novartis, Tribute, Merck, CSL Behring, Shire, Pfizer, Alcon, the past 5 years. About \$40,000.	yes	yes	yes	I have presented lectures on urticaria and angioedema at local, national and international meetings and received honoraria from Novartis and Merck and Tribute. About \$20,000.I have done research studies in urticaria and hereditary angioedema. The companies include Novartis, Genentech, CSL behring, Dyax, BioChris. About \$200,00.	no	no		no	no	
mathelier fusade	pascale	no	yes	3 brainstorming meetings organized by Novartis between 2013 and 2015About 1000€ each meetingNothing en 2016	no	no	no		no	no		no	no	
Clive	Grattan	no	yes	Novartis: Advisory BoardCSL Behring: Consultancy	no	no	no		no	no		no	no	

		5. PUBLIC STATEMENTS AND POSITIONS (during the past 3 years)			6. ADDITIONAL INFORMATION						7. TOBACCO OR TOBACCO PRODUCTS (answer without regard to relevance to the subject of this guideline work)		8. DECLARATION
		a) As part of a regulatory, legislative or judicial process, have you provided an expert opinion or testimony, related to the subject of this guideline work, for a commercial entity or other organization?	b) Have you held an office or other position, paid or unpaid, where you represented interests or defended a position related to the subject of this guideline work?	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	a) If not already disclosed above, have you worked for the competitor of a product that is the subject of this guideline work?	b) If not yet disclosed, will your participation in this guideline work enable you to obtain access to a competitor's confidential proprietary information, or create for you a personal, professional, financial or business competitive advantage?	c) To your knowledge, would the outcome of this guideline work benefit or adversely affect interests of others with whom you have substantial common personal interests (such as your adult children or siblings)?	d) To your knowledge, would the outcome of this guideline work benefit or adversely affect interests of others with whom you have substantial common professional, financial or business interests (such as your close colleagues or department)?	e) Is there any other aspect of your background or present circumstances not addressed above that might be perceived as affecting your objectivity or independence?	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	a) Within the past 4 years, have you had employment or received research support or other funding from, or had any other professional relationship with, an entity directly involved in the production, manufacture, distribution or sale of tobacco or tobacco products or representing the interests of any such entity?	If the answer to any of the above questions is "yes", please indicate the category (e.g. a, b, c) and provide the: (1) Type of interest declared and a basic description, (2) Name of company, organization, or institution, (3) Whether the interest belongs to you, a family member, employer, research unit or other, (4) Amount of income or value of the interest, (5) Whether this is a current interest or the year it was ceased.	I hereby declare on my honour that the disclosed information is true and complete to the best of my knowledge. Should there be any change to the above information, I will promptly notify the responsible guideline project staff and complete a new declaration of interest form that describes the changes. This includes any change that occurs before or during the guideline work itself and through the period up to the publication of the final results or completion of the activity concerned. INITIALS
Danilycheva	Inna	no	no		no	no	no	no	no		no		DI
staubach	petra	no	no		no	no	no	no	no		no		PS
Craig	Timothy	no	no		no	no	no	no	no		no		TJC
Larenas	Désirée	no	no		no	no	no	no	no		no		DLL
Sussman	Gordon	no	no		no	no	no	no	no		no		GS
mathelier fusade	pascale	no	no		no	no	no	no	no		no		paf
Clive	Grattan	yes	no	NATIONAL INSITUTE OF CLINICAL EXCELLENCE; technology appraisal for omalizumab	no	no	no	no	no		no		CEHG