Evidence Report

The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria

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Evidence Report ***The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria***	**EuroGuiDerm** Centre for Guideline Development

Introduction

The last revision of the ***international guideline for urticaria*** was published in 2018. Three years later, we have now updated the evidence, conducting a systematic review, meta-analysis and GRADE evaluation according to the same criteria used in the previous version of the guideline. These criteria were published in the Methods & Evidence Report for that version of the guideline (https://onlinelibrary.wiley.com/action/downloadSupplement?doi=10.1111%2Fall.13414&file=all13414-sup-0001-SupInfo.pdf).

1. **The present Evidence Report contains all the evidence we identified for chronic spontaneous urticaria (CSU) and for chronic inducible urticaria (CINDU).**
2. **Part 1 includes the evidence-to-decision frameworks for all comparisons pertaining to the treatment of chronic spontaneous urticaria.**
3. **Part 2 includes the evidence-to-decision frameworks for all comparisons pertaining to the treatment of chronic inducible urticaria.**
4. **For your convenience, we have also listed the guideline questions in the same order and in the same format as they appear in the old guideline. These are for reference only and may change during the process of guideline development.**

Classification + diagnosis *(consensus-based questions):*

- How should urticaria be classified?
- Should we maintain the current classification of chronic urticaria?
- Should routine diagnostic measures be performed in acute urticaria?
- Should differential diagnoses be considered in patients with chronic spontaneous urticaria?
- What routine diagnostic measures should be performed in chronic spontaneous urticaria?
- Should routine diagnostic measures be performed in inducible 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?

Management questions *(evidence-based questions in bold):*

- Should treatment aim at complete symptom control in urticaria?
- Should patients with chronic spontaneous urticaria be advised to discontinue medication that is suspected to worsen the disease?
- **Are 2nd generation H1-antihistamines to be preferred over 1st generation H1-antihistamines for the treatment of urticaria? No new evidence identified**
- **Should modern 2nd generation H1-antihistamines be used as first-line treatment of urticaria? New evidence found, EtD framework updated**
- **Should modern 2nd generation H1-antihistamines be taken regularly or as needed by patients with chronic urticaria? No new evidence identified**
- **Should different 2nd generation H1-antihistamines be used at the same time? New evidence identified, EtD framework created**
- **Is an increase in the dose to fourfold of modern 2nd generation H1-antihistamines useful and to be preferred over other treatments in urticaria (second-line treatment)? New evidence found, EtD framework updated**
- **If there is no improvement, should higher than fourfold doses of 2nd generation H1-antihistamines be used? No evidence identified**
- **Is omalizumab useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines (third-line treatment)? New evidence found, EtD framework updated**
- **Is cyclosporine A useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines? No new evidence identified**
- **Are leukotriene antagonists useful as add-on treatment in patients unresponsive to high doses of H1-antihistamines? New evidence found, EtD framework updated**
- **Should oral corticosteroids be used as add-on treatment in the treatment of urticaria? No evidence identified**
- Are H2-antihistamines useful as add-on treatment in patients unresponsive to low or high doses of H1-antihistamines?
- **Could any other treatment options be recommended as third line treatment for treatment in urticaria? New evidence found, EtD frameworks updated**
- Should the same treatment algorithm be used in children?
- Should the same treatment algorithm be used in pregnant women and during lactation?

Box 1: Key questions

Results of the systematic review, meta-analysis and GRADE evaluation 2020:

We included a total of 21 new records and produced a total of 13 new or updated evidence-to-decision frameworks in 2020. Please note that the present Evidence Report contains *all* of the evidence-to-decision frameworks for the guideline – whether new or unchanged since 2016 – in order to provide the reader with a clearer overview of the entirety of the available evidence.

List of included comparisons for CSU (Part I) and CINDU (Part II):

PART I: CSU

2nd generation H1-AH versus 1st generation H1-AH for CSU

Should 2nd gen H1-AH vs. 1st gen H1-AH be used for urticaria - KQ09?	
POPULATION:	patients with CSU
INTERVENTION:	2nd gen H1-AH
COMPARISON:	1st gen H1-AH
BIBLIOGRAPHY	Monroe 1992, Monroe 1992a, Ishibashi 1990, Kukita 194, Mensing 1991, Breneman 1996, Kalivas 1990

Assessment

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT

- ● Trivial
- ○ Small
- ○ Moderate
- ○ Large
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Evidence week 1-2:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with 1st gen H1-AH	Risk difference with 2nd gen H1-AH
good or excellent response (by investigator and patient) - w1	147 (2 RCTs)	⨁⨁◯◯ LOW[a,b]	**RR 1.04** (0.80 to 1.35)	Study population	
				595 per 1.000	**24 more per 1.000** (119 fewer to 208 more)
good or excellent response (by investigtor) - w1-2	766 (4 RCTs)	⨁⨁⨁⨁ HIGH	**RR 1.04** (0.93 to 1.17)	Study population	
				599 per 1.000	**24 more per 1.000** (42 fewer to 102 more)

a. unclear randomization method and allocation concealment, selective reporting
b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
c. wide CI
d. statistical heterogeneity (I^2 = 86%) maybe due to methodological differences
e. statistical heterogeneity (I^2 = 82%) maybe due to methodological differences

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

Evidence week 4:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with 1st gen H1-AH	Risk difference with 2nd gen H1-AH
good or excellent response (by investigator and patient) - w4	135 (1 RCT)	⨁⨁◯◯ LOW[a,b]	**RR 1.01** (0.79 to 1.30)	Study population	
				647 per 1.000	**6 more per 1.000** (136 fewer to 194 more)
good or excellent response (by investigator) - w4	197 (2 RCTs)	⨁⨁◯◯ LOW[a,b]	**RR 1.09** (0.87 to 1.37)	Study population	
				571 per 1.000	**51 more per 1.000** (74 fewer to 211 more)
patients with relapse after 1w of stopping treatment	68 (1 RCT)	⨁⨁⨁◯ MODERATE[b]	**RR 0.66** (0.41 to 1.06)	Study population	
				625 per 1.000	**212 fewer per 1.000** (369 fewer to 38 more)

a. unclear randomization method and allocation concealment, selective reporting
b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
c. wide CI
d. unclear/high risk of bias assessment
e. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
f. unclear risk of bias assessment
g. statistical heterogeneity (I^2 = 88%) maybe due to methodological differences

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

- ○ Large
- ○ Moderate
- ○ Small
- ● Trivial
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Evidence week 1-2:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with 1st gen H1-AH	Risk difference with 2nd gen H1-AH
				Study population	

withdrawal due to AE - w2	637 (2 RCTs)	⨁⨁◯◯ LOW[b,c]	**RR 0.14** (0.01 to 2.76)	12 per 1.000	**10 fewer per 1.000** (12 fewer to 21 more)
patients with at least 1 AE (w2)	637 (2 RCTs)	⨁◯◯◯ VERY LOW[b,d]	**RR 0.55** (0.23 to 1.33)	Study population	
				298 per 1.000	**134 fewer per 1.000** (229 fewer to 98 more)
AE: somnolence - w2	637 (2 RCTs)	⨁◯◯◯ VERY LOW[b,e]	**RR 0.49** (0.20 to 1.19)	Study population	
				259 per 1.000	**132 fewer per 1.000** (207 fewer to 49 more)
AE: tiredness (w2)	636 (2 RCTs)	⨁⨁◯◯ LOW[c,f]	**RR 0.29** (0.08 to 0.97)	Study population	
				39 per 1.000	**28 fewer per 1.000** (36 fewer to 1 fewer)

a. unclear randomization method and allocation concealment, selective reporting
b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
c. wide CI
d. statistical heterogeneity (I^2 = 86%) maybe due to methodological differences
e. statistical heterogeneity (I^2 = 82%) maybe due to methodological differences
f. CI crosses MID threshold: statistically significant difference of uncertain clinical importance

Evidence week 4:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with 1st gen H1-AH	Risk difference with 2nd gen H1-AH
withdrawal due to AE - w2	637 (2 RCTs)	⨁⨁◯◯ LOW[b,c]	**RR 0.14** (0.01 to 2.76)	Study population	
				12 per 1.000	**10 fewer per 1.000** (12 fewer to 21 more)
withdrawal due to AE - w4	399 (3 RCTs)	⨁⨁◯◯ LOW[d,e]	**RR 0.22** (0.06 to 0.87)	Study population	
				64 per 1.000	**50 fewer per 1.000** (60 fewer to 8 fewer)
AE: sedation (w4)				Study population	

	258 (2 RCTs)	⨁◯◯◯ VERY LOW[b,c,f,g]	**RR 0.34** (0.07 to 1.64)	397 per 1.000	**262 fewer per 1.000** (369 fewer to 254 more)
AE: somnolence - w4	264 (2 RCTs)	⨁⨁◯◯ LOW[e,f]	**RR 0.60** (0.38 to 0.94)	Study population	
				296 per 1.000	**119 fewer per 1.000** (184 fewer to 18 fewer)
AE: fatigue (w4)	141 (1 RCT)	⨁⨁◯◯ LOW[b,d]	**RR 1.04** (0.27 to 4.01)	Study population	
				56 per 1.000	**2 more per 1.000** (41 fewer to 167 more)
patients with relapse after 1w of stopping treatment	68 (1 RCT)	⨁⨁⨁◯ MODERATE[b]	**RR 0.66** (0.41 to 1.06)	Study population	
				625 per 1.000	**212 fewer per 1.000** (369 fewer to 38 more)

a. unclear randomization method and allocation concealment, selective reporting
b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
c. wide CI
d. unclear/high risk of bias assessment
e. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
f. unclear risk of bias assessment
g. statistical heterogeneity (I^2 = 88%) maybe due to methodological differences

Values and overall certainty of evidence

What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Very low ● Low ○ Moderate ○ High ○ No included studies	**The relative importance or values of the main outcomes of interest:**

Outcome	Relative importance	Certainty of the evidence (GRADE)
good or excellent response (by investigator and patient) - w1	critical	⨁⨁◯◯ LOW
good or excellent response (by investigator and patient) - w4	critical	⨁⨁◯◯ LOW
good or excellent response (by investiagtor) - w1-2	critical	⨁⨁⨁⨁ HIGH
good or excellent response (by investiagtor) - w4	critical	⨁⨁◯◯ LOW
withdrawal due to AE - w2	critical	⨁⨁◯◯ LOW
withdrawal due to AE - w4	critical	⨁⨁◯◯ LOW
patients with at least 1 AE (w2)	important	⨁◯◯◯ VERY LOW
AE: sedation (w4)	critical	⨁◯◯◯ VERY LOW
AE: somnolence - w2	critical	⨁◯◯◯ VERY LOW
AE: somnolence - w4	critical	⨁⨁◯◯ LOW

AE: tiredness (w2)	critical	⊕⊕◯◯ LOW
AE: fatigue (w4)	critical	⊕⊕◯◯ LOW
patients with relapse after 1w of stopping treatment	important	⊕⊕⊕◯ MODERATE

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT

- ○ 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

RESEARCH EVIDENCE

Summary of findings:

Outcomes	With 1st gen H1-AH	With 2nd gen H1-AH	Difference	Relative effect (95% CI)
good or excellent response (by investigator and patient) - w1	595 per 1.000	**618 per 1.000** (476 to 803)	**24 more per 1.000** (119 fewer to 208 more)	**RR 1.04** (0.80 to 1.35)
good or excellent response (by investigator and patient) - w4	647 per 1.000	**654 per 1.000** (511 to 841)	**6 more per 1.000** (136 fewer to 194 more)	**RR 1.01** (0.79 to 1.30)
good or excellent response (by investiagtor) - w1-2	599 per 1.000	**623 per 1.000** (557 to 701)	**24 more per 1.000** (42 fewer to 102 more)	**RR 1.04** (0.93 to 1.17)
good or excellent response (by investiagtor) - w4	571 per 1.000	**623 per 1.000** (497 to 783)	**51 more per 1.000** (74 fewer to 211 more)	**RR 1.09** (0.87 to 1.37)
withdrawal due to AE - w2	12 per 1.000	**2 per 1.000** (0 to 32)	**10 fewer per 1.000** (12 fewer to 21 more)	**RR 0.14** (0.01 to 2.76)
withdrawal due to AE - w4	64 per 1.000	**14 per 1.000** (4 to 56)	**50 fewer per 1.000** (60 fewer to 8 fewer)	**RR 0.22** (0.06 to 0.87)
patients with at least 1 AE (w2)	298 per 1.000	**164 per 1.000** (69 to 396)	**134 fewer per 1.000** (229 fewer to 98 more)	**RR 0.55** (0.23 to 1.33)
AE: sedation (w4)	397 per 1.000	**135 per 1.000** (28 to 651)	**262 fewer per 1.000** (369 fewer to 254 more)	**RR 0.34** (0.07 to 1.64)
AE: somnolence - w2	259 per 1.000	**127 per 1.000** (52 to 308)	**132 fewer per 1.000** (207 fewer to 49 more)	**RR 0.49** (0.20 to 1.19)

	AE: somnolence - w4	296 per 1.000	**178 per 1.000** (113 to 279)	**119 fewer per 1.000** (184 fewer to 18 fewer)	**RR 0.60** (0.38 to 0.94)
	AE: tiredness (w2)	39 per 1.000	**11 per 1.000** (3 to 38)	**28 fewer per 1.000** (36 fewer to 1 fewer)	**RR 0.29** (0.08 to 0.97)
	AE: fatigue (w4)	56 per 1.000	**58 per 1.000** (15 to 223)	**2 more per 1.000** (41 fewer to 167 more)	**RR 1.04** (0.27 to 4.01)
	patients with relapse after 1w of stopping treatment	625 per 1.000	**413 per 1.000** (256 to 663)	**212 fewer per 1.000** (369 fewer to 38 more)	**RR 0.66** (0.41 to 1.06)

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary

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).

Expert opinion with supporting references:

In addition to the trials identified in the systematic search comparing first and second generation antihistamines in urticaria patients, the following selection of studies provide indirect evidence from from healthy volunteers or from study designs not matching the inclusion criteria to support the use of second generation H1:

The use of first generation antihistamines at night-time (hydroxyzine 50 mg) plus second generation antihistamines (levocetirizine 15 mg daily) versus second generation antihistamines alone (20 mg

levocetirizin daily) was shown to increase daytime somnolence without differences in night time sleep disturbances or quality of life parameters. [1]

Second generation antihistamines were found to have no or less impact on central nervous system functions in healthy volunteers than first generation antihistamines (demonstrated e.g. with psychomotor function tests, self-reported alertness, driving performance. [2-6]

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7. *Finkle WD, Adams JL, Greenland S, Melmon KL. Ann Allergy Asthma Immunol. 2002 Sep;89(3):244-50*

2nd gen H1-AH 1-fold versus placebo

POPULATION:	patients with CSU
INTERVENTION:	2nd gen H1-AH 1-fold
COMPARISON:	placebo
BIBLIOGRAPHY	Belaich 1990, Breneman 1995, Bristoff 1996, Camarasa 2001, Di Lorenzo 2004, Dubertret 2007, Gimenez-Arnau 2007, Grob 2008/Ortonne 2007, Guerra 1994, Hide 2017*, Hide 2019*, Hisada 2016*, 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 *studies added in the 2020 update

Assessment

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Evidence week 1-2:**

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with 2nd gen H1-AH 1-fold
complete suppression - w1	230 (2 RCTs)	⨁⨁⨁◯ MODERATE[a]	**RR 4.33** (1.71 to 10.92)	Study population	
				41 per 1.000	**136 more per 1.000** (29 more to 405 more)
good or excellent response (by investigator) - w1-2*	1092 (7 RCTs)	⨁⨁◯◯ LOW[a,b]	**RR 2.59** (1.96 to 3.43)	Study population	
				218 per 1.000	**347 more per 1.000** (209 more to 530 more)
good or excellent response (by patient) - w1	135 (1 RCT)	⨁⨁⨁◯ MODERATE[a]	**RR 2.84** (1.75 to 4.61)	Study population	
				221 per 1.000	**406 more per 1.000** (165 more to 796 more)

mean change in symptom score - w1-2 (SMD)*	966 (6 RCTs)	⨁⨁⨁◯ MODERATE[c]	-		**SMD 0.72 lower** (0.99 lower to 0.45 lower)
mean change in SF-36 - w1	36 (1 RCT)	⨁⨁◯◯ LOW[d,e]	-		MD **1.41 higher** (1.07 lower to 3.89 higher)
mean change in DLQI - w2*	356 (2 RCTs)	⨁⨁⨁⨁ HIGH[f]	-		MD **1.91 lower** (2.71 lower to 1.11 lower)

a. unclear method of randomization and allocation concealment; selective reporting
b. statistical heterogeneity (I^2=63%) may be due to methodological differences
c. statistical heterogeneity (I^2=71%) may be due to methodological differences
d. unclear allocation concealment, blinding, selective reporting
e. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
f. CI does not cross MID, statistically significant but not clinically
g. unclear method of randomization and allocation concealment
h. wide CI
i. statistical heterogeneity (I^2= 66%) may be due to methodological differences

Evidence week 3-4:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with 2nd gen H1-AH 1-fold
complete suppression - w3-w4	730 (5 RCTs)	⨁⨁⨁◯ MODERATE[a]	**RR 3.06** (1.93 to 4.84)	Study population	
				86 per 1.000	**177 more per 1.000** (80 more to 330 more)
good or excellent response (by investigator) - w3-4	897 (7 RCTs)	⨁⨁⨁◯ MODERATE[a]	**RR 2.04** (1.70 to 2.44)	Study population	
				260 per 1.000	**271 more per 1.000** (182 more to 375 more)
good or excellent response (by patient) - w4	301 (2 RCTs)	⨁⨁⨁◯ MODERATE[a]	**RR 1.98** (1.49 to 2.61)	Study population	
				294 per 1.000	**288 more per 1.000** (144 more to 474 more)
mean change in symptom score - w3-4	606 (3 RCTs)	⨁⨁⨁◯ MODERATE[b]	-		MD **1.35 lower** (1.92 lower to 0.77 lower)

mean change in SF-36 - w3	35 (1 RCT)	⨁⨁◯◯ LOW[c,d]	-		MD **1.95 higher** (0.88 lower to 4.78 higher)
mean change in DLQI - w4	696 (2 RCTs)	⨁⨁⨁◯ MODERATE[b]	-		MD **3.82 lower** (4.94 lower to 2.71 lower)
mean difference (mean change in DLQI) - w4	258 (1 RCT)	⨁⨁⨁◯ MODERATE[a]	-		**1.5 higher** (0.2 higher to 2.9 higher)

a. unclear method of randomization and allocation concealment; selective reporting
b. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
c. unclear allocation concealment, blinding, selective reporting
d. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Evidence week 5-6:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with 2nd gen H1-AH 1-fold
complete suppression - w6	100 (1 RCT)	⨁⨁◯◯ LOW[a,b]	**RR 52.88** (3.31 to 843.81)	Study population	
				0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
good or excellent response (by investigator) - w6	367 (2 RCTs)	⨁◯◯◯ VERY LOW[c,d,e]	**RR 1.54** (0.97 to 2.43)	Study population	
				442 per 1.000	**239 more per 1.000** (13 fewer to 632 more)
good or excellent response (by patient) - w6	93 (1 RCT)	⨁⨁◯◯ LOW[c,f]	**RR 1.55** (1.03 to 2.32)	Study population	
				413 per 1.000	**227 more per 1.000** (12 more to 545 more)
mean difference (mean change in TSS) - w6	80 (1 RCT)	⨁⨁⨁◯ MODERATE[g]	-		**1.77 higher** (1.89 lower to 1.66 higher)
mean change in DLQI - w6	137 (1 RCT)	⨁⨁◯◯ LOW[c,f]	-		MD **3.8 lower** (5.71 lower to 1.89 lower)

a. wide CI

b. unclear method of randomization and allocation concealment; selective reporting
c. unclear allocation concealment, blinding, selective reporting
d. statistical heterogeneity (I^2 = 79%) maybe due to methodological differences
e. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
f. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
g. unclear method of randomization and allocation concealment

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

- ○ Large
- ○ Moderate
- ○ Small
- ● Trivial
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Evidence week 1-2:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with 2nd gen H1-AH 1-fold
withdrawal due to AE - w2 (RD) *	449 (3 RCTs)	⨁◯◯◯ LOW[g]	not estimable *(2/222;0/227)*	Study population	
				0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
patients with at least 1 AE - w2*	430 (3 RCTs)	⨁⨁◯◯ LOW[e,h]	**RR 1.26** (0.52 to 3.04)	Study population	
				143 per 1.000	**37 more per 1.000** (69 fewer to 291 more)

a. unclear method of randomization and allocation concealment; selective reporting
b. statistical heterogeneity (I^2=70%) may may be due to methodological differences
c. statistical heterogeneity (I^2=71%) may be due to methodological differences
d. unclear allocation concealment, blinding, selective reporting
e. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
f. CI does not cross MID, statistically significant but not clinically
g. unclear method of randomization and allocation concealment

h. statistical heterogeneity (I^2= 66%) may be due to methodological differences

Evidence week 3-4:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with 2nd gen H1-AH 1-fold
withdrawal due to AE - w3-4*	1223 (10 RCTs)	⨁⨁◯◯ LOW[a,d]	**RR 0.86** (0.33 to 2.26)	Study population	
				16 per 1.000	**2 fewer per 1.000** (10 fewer to 20 more)

patients with at least 1 AE - w4*	852 (6 RCTs)	⨁⨁⨁◯ MODERATE[b]	**RR 1.28** (1.02 to 1.60)	Study population	
				246 per 1.000	**69 more per 1.000** (5 more to 148 more)

a. unclear method of randomization and allocation concealment; selective reporting
b. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
c. unclear allocation concealment, blinding, selective reporting
d. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Evidence week 5-6:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with 2nd gen H1-AH 1-fold
withdrawal due to AE - w6	362 (2 RCTs)	⨁◯◯◯ VERY LOW[a,c,e]	**RR 1.06** (0.11 to 10.08)	Study population	
				5 per 1.000	**0 fewer per 1.000** (5 fewer to 49 more)
patients with at least 1 AE - w6	127 (2 RCTs)	⨁⨁⨁◯ MODERATE[b]	not pooled *(zero in both groups)*	Study population: Zero events in both RCTs	

a. wide CI
b. unclear method of randomization and allocation concealment; selective reporting
c. unclear allocation concealment, blinding, selective reporting
d. statistical heterogeneity (I^2 = 79%) maybe due to methodological differences
e. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
f. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
g. unclear method of randomization and allocation concealment

Values and overall certainty of the evidence

JUDGEMENT	RESEARCH EVIDENCE
● low	**The relative importance or values of the main outcomes of interest:**

Outcome	Relative importance	Certainty of the evidence (GRADE)
complete suppression - w1	critical	⨁⨁⨁◯ MODERATE
complete suppression - w3-4	critical	⨁⨁⨁◯ MODERATE
complete suppression - w6	critical	⨁⨁◯◯ LOW
good or excellent response (by investigator) - w1-2	critical	⨁⨁◯◯ LOW
good or excellent response (by investigator) - w3-4	critical	⨁⨁⨁◯ MODERATE
good or excellent response (by investigator) - w6	critical	⨁◯◯◯ VERY LOW

good or excellent response (by patient) - w1	critical	⊕⊕⊕◯ MODERATE
good or excellent response (by patient) - w4	critical	⊕⊕⊕◯ MODERATE
good or excellent response (by patient) - w6	critical	⊕⊕◯◯ LOW
mean change in symptom score - w1	critical	⊕⊕⊕◯ MODERATE
mean change in symptom score - w3-4	critical	⊕⊕⊕◯ MODERATE
mean difference (mean change in TSS) - w6	critical	⊕⊕⊕◯ MODERATE
mean change in SF-36 - w1	critical	⊕⊕◯◯ LOW
mean change in SF-36 - w3	critical	⊕⊕◯◯ LOW
mean change in DLQI - w4	critical	⊕⊕⊕◯ MODERATE
mean change in DLQI - w6	critical	⊕⊕◯◯ LOW
mean difference (mean change in DLQI) - w4	critical	⊕⊕⊕◯ MODERATE
withdrawal due to AE - w2	critical	⊕⊕⊕◯ MODERATE
withdrawal due to AE - w3-4	critical	⊕⊕◯◯ LOW
withdrawal due to AE - w6	critical	⊕◯◯◯ VERY LOW
patients with at least 1 AE - w2	important	⊕⊕◯◯ LOW
patients with at least 1 AE - w4	important	⊕⊕⊕◯ MODERATE
patients with at least 1 AE - w6	important	⊕⊕⊕◯ MODERATE

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT

○ 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

RESEARCH EVIDENCE

Summary of findings:

Outcomes	With placebo	With 2nd gen H1-AH 1-fold	Difference	Relative effect (95% CI)
complete suppression - w1	41 per 1.000	**177 per 1.000** (70 to 446)	**136 more per 1.000** (29 more to 405 more)	**RR 4.33** (1.71 to 10.92)
complete suppression - w3-w4	86 per 1.000	**263 per 1.000** (166 to 416)	**177 more per 1.000** (80 more to 330 more)	**RR 3.06** (1.93 to 4.84)
complete suppression - w6	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer per 1.000** (0 fewer to 0 fewer)	**RR 52.88** (3.31 to 843.81)
good or excellent response (by investigator) - w1-2*	218 per 1.000	**615 per 1.000** (439 to 864)	**397 more per 1.000** (220 more to 646 more)	**RR 2.82** (2.01 to 3.96)

good or excellent response (by investigator) - w3-4	260 per 1.000	**531 per 1.000** (443 to 635)	**271 more per 1.000** (182 more to 375 more)	**RR 2.04** (1.70 to 2.44)
good or excellent response (by investigator) - w6	442 per 1.000	**681 per 1.000** (429 to 1.000)	**239 more per 1.000** (13 fewer to 632 more)	**RR 1.54** (0.97 to 2.43)
good or excellent response (by patient) - w1	221 per 1.000	**626 per 1.000** (386 to 1.000)	**406 more per 1.000** (165 more to 796 more)	**RR 2.84** (1.75 to 4.61)
good or excellent response (by patient) - w4	294 per 1.000	**582 per 1.000** (438 to 768)	**288 more per 1.000** (144 more to 474 more)	**RR 1.98** (1.49 to 2.61)
good or excellent response (by patient) - w6	413 per 1.000	**640 per 1.000** (425 to 958)	**227 more per 1.000** (12 more to 545 more)	**RR 1.55** (1.03 to 2.32)
mean change in symptom score - w1-2 (SMD)*		The meanchange in symptom score in the intervention group was 0,72 standard deviations points lower (0,99 lower to 0,45 lower)	SMD **0.72 lower** (0.99 lower to 0.45 lower)	-
mean change in symptom score - w3-4		The mean change in symptom score - w3-4 in the intervention group was 1,35 points lower (1,92 lower to 0,77 lower)	MD **1.35 lower** (1.92 lower to 0.77 lower)	-
mean difference (mean change in TSS) - w6		The mean difference in TSS in the intervention group was 1,77 points higher (1,89 lower to 1,66 higher)	**1.77 higher** (1.89 lower to 1.66 higher)	-
mean change in SF-36 - w1		The mean change in SF-36 in the intervention group was 1,41 points higher	MD **1.41 higher** (1.07 lower to 3.89 higher)	-

		(1,07 lower to 3,89 higher)		
mean change in SF-36 - w3		The mean change in SF-36 - in the intervention group was 1,95 points higher (0,88 lower to 4,78 higher)	MD **1.95 higher** (0.88 lower to 4.78 higher)	-
mean change in DLQI - w2*		The mean change in DLQI * in the intervention group was 1,91 points lower (2,71 lower to 1,11 lower)	MD **1.91 lower** (2.71 lower to 1.11 lower)	-
mean change in DLQI - w4		The mean change in DLQI in the intervention group was 3,82 points lower (4,94 lower to 2,71 lower)	MD **3.82 lower** (4.94 lower to 2.71 lower)	-
mean change in DLQI - w6		The mean change in DLQI in the intervention group was 3,8 points lower (5,71 lower to 1,89 lower)	MD **3.8 lower** (5.71 lower to 1.89 lower)	-
mean difference (mean change in DLQI) - w4		The mean change in DLQI in the intervention group was 1,5 points higher (0,2 higher to 2,9 higher)	**1.5 higher** (0.2 higher to 2.9 higher)	-
withdrawal due to AE - w2 (RD) *	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer per 1.000** (0 fewer to 0 fewer)	not estimable
withdrawal due to AE - w3-4*	16 per 1.000	**13 per 1.000** (5 to 35)	**2 fewer per 1.000** (10 fewer to 20 more)	**RR 0.86** (0.33 to 2.26)

	withdrawal due to AE - w6	5 per 1.000	**6 per 1.000** (1 to 54)	**0 fewer per 1.000** (5 fewer to 49 more)	**RR 1.06** (0.11 to 10.08)
	patients with at least 1 AE - w2*	143 per 1.000	**180 per 1.000** (74 to 434)	**37 more per 1.000** (69 fewer to 291 more)	**RR 1.26** (0.52 to 3.04)
	patients with at least 1 AE - w4*	246 per 1.000	**315 per 1.000** (251 to 394)	**69 more per 1.000** (5 more to 148 more)	**RR 1.28** (1.02 to 1.60)
	patients with at least 1 AE - w6	not pooled	not pooled	not pooled	not pooled

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary:

2ND GENERATION H1-AH 1-FOLD vs. PLACEBO

Data added in 2020 update from 3 new studies (differences to 2016 marked in purple)

Efficacy

2nd generation H1-AH 1-fold was superior to placebo based on the outcomes: 'complete suppression' (low/moderate quality), 'good or excellent response' at weeks 1-2 and weeks 3-4 (low/moderate quality), 'change in symptom score [standardized mean difference]' (moderate quality), 'mean change in DLQI' at weeks 1-2 (high quality), 'mean change in DLQI' at week 4 (low) and 'mean change in DLQI' at week 6 (moderate quality).

No difference was found for the outcomes: 'good or excellent response' at week 6 (very low quality), 'mean difference in symptom score' (moderate quality) and 'mean change in SF-36' (low quality).

Safety

No difference was found for the outcomes: 'withdrawal due to adverse event' (very low/moderate quality) and 'patients with at least one adverse event' (low/moderate quality).

2nd generation H1-AH taken regularly versus 2nd generation H1-AH taken as needed

POPULATION:	patients with chronic spontanious urticaria
INTERVENTION:	2nd gen AH taken regularly
COMPARISON:	2nd gen AH taken as needed
BIBLIOGRAPHY	Grob 2008

Assessment

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT: RESEARCH EVIDENCE

○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 2nd gen AH as needed	Risk difference with 2nd gen AH regular
complete suppression - w8	106 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	**RR 1.71** (1.01 to 2.89)	267 per 1.000	**189 more per 1.000** (3 more to 504 more)

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

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT: RESEARCH EVIDENCE

○ Large
○ Moderate
● Small
○ Trivial
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 2nd gen AH as needed	Risk difference with 2nd gen AH regular
withdrawal due to AE - w8	106 (1 RCT)	⨁⨁◯◯ LOW [a,b]	not estimable *(zero in both groups)*	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
patients with at least 1 AE - w8	106 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,d]	**RR 1.55** (0.90 to 2.67)		

a. unclear allocation concealment; unclear blinding of outcome assessment; >10% loss to follow-up
b. only patients responding to previous treatment with desloratadine 5mg QD for 4w included
c. CI crosses MID threshold: statistically significant difference of uncertain clinical importance

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

Values and overall certainty of the evidence

JUDGEMENT	RESEARCH EVIDENCE
● Very low ○ Low ○ Moderate ○ High ○ No included studies	**The relative importance or values of the main outcomes of interest:**

Outcome	Relative importance	Certainty of the evidence (GRADE)
complete suppression - w8	critical	⨁◯◯◯ VERY LOW
withdrawal due to AE - w8	critical	⨁⨁◯◯ LOW
patients with at least 1 AE - w8	important	⨁◯◯◯ VERY LOW

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ 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	**Summary of findings**:

Outcome	With 2nd gen AH as needed	With 2nd gen AH regular	Difference (95% CI)	Relative effect (RR) (95% CI)
complete suppression - w8	267 per 1.000	**456 per 1.000** (269 to 771)	**189 more per 1.000** (from 3 more to 504 more)	**RR 1.71** (1.01 to 2.89)
withdrawal due to AE - w8	0 per 1.000	**0 per 1.000** (0 to 0)		not estimable
patients with at least 1 AE - w8	267 per 1.000	**413 per 1.000** (240 to 712)	**147 more per 1.000** (from 27 fewer to 445 more)	**RR 1.55** (0.90 to 2.67)

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary

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).

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

2nd gen H1-AH + 2nd gen H1-AH (different H1AH) versus 2nd gen H1-AH alone

POPULATION:	patients with chronic spontaneous urticaria
INTERVENTION:	2nd gen H1-AH + 2nd gen H1-AH (different H1AH)
COMPARISON:	2nd gen H1-AH alone
BIBLIOGRAPHY	Wang 2019* *- studies added in the 2020 update

Assessment

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT

● Trivial
○ Small
○ Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with 2nd gen H1-Ah alone	Risk difference with 2nd gen H1-AH +2nd gen H1-AH (different H1AH)
good or excellent response	234 (1 RCT)	⨁◯◯◯ VERY LOW[a,b]	**RR 1.14** (1.03 to 1.26)	Study population	
				812 per 1.000	114 more per 1.000 (24 more to 211 more)

a. open-label trial
b. CI crossed MID, statistically significant of uncertain clinical importance
c. CI crossed line of no effect and MID threshold: uncertain whether there is any difference

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with 2nd gen H1-Ah alone	Risk difference with 2nd gen H1-AH +2nd gen H1-AH (different H1AH)
				Study population	

patients with at least 1 AE	234 (1 RCT)	⨁◯◯◯ VERY LOW[a,c]	**RR 0.70** (0.28 to 1.78)	85 per 1.000	26 fewer per 1.000 (62 fewer to 67 more)
withdrawal due to AE	234 (1 RCT)	⨁⨁◯◯ LOW[a]	not estimable *(zero in both groups)*	Study population	
				0 per 1.000	0 fewer per 1.000 (0 fewer to 0 fewer)

a. open-label trial
b. CI crossed MID, statistically significant of uncertain clinical importance
c. CI crossed line of no effect and MID threshold: uncertain whether there is any difference

Values and overall certainty of evidence

JUDGEMENT

● Very low

RESEARCH EVIDENCE

Outcome	Relative importance	Certainty of the evidence (GRADE)
good or excellent response	critical	⨁◯◯◯ VERY LOW
withdrawal due to AE	critical	⨁◯◯◯ VERY LOW
patients with at least 1 AE	important	⨁◯◯◯ VERY LOW

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT

○ 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

RESEARCH EVIDENCE

Summary of finding:

Outcomes	With 2nd gen H1-Ah alone	With 2nd gen H1-AH +2nd gen H1-AH (different H1AH)	Difference	Relative effect (95% CI)
good or excellent response	812 per 1.000	926 per 1.000 (836 to 1.000)	114 more per 1.000 (24 more to 211 more)	**RR 1.14** (1.03 to 1.26)
patients with at least 1 AE	85 per 1.000	60 per 1.000 (24 to 152)	26 fewer per 1.000 (62 fewer to 67 more)	**RR 0.70** (0.28 to 1.78)
withdrawal due to AE	0 per 1.000	0 per 1.000 (0 to 0)	0 fewer per 1.000 (0 fewer to 0 fewer)	not estimable

Feasibility Is the intervention feasible to implement?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary

2ND GENERATION H1-AH + DIFFERENT 2ND GENERATION H1-AH vs. 2ND GENERATION H1-AH ALONE

Data added in 2020 update from 1 new study (differences to 2016 marked in purple)

Efficacy

No difference was found for the outcome: 'good or excellent response' (very low quality).

Safety

No difference was found for the outcomes: 'withdrawal due to adverse event' (very low quality) or 'patients with at least one adverse event' (very low/low).

2nd gen H1-AH x-fold versus 2nd gen H1-AH x-fold

POPULATION:	patients with CSU unresponsive to H1-AH
INTERVENTION:	2nd gen H1-AH 2-fold versus 2nd gen H1-AH 1-fold
COMPARISON:	2nd gen H1-AH 4-fold versus 2nd gen H1-AH 1-fold 2nd gen H1-AH 4-fold versus 2nd gen H1-AH 2-fold
BIBLIOGRAPHY	Gimenez-Arnau 2007, Hide 2019*, Hisada 2019*, Ishibashi 1989, Ishibashi 1990, Kukita 1994, Niimura 1990, NCT00536389, NCT00536389 NCT00536389 *studies added in the 2020 update

Assessment

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT

- ● Trivial
- ○ Small
- ○ Moderate
- ○ Large
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

1) 2nd gen H1-AH 2-fold versus 2nd gen H1-AH 1-fold

Evidence week 1-2:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with 2nd gen H1-AH 1-fold	Risk difference with 2nd gen H1-AH 2-fold
good or excellent response - w1-2*	1042 (7 RCTs)	⨁⨁◯◯ LOW[a,b]	**RR 1.01** (0.93 to 1.10)	Study population	
				658 per 1,000	7 more per 1,000 (46 fewer to 66 more)
sum, itch+rash - w2*	159 (1 RCT)	⨁⨁◯◯ LOW[b,c]	-		MD 0.03 higher (0.48 lower to 0.54 higher)
DLQI w2*	156 (1 RCT)	⨁⨁◯◯ LOW[b,c]	-		MD 0.09 higher (0.93 lower to 1.11 higher)
				Study population	

patients with relapse after 1w of stopping treatment	44 (1 RCT)	⨁⨁◯◯ LOW[b,d]	**RR 0.76** (0.36 to 1.60)	458 per 1,000	110 fewer per 1,000 (293 fewer to 275 more)

a. two open label studies included; unclear allocation +randomization method
b. unclear if patients were nonresponders
c. unclear randomization, allocation
d. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Evidence week 4-6:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with 2nd gen H1-AH 1-fold	Risk difference with 2nd gen H1-AH 2-fold
good or excellent response - w6	221 (1 RCT)	⨁⨁◯◯ LOW[a,b]	**RR 1.19** (0.99 to 1.42)	Study population	
				625 per 1,000	119 more per 1,000 (6 fewer to 262 more)
mean change in UAS - w4	208 (1 RCT)	⨁⨁⨁◯ MODERATE[c]	-		MD 0.1 lower (0.43 lower to 0.23 higher)

a. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
b. unclear if patients were nonresponders
c. unclear risk of bias assessment
d. unclear randomization, allocation, and blinding
e. only one of the two studies included nonresponders
f. CU crossed 0.02 and the line of no effect

2) 2nd gen H1-AH 4-fold versus 2nd gen H1-AH 1-fold

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 2nd gen H1-AH 1 fold	Risk difference with 2nd gen H1-AH 4 fold
mean change in UAS - w4	204 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	-		MD **0** (0.33 lower to 0.33 higher)

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

3) 2nd gen H1-AH 4-fold versus 2nd gen H1-AH 2-fold

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 2nd gen H1-AH 2 fold	Risk difference with 2nd gen H1-AH 4 fold
mean change in UAS - w4	204 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	-		MD **0.1 higher** (0.23 lower to 0.43 higher)

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

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
○ Small
○ Trivial
● Varies
○ Don't know

RESEARCH EVIDENCE

1) 2nd gene H1-AH 2-fold versus 2nd gen H1-AH 1-fold

Evidence week 1-2:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with 2nd gen H1-AH 1-fold	Risk difference with 2nd gen H1-AH 2-fold
patients with at least 1 AE - w1-2*	696 (5 RCTs)	⊕⊕◯◯ LOW[b,d]	**RR 1.00** (0.75 to 1.34)	Study population	
				207 per 1,000	0 fewer per 1,000 (52 fewer to 70 more)
withdrawal due to AE - w1-2*	700 (5 RCTs)	⊕⊕⊕◯ MODERATE[b]	not estimable *(RD -0.00(-0.01,0.01))*	Study population	
				6 per 1,000	6 fewer per 1,000 (6 fewer to 6 fewer)
patients with relapse after 1w of stopping treatment	44 (1 RCT)	⊕⊕◯◯ LOW[b,d]	**RR 0.76** (0.36 to 1.60)	Study population	
				458 per 1,000	110 fewer per 1,000 (293 fewer to 275 more)

a. two open label studies included; unclear allocation +randomization method
b. unclear if patients were nonresponders
c. unclear randomization, allocation, and blinding
d. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Evidence week 4-6:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with 2nd gen H1-AH 1-fold	Risk difference with 2nd gen H1-AH 2-fold
patients with at least 1 AE - w3-4*	159 (1 RCT)	⨁◯◯◯ VERY LOW[a,b,d]	**RR 0.76** (0.45 to 1.29)	Study population	
				300 per 1,000	72 fewer per 1,000 (165 fewer to 87 more)
withdrawal due to AE - w4*	370 (2 RCTs)	⨁⨁◯◯ LOW[d,e,f]	not estimable *(RD 0.01(-0.01,0.03))*	Study population	
				0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)
withdrawal due to AE - w6	221 (1 RCT)	⨁⨁⨁◯ MODERATE[b]	not estimable *(zero in both groups)*	Study population	
				0 per 1,000	0 fewer per 1,000 (0 fewer to 0 fewer)

a. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
b. unclear if patients were nonresponders
c. unclear risk of bias assessment
d. unclear randomization, allocation, and blinding
e. only one of the two studies included nonresponders
f. CU crossed 0.02 and the line of no effect

2) 2nd gen H1-AH 4-fold versus 2nd gen H1-AH 1-fold

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 2nd gen H1-AH 1 fold	Risk difference with 2nd gen H1-AH 4 fold
withdrawal due to AE - w4	210 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	**RR 5.10** (0.25 to 104.87)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

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

3) 2nd gen H1-AH 4-fold versus 2nd gen H1-AH 2-fold

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 2nd gen H1-AH 2 fold	Risk difference with 2nd gen H1-AH 4 fold
withdrawal due to AE- w4	208 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	**RR 1.00** (0.14 to 6.97)	19 per 1.000	0 fewer per 1.000 (17 fewer to 115 more)

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

Values and overall Certainty of evidence

JUDGEMENT	RESEARCH EVIDENCE
• Low	

The relative importance or values of the main outcomes of interest:

1) 2nd gene H1-AH 2-fold versus 2nd gen H1-AH 1-fold

Outcome	Relative importance	Certainty of the evidence (GRADE)
good or excellent response - w1-2	critical	⊕⊕⊕◯ MODERATE
good or excellent response - w6	critical	⊕⊕◯◯ LOW
sum, itch+rash - w2*	critical	⊕⊕◯◯ LOW
mean change in UAS - w4	critical	⊕⊕⊕◯ MODERATE
DLQI w2*	critical	⊕⊕◯◯ LOW
withdrawal due to AE - w1-2	critical	⊕⊕⊕◯ MODERATE
withdrawal due to AE - w4	critical	⊕◯◯◯ VERY LOW
withdrawal due to AE - w6	critical	⊕⊕⊕◯ MODERATE
patients with at least 1 AE -w1 - w2	important	⊕⊕◯◯ LOW
patients with relapse after 1w of stopping treatment	important	⊕⊕◯◯ LOW

2) 2nd gen H1-AH 4-fold versus 2nd gen H1-AH 1-fold

The relative importance or values of the main outcomes of interest:

Outcome	Relative importance	Certainty of the evidence (GRADE)
mean change in UAS - w4	critical	⊕⊕⊕◯ MODERATE
withdrawal due to AE - w4	critical	⊕◯◯◯ VERY LOW

3) 2nd gen H1-AH 4-fold versus 2nd gen H1-AH 2-fold

Outcome	Relative importance	Certainty of the evidence (GRADE)
mean change in UAS - w4	critical	⊕⊕⊕◯ MODERATE
withdrawal due to AE- w4	critical	⊕⊕⊕◯ MODERATE

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT

○ 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

RESEARCH EVIDENCE

1) 2nd gene H1-AH 2-fold versus 2nd gen H1-AH 1-fold

Summary of findings:

Outcomes	With 2nd gen H1-AH 1-fold	With 2nd gen H1-AH 2-fold	Difference	Relative effect (95% CI)
good or excellent response - w1-2*	658 per 1,000	664 per 1,000 (612 to 723)	7 more per 1,000 (46 fewer to 66 more)	**RR 1.01** (0.93 to 1.10)
good or excellent response - w6	625 per 1,000	744 per 1,000 (619 to 888)	119 more per 1,000 (6 fewer to 262 more)	**RR 1.19** (0.99 to 1.42)
sum, itch+rash - w2*		The mean itch and rash score in the intervention group was 0.03 points higher (0.48 lower to 0.54 higher)	MD 0.03 higher (0.48 lower to 0.54 higher)	-
mean change in UAS - w4		The mean change in UAS in the intervention group was 0.1 lower (0.43 lower to 0.23 higher)	MD 0.1 lower (0.43 lower to 0.23 higher)	-
DLQI w2*		The mean DLQI in the intervention group was 0.09 pointshigher (0.93 lower to 1.11 higher)	MD 0.09 higher (0.93 lower to 1.11 higher)	-
patients with at least 1 AE - w1-2*	207 per 1,000	207 per 1,000 (155 to 277)	0 fewer per 1,000 (52 fewer to 70 more)	**RR 1.00** (0.75 to 1.34)
patients with at least 1 AE - w3-4*	300 per 1,000	228 per 1,000 (135 to 387)	72 fewer per 1,000 (165 fewer to 87 more)	**RR 0.76** (0.45 to 1.29)

withdrawal due to AE - w1-2*	6 per 1,000	0 per 1,000 (0 to 0)	6 fewer per 1,000 (6 fewer to 6 fewer)	not estimable
withdrawal due to AE - w4*	0 per 1,000	0 per 1,000 (0 to 0)	0 fewer per 1,000 (0 fewer to 0 fewer)	not estimable
withdrawal due to AE - w6	0 per 1,000	0 per 1,000 (0 to 0)	0 fewer per 1,000 (0 fewer to 0 fewer)	not estimable
patients with relapse after 1w of stopping treatment	458 per 1,000	348 per 1,000 (165 to 733)	110 fewer per 1,000 (293 fewer to 275 more)	**RR 0.76** (0.36 to 1.60)

2) 2nd gen H1-AH 4-fold versus 2nd gen H1-AH 1-fold

Outcome	With 2nd gen H1-AH 1 fold	With 2nd gen H1-AH 4 fold	Difference (
mean change in UAS - w4		The mean change in UAS in the intervention group was 0 points (0,33 lower to 0,33 higher)	MD 0 (0.33 lower highe
withdrawal due to AE - w4	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer pe** (from 0 fev fewe

3) 2nd gen H1-AH 4-fold versus 2nd gen H1-AH 2-fold

Outcome	With 2nd gen H1-AH 2 fold	With 2nd gen H1-AH 4 fold	Difference (95% CI)	Relative effect (RR) (95% CI)
mean change in UAS - w4		The mean change in UAS in the intervention group was 0,1 points higher (0,23 lower to 0,43 higher)	MD **0.1 higher** (0.23 lower to 0.43 higher)	-

	withdrawal due to AE- w4	19 per 1.000	**19 per 1.000** (3 to 134)	**0 fewer per 1.000** (from 17 fewer to 115 more)	

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.	

Summary

1) COMPARISON: 2ND GENERATION H1-AH 2-FOLD vs. 2ND GENERATION H1-AH 1-FOLD
Data added in 2020 update from 2 new studies (differences to 2016 marked in purple)

Efficacy

No difference was found for the outcomes: 'good or excellent response' (low quality), 'itch+rash score'/'UAS7'/'DLQI' (low/moderate quality) and 'relapse' (low quality).

Safety

No difference was found for the outcomes: 'withdrawal due to adverse event' (moderate quality) and 'patients with at least one adverse event' (very low/low quality).

2) COMPARISON: 2ND GENERATION H1-AH 4-FOLD vs. 2ND GENERATION H1-AH 1-FOLD
No new data added in 2020

Efficacy

No difference was found for the outcome: 'mean change in UAS' (moderate quality).

Safety

No difference was found for the outcome: 'withdrawal due to adverse event' (very low quality).

3) COMPARISON: 2ND GENERATION H1-AH 4-FOLD VS. 2ND GENERATION H1-AH 2-FOLD
No new data added in 2020

Efficacy

No difference was found for the outcome: 'mean change in UAS' (moderate quality).

Safety

No difference was found for the outcome: 'withdrawal due to adverse event' (moderate quality).

Higher than fourfold doses of 2nd gen H1-AH

No evidence identified

Omalizumab versus placebo

POPULATION:	patients with chronic spontanious urticaria unresponsive to 2nd gen H1-AH
INTERVENTION(S):	1) add-on omalizumab 300mg every 4w, 2) add-omalizumab 150mg every 4w
COMPARISON:	placebo
BIBLIOGRAPHY	1) omalizumab 300mg: Hide 2017*, Jörg 2018*, Kaplan 2013/2016, Maurer 2013, Maurer 2018*, Metz 2017*, Saini 2011, Saini 2015/Kaplan 2016, Staubach 2016, Staubach 2018* 2) omalizumab 150mg: Hide 2017*, Maurer 2013, Saini 2015/Kaplan 2016 * studies added in the 2020 update/ outcome with new data added 2020

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

1) omalizumab 300mg every 4w vs. placebo

○ Trivial
○ Small
○ Moderate
● Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

1) omalizumab 300mg every 4w compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with add-on omalizumab 300mg every 4w
complete suppression w4*	848 (5 RCTs)	⨁⨁⨁⨁ HIGH	**RR 17.32** (5.97 to 50.24)	Study population	
				6 per 1,000	**97 more per 1,000** (29 more to 291 more)
complete suppression w8	655 (3 RCTs)	⨁⨁⨁⨁ HIGH	**RR 5.36** (3.13 to 9.18)	Study population	
				58 per 1,000	**251 more per 1,000** (123 more to 471 more)
complete suppression w12*	923 (6 RCTs)	⨁⨁⨁⨁ HIGH	**RR 6.34** (4.13 to 9.74)	Study population	
				56 per 1,000	**300 more per 1,000** (176 more to 491 more)
good or excellent response w1-2*	30 (1 RCT)	⨁◯◯◯ VERY LOW[a,b]	**RR 1.57** (0.07 to 35.46)	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

	good or excellent response w4	701 (4 RCTs)	⊕⊕⊕⊕ HIGH	**RR 6.10** (3.40 to 10.92)	Study population	
					68 per 1,000	**348 more per 1,000** (164 more to 676 more)
	good or excellent response w8	655 (3 RCTs)	⊕⊕⊕⊕ HIGH	**RR 4.29** (2.65 to 6.94)	Study population	
					115 per 1,000	**379 more per 1,000** (190 more to 684 more)
	good or excellent response w12*	862 (6 RCTs)	⊕⊕⊕⊕ HIGH	**RR 3.70** (2.83 to 4.82)	Study population	
					151 per 1,000	**409 more per 1,000** (277 more to 578 more)
	UAS7 w4	46 (1 RCT)	⊕⊕⊕◯ MODERATE[c]	-		MD **13 lower** (19.42 lower to 6.58 lower)
	UAS7 w12*	827 (5 RCTs)	⊕⊕⊕◯ MODERATE[c]	-		MD **13 lower** (19.42 lower to 6.58 lower)
	DLQI w12*	745 (5 RCTs)	⊕⊕⊕⊕ HIGH	-		MD **3.85 lower** (4.79 lower to 2.9 lower)
	CU-Q2oL w4	91 (1 RCT)	⊕⊕⊕⊕ HIGH	-		MD **20.7 lower** (29 lower to 12.5 lower)
	CU-Q_2oL w12	336 (1 RCT)	⊕⊕⊕◯ MODERATE[c]	-		MD **13 lower** (18.44 lower to 7.56 lower)
	relapse: DLQI 12w after last treatment*	57 (1 RCT)	⊕⊕⊕⊕ HIGH	-		MD **3.4 lower** (7.72 lower to 0.92 higher)
2) omalizumab 150mg every 4w vs. placebo ○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	relapse: percent w/clinical worsening (UAS7>6 for 2w) w24-48*	134 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	**RR 0.50** (0.34 to 0.73)	Study population	
					642 per 1,000	**321 fewer per 1,000** (423 fewer to 173 fewer)

a. Several risk-of-bias items unclear, incl. blinding of outcome assessment
b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
c. CI crosses MID threshold: statistically significant difference of uncertain clinical importance

2) omalizumab 150mg every 4w compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with add-on omalizumab 150mg every 4w
complete suppression w4*	467 (3 RCTs)	⊕⊕⊕⊕ HIGH	**RR 6.81** (1.82 to 25.43)	Study population	
				9 per 1,000	**50 more per 1,000** (7 more to 210 more)
complete suppression w8	322 (2 RCTs)	⊕⊕⊕◯ MODERATE[a]	**RR 2.20** (1.15 to 4.18)	Study population	
				75 per 1,000	**91 more per 1,000** (11 more to 240 more)
complete suppression w12*	467 (3 RCTs)	⊕⊕⊕⊕ HIGH	**RR 2.95** (1.53 to 5.69)	Study population	
				60 per 1,000	**117 more per 1,000** (32 more to 282 more)
good or excellent response w4	322 (2 RCTs)	⊕⊕⊕⊕ HIGH	**RR 2.70** (1.47 to 4.96)	Study population	
				88 per 1,000	**150 more per 1,000** (41 more to 349 more)
good or excellent response w8	322 (2 RCTs)	⊕⊕⊕⊕ HIGH	**RR 2.48** (1.39 to 4.44)	Study population	
				145 per 1,000	**214 more per 1,000** (56 more to 498 more)
good or excellent response w12*	467 (3 RCTs)	⊕⊕⊕⊕ HIGH	**RR 2.49** (1.79 to 3.46)	Study population	
				163 per 1,000	**243 more per 1,000** (129 more to 401 more)
UAS7 w12*	465 (3 RCTs)	⊕⊕⊕⊕ HIGH	-		MD 6.2 **lower** (8.35 lower to 4.05 lower)
DLQI w12*	429 (3 RCTs)	⊕⊕⊕◯ MODERATE[a]	-		MD **1.97 lower** (3.04 lower to 0.9 lower)

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

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE

1) omalizumab 300mg every 4w vs. placebo

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

1) omalizumab 300mg every 4w compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with add-on omalizumab 300mg every 4w
withdrawal due to AE up to w12*	223 (3 RCTs)	⨁⨁⨁⨁ HIGH	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
patients with at least 1 AE w4	46 (1 RCT)	⨁⨁⨁◯ MODERATE[a]	**RR 1.01** (0.55 to 1.85)	Study population	
				476 per 1,000	**5 more per 1,000** (214 fewer to 405 more)
patients with at least 1 AE w12	249 (2 RCTs)	⨁⨁⨁⨁ HIGH	**RR 1.01** (0.84 to 1.20)	Study population	
				651 per 1,000	**7 more per 1,000** (104 fewer to 130 more)

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

2) omalizumab 150mg every 4w vs. placebo

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

2) omalizumab 150mg every 4w compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with add-on omalizumab 150mg every 4w
withdrawal due to AE up to w12*	306 (2 RCTs)	⨁⨁⨁◯ MODERATE[a]	**RR 1.59** (0.20 to 12.80)	Study population	
				7 per 1,000	**4 more per 1,000** (5 fewer to 77 more)
patients with at least 1 AE w12	167 (1 RCT)	⨁⨁⨁◯ MODERATE[a]	**RR 1.10** (0.88 to 1.39)	Study population	
				608 per 1,000	**61 more per 1,000** (73 fewer to 237 more)

a. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
* outcomes with new data added in 2020

Values and overall certainty of the evidence

JUDGEMENT	RESEARCH EVIDENCE
1) omalizumab 300mg every	**The relative importance or values of the main outcomes of interest:** **1) omalizumab 300mg every 4w compared to placebo**

4w vs. placebo

○ Very low
○ Low
● Moderate
High
○ No included studies

Outcomes	Importance	Certainty of the evidence (GRADE)
complete suppression w4*	critical	⊕⊕⊕⊕ HIGH
complete suppression w8	critical	⊕⊕⊕⊕ HIGH
complete suppression w12*	critical	⊕⊕⊕⊕ HIGH
good or excellent response w1-2*	critical	⊕◯◯◯ VERY LOW
good or excellent response w4	critical	⊕⊕⊕⊕ HIGH
good or excellent response w8	critical	⊕⊕⊕⊕ HIGH
good or excellent response w12*	critical	⊕⊕⊕⊕ HIGH
UAS7 w4	critical	⊕⊕⊕◯ MODERATE
UAS7 w12*	critical	⊕⊕⊕◯ MODERATE
DLQI w12*	critical	⊕⊕⊕⊕ HIGH
CU-Q2oL w4	critical	⊕⊕⊕⊕ HIGH
CU-Q_2oL w12	critical	⊕⊕⊕◯ MODERATE
withdrawal due to AE up to w12*	critical	⊕⊕⊕⊕ HIGH
patients with at least 1 AE w4	important	⊕⊕⊕◯ MODERATE
patients with at least 1 AE w12	important	⊕⊕⊕⊕ HIGH
relapse: DLQI 12w after last treatment*	important	⊕⊕⊕⊕ HIGH
relapse: percent w/clinical worsening (UAS7>6 for 2w) w24-48*	important	⊕⊕⊕◯ MODERATE

2) omalizumab 150mg every 4w compared to placebo

2) omalizumab 150mg every 4w vs. placebo

○ Very low
○ Low
● Moderate
○ High
○ No included studies

Outcomes	Importance	Certainty of the evidence (GRADE)
complete suppression w4*	critical	⊕⊕⊕⊕ HIGH
complete suppression w8	critical	⊕⊕⊕◯ MODERATE
complete suppression w12*	critical	⊕⊕⊕⊕ HIGH
good or excellent response w4	critical	⊕⊕⊕⊕ HIGH
good or excellent response w8	critical	⊕⊕⊕⊕ HIGH
good or excellent response w12*	critical	⊕⊕⊕⊕ HIGH

mean change in UAS7 w12*	critical	⨁⨁⨁⨁ HIGH
DLQI w12*	critical	⨁⨁⨁◯ MODERATE
withdrawal due to AE up to w12*	critical	⨁⨁⨁◯ MODERATE
patients with at least 1 AE w12	important	⨁⨁⨁◯ MODERATE

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT

1) omalizumab 300mg every 4w vs. placebo

○ 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

RESEARCH EVIDENCE

1) omalizumab 300mg every 4w compared to placebo

Outcomes	With placebo	With add-on omalizumab 300mg every 4w	Difference	Relative effect (95% CI)
complete suppression w4*	6 per 1,000	**102 per 1,000** (35 to 297)	**97 more per 1,000** (29 more to 291 more)	**RR 17.32** (5.97 to 50.24)
complete suppression w8	58 per 1,000	**309 per 1,000** (180 to 529)	**251 more per 1,000** (123 more to 471 more)	**RR 5.36** (3.13 to 9.18)
complete suppression w12*	56 per 1,000	**356 per 1,000** (232 to 547)	**300 more per 1,000** (176 more to 491 more)	**RR 6.34** (4.13 to 9.74)
good or excellent response w1-2*	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 1.57** (0.07 to 35.46)
good or excellent response w4	68 per 1,000	**416 per 1,000** (232 to 745)	**348 more per 1,000** (164 more to 676 more)	**RR 6.10** (3.40 to 10.92)
good or excellent response w8	115 per 1,000	**494 per 1,000** (305 to 800)	**379 more per 1,000** (190 more to 684 more)	**RR 4.29** (2.65 to 6.94)

good or excellent response w12*	151 per 1,000	**560 per 1,000** (428 to 729)	**409 more per 1,000** (277 more to 578 more)	**RR 3.70** (2.83 to 4.82)
UAS7 w4	The mean UAS7 w4 was **0**	The mean UAS7 w4 in the intervention group was 13 undefined lower (19.42 lower to 6.58 lower)	MD **13 lower** (19.42 lower to 6.58 lower)	-
UAS7 w12*	The mean UAS7 w12* was **0**	The mean UAS7 w12* in the intervention group was 10.76 undefined lower (12.47 lower to 9.05 lower)	MD **10.76 lower** (12.47 lower to 9.05 lower)	-
DLQI w12*	The mean DLQI w12* was **0**	The mean DLQI w12* in the intervention group was 3.85 undefined lower (4.79 lower to 2.9 lower)	MD **3.85 lower** (4.79 lower to 2.9 lower)	-
CU-Q2oL w4	The mean cU-Q2oL w4 was **0**	The mean cU-Q2oL w4 in the intervention group was 20.7 lower (29 lower to 12.5 lower)	MD **20.7 lower** (29 lower to 12.5 lower)	-
CU-Q_2oL w12	The mean cU-Q_2oL w12 was **0**	The mean cU-Q_2oL w12 in the intervention group was 13 undefined lower (18.44 lower to 7.56 lower)	MD **13 lower** (18.44 lower to 7.56 lower)	-
withdrawal due to AE up to w12*	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	not estimable
patients with at least 1 AE w4	476 per 1,000	**481 per 1,000** (262 to 881)	**5 more per 1,000** (214 fewer to 405 more)	**RR 1.01** (0.55 to 1.85)
patients with at least 1 AE w12	651 per 1,000	**657 per 1,000** (547 to 781)	**7 more per 1,000** (104 fewer to 130 more)	**RR 1.01** (0.84 to 1.20)

2) omalizumab 150mg every 4w vs. placebo

○ 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

relapse: DLQI 12w after last treatment*	The mean relapse: DLQI 12w after last treatment* was **0**	The mean relapse: DLQI 12w after last treatment* in the intervention group was 3.4 undefined lower (7.72 lower to 0.92 higher)	MD **3.4 lower** (7.72 lower to 0.92 higher)	-
relapse: percent w/clinical worsening (UAS7>6 for 2w) w24-48*	642 per 1,000	**321 per 1,000** (218 to 468)	**321 fewer per 1,000** (423 fewer to 173 fewer)	**RR 0.50** (0.34 to 0.73)

2) omalizumab 150mg every 4w compared to placebo

Outcomes	With placebo	With add-on omalizumab 150mg every 4w	Difference	Relative effect (95% CI)
complete suppression w4*	9 per 1,000	**58 per 1,000** (16 to 218)	**50 more per 1,000** (7 more to 210 more)	**RR 6.81** (1.82 to 25.43)
complete suppression w8	75 per 1,000	**166 per 1,000** (87 to 315)	**91 more per 1,000** (11 more to 240 more)	**RR 2.20** (1.15 to 4.18)
complete suppression w12*	60 per 1,000	**177 per 1,000** (92 to 342)	**117 more per 1,000** (32 more to 282 more)	**RR 2.95** (1.53 to 5.69)
good or excellent response w4	88 per 1,000	**238 per 1,000** (129 to 437)	**150 more per 1,000** (41 more to 349 more)	**RR 2.70** (1.47 to 4.96)
good or excellent response w8	145 per 1,000	**359 per 1,000** (201 to 642)	**214 more per 1,000** (56 more to 498 more)	**RR 2.48** (1.39 to 4.44)
good or excellent response w12*	163 per 1,000	**406 per 1,000** (292 to 564)	**243 more per 1,000** (129 more to 401 more)	**RR 2.49** (1.79 to 3.46)
mean change in UAS7 w12*	The mean mean change in UAS7 - w12* was **0**	The mean mean change in UAS7 - w12* in the intervention group was 6.2	MD **6.2 lower** (8.35 lower	-

			undefined lower (8.35 lower to 4.05 lower)	to 4.05 lower)	
	DLQI w12*	The mean DLQI w12* was **0**	The mean DLQI w12* in the intervention group was 1.97 undefined lower (3.04 lower to 0.9 lower)	MD **1.97 lower** (3.04 lower to 0.9 lower)	-
	withdrawal due to AE up to w12*	7 per 1,000	**10 per 1,000** (1 to 84)	**4 more per 1,000** (5 fewer to 77 more)	**RR 1.59** (0.20 to 12.80)
	patients with at least 1 AE w12	608 per 1,000	**668 per 1,000** (535 to 845)	**61 more per 1,000** (73 fewer to 237 more)	**RR 1.10** (0.88 to 1.39)

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
omalizumab 300mg or 150mg every 4w vs. placebo ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**omalizumab 300mg or 150mg every 4w vs. placebo** Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary

1) COMPARISON: OMALIZUMAB 300MG EVERY 4 WEEKS AS ADD-ON TREATMENT vs. PLACEBO

Data added in 2020 update from 5 new studies (differences to 2016 marked in purple

Efficacy

Omalizumab 300mg every 4 weeks as add-on treatment was superior to placebo for the outcomes: 'complete suppression' (high quality), 'good or excellent response' at weeks 4, 8 and 12 (high quality), 'UAS7' (moderate quality), 'DLQI' (high quality), 'CU-Q2oL' (moderate/high quality), 'relapse: DLQI 12 weeks after last treatment' (high quality) and 'relapse: percent of patients with clinical worsening (UAS7>6 for 2 weeks) from week 24-48' (moderate quality).

No difference was found for the outcome: 'good or excellent response' at weeks 1-2 (very low quality)

Safety

No difference was found for the outcomes: 'withdrawal due to adverse events up to week 12' (high quality) and 'patients with at least one adverse event' (moderate/high quality).

2) COMPARISON: OMALIZUMAB 150MG EVERY 4 WEEKS AS ADD-ON TREATMENT vs. PLACEBO

Data added in 2020 update from 1 new study

Efficacy

Omalizumab 150mg every 4 weeks as add-on treatment was superior to placebo for the outcomes: 'complete suppression' (moderate/high quality), 'good or excellent response' at weeks 4, 8 and 12 (high quality), 'UAS7' (high quality) and 'DLQI' (moderate quality).

Safety

No difference was found for the outcomes: 'withdrawal due to adverse event up to week 12' (moderate quality) and for 'patients with at least one adverse event' (moderate quality).

Cyclosporine versus placebo

POPULATION:	patients with chronic spontanious urticaria
INTERVENTION:	CSA
COMPARISON:	placebo
BIBLIOGRAPHY	Grattan 2000, Toubi 1997

Assessment

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
○ Small
○ Moderate
○ Large
○ Varies
● Don't know

RESEARCH EVIDENCE

Evidence week 1-2:

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no add-on intervention	Risk difference with add-on CSA
complete suppression - w1	35 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	**RR 11.42** (0.74 to 175.71)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
good or excellent response - w1-2	65 (2 RCTs)	⊕⊕◯◯ LOW [a,c]	**RR 14.11** (2.05 to 97.04)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

Evidence week 4:

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no add-on intervention	Risk difference with add-on CSA
complete suppression - w4	35 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	**RR 8.88** (0.57 to 138.71)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
good or excellent response - w4	30 (1 RCT)	⊕⊕◯◯ LOW [b,c]	**RR 8.90** (0.57 to 140.31)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
mean change in UAS7 - w4	29 (1 RCT)	⊕⊕⊕◯ MODERATE d	-		MD **10.4 lower** (18.68 lower to 2.12 lower)

Evidence week 12:

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no add-on intervention	Risk difference with add-on CSA
complete suppression - w12	35 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c]	**RR 11.42** (0.74 to 175.71)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

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

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT | RESEARCH EVIDENCE

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with no add-on intervention	Risk difference with add-on CSA
withdrawal due to AE - w4	29 (1 RCT)	⊕⊕⊕⊕ HIGH	not estimable	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

Values and overall certainty of the evidence

JUDGEMENT | **RESEARCH EVIDENCE**

● Very low

The relative importance or values of the main outcomes of interest:

Outcome	Relative importance	Certainty of the evidence (GRADE)
complete suppression - w1	critical	⊕◯◯◯ VERY LOW
complete suppression – w4	critical	⊕◯◯◯ VERY LOW
complete suppression – w12	critical	⊕◯◯◯ VERY LOW
good or excellent response - w1-2	critical	⊕⊕◯◯ LOW
good or excellent response – w4	critical	⊕⊕◯◯ LOW
mean change UAS7 –w4	critical	⊕⊕⊕◯ MODERATE
withdrawal due to AE – w4	critical	⊕⊕⊕⊕HIGH

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT | **RESEARCH EVIDENCE**

○ 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

Summary of findings:

Outcome	With no add-on intervention	With add-on CSA	Difference (95% CI)	Relative effect (RR) (95% CI)
complete suppression - w1	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	**RR 11.42** (0.74 to 175.71)
complete suppression - w4	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	**RR 8.88** (0.57 to 138.71)
complete suppression - w12	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	**RR 11.42** (0.74 to 175.71)
good or excellent response - w1-2	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	**RR 14.11** (2.05 to 97.04)
good or excellent response - w4	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	**RR 8.90** (0.57 to 140.31)
mean change in UAS7 - w4		The mean change in UAS7 in the intervention group was 10,4 points lower (18,68 lower to 2,12 lower)	MD **10.4 lower** (18.68 lower to 2.12 lower)	-
withdrawal due to AE - w4	0 per 1.000	**0 per 1.000** (0 to 0)		not estimable

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary

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

Montelukast + 2nd gen H1-AH versus 2nd gen H1-AH 1-fold or 2-fold or placebo

POPULATION:	Patients wtih chronic urticaria , who failed to respond to 1-fold 2nd gen H1-AH
INTERVENTION:	montelukast+ 2nd gen H1-AH
COMPARISON:	2nd gen H1-AH 1-fold, 2nd gen H1-AH 2 fold, placebo
BIBLIOGRAPHY	Di Lorenzo 2004, Wan 2009 Erbagci 2002, Nettis 2004, DiLorenzo 2004 Sarkar 2017* *studies added in the 2020 update

Assessment

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
○ Small
○ Moderate
○ Large
● Varies
○ Don't know

RESEARCH EVIDENCE

1) Montelukast+2nd gen H1-AH 1-fold compared to placebo

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with montelukast + H1-AH
mean change in TSS) - w6	80 (1 RCT)	⊕⊕◯◯ LOW [a,b]	-		MD **1.76 lower** (1.87 lower to 1.64 higher)
good or excellent response - - w4	60 (1 RCT)	⊕◯◯◯ VERY LOW [a,b,c,d]	**RR 17.00** (1.03 to 281.91)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

a. unclear method of randomiz ation and allocation concealment
b. all patients with CU were included (not only non-responders to H1-AH)
c. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
d. wide CI

2) Montelukast+2nd gen H1-AH 1-fold compared to 2nd gen H1-AH 1-fold

Outcomes	№ 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 [a,b]	**RR 4.77** (1.95 to 11.66)	83 per 1.000	**314 more per 1.000** (79 more to 888 more)
mean change in TSS	80 (1 RCT)	⊕⊕◯◯ LOW [a,b]	-		MD **0.01 higher** (0.13 higher to 0.09 lower)

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

3) Montelukast+levocetirizin 1-fold compared to levocetirizin 2-fold

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with levocetirizin 2-fold	Risk difference with montelukast+levocetirizin 1-fold
good or excellent response w4	120 (1 RCT)	⊕⊕◯◯ LOW[a,b]	**RR 1.04** (0.69 to 1.55)	Study population	
				433 per 1.000	17 more per 1.000 (134 fewer to 238 more)
UAS w2	103 (1 RCT)	⊕◯◯◯ VERY LOW[a,b,c]	-		MD 0.15 higher (0.48 lower to 0.78 higher)
UAS w4	103 (1 RCT)	⊕⊕◯◯ LOW[a,c]	-		MD 0.12 higher (0.51 lower to 0.75 higher)
DLQI w4	103 (1 RCT)	⊕◯◯◯ VERY LOW[a,c,d]	-		MD 4.08 lower (5.91 lower to 2.25 lower)

a. 25-30% of patients had inducable urticaria
b. CI crossed MID and line of no effect: uncertain whether there is any difference
c. LOCF for continous outcomes
d. CI crossed MID: statistically significant of uncertain clinical importance

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE

○ Large
○ Moderate
○ Small
○ Trivial
○ Varies
● Don't know

1) Montelukast+2nd gen H1-AH 1-fold compared to placebo

No evidence

2) Montelukast+2nd gen H1-AH 1-fold compared to 2nd gen H1-AH 1-fold

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolut	
				Risk with placebo + H1-AH	Risk diffe
patients with at least 1 AE - w6	54 (1 RCT)	⊕⊕◯◯ LOW [a,b]	not estimable *(zero in both groups)*	0 per 1.000	**0 fewer pe** (0 fewer to
withdrawal due to AE - w6	42 (1 RCT)	⊕⊕⊕◯ MODERATE a	not estimable *(zero in both groups)*	0 per 1.000	**0 fewer pe** (0 fewer to

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

3) Montelukast+levocetirizin 1-fold compared to levocetirizin 2-fold

No evidence

Values and certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE

● Very low

1) Montelukast+2nd gen H1-AH 1-fold compared to placebo

Outcome	Relative importance	Certainty of the evidence (GRADE)
TSS- w6	critical	⊕⊕◯◯ LOW
good or excellent response - w4	critical	⊕◯◯◯ VERY LOW

2) Montelukast+2nd gen H1-AH 1-fold compared to 2nd gen H1-AH 1-fold

Outcome	Relative importance	Certainty of the evidence (GRADE)
excellent response - w6	critical	⊕⊕◯◯ LOW
TSS	critical	⊕⊕◯◯ LOW
patients with at least 1 AE - w6	critical	⊕⊕◯◯ LOW
withdrawal due to AE - w6	critical	⊕⊕⊕◯ MODERATE

3) Montelukast+levocetirizin 1-fold compared to levocetirizin 2-fold

Outcome	Relative importance	Certainty of the evidence (GRADE)
Good or excellent response	critical	⊕⊕◯◯ LOW
UAS w2	critical	⊕◯◯◯ VERY LOW
UAS w4	critical	⊕⊕◯◯ LOW
DLQI w4	critical	⊕◯◯◯ VERY LOW

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ Favors the comparison
○ Probably favors the comparison
● Does not favor either the intervention or the comparison
○ Probably favors the interventi

1) Montelukast+2nd gen H1-AH 1-fold compared to placebo

Outcome	With placebo	With montelukast + H1-AH	Difference (95% CI)	Relative effect (RR) (95% CI)
TSS - w6		The mean difference in TSS in the intervention group was 1,76 points lower (1,87 lower to 1,64 higher)	MD **1.76 lower** (1.87 lower to 1.64 higher)	-
good or excellent response - w4	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	**RR 17.00** (1.03 to 281.91)

2) Montelukast+2nd gen H1-AH 1-fold compared to 2nd gen H1-AH 1-fold

on
○ Favors the intervention
○ Varies
○ Don't know

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)
TSS		The mean difference in TSS in the intervention group was 0,01 points 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

3) Montelukast+levocetirizin 1-fold compared to levocetirizin 2-fold

Outcomes	With levocetirizin 2-fold	With montelukast+levocetirizin 1-fold	Difference	Relative effect (95% CI)
good or excellent response w4	433 per 1.000	416 per 1.000 (273 to 633)	17 fewer per 1.000 (160 fewer to 199 more)	**RR 0.96** (0.63 to 1.46)
UAS w2	The mean UAS w2 was 0	The mean UAS in the intervention group was 0,15 points higher (0,48 lower to 0,78 higher)	MD 0.15 higher (0.48 lower to 0.78 higher)	-
UAS w4	The mean UAS w4 was 0	The mean UAS in the intervention group was 0,12 points higher (0,51 lower to 0,75 higher)	MD 0.12 higher (0.51 lower to 0.75 higher)	-
DLQI w4	The mean DLQI w4 was 0	The mean DLQI in the intervention group was 4,08 points lower (5,91 lower to 2,25 lower)	MD 4.08 lower (5.91 lower to 2.25 lower)	-

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS

○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary

(Differences to 2016 marked in purple)

1) COMPARISON: MONTELUKAST + 2ND GENERATION H1-AH 1-FOLD vs. PLACEBO
No new data added in 2020

Efficacy
No difference was found for the outcomes: 'mean difference in total symptom score' (low quality) and 'good or excellent response' (very low quality).

Safety
No safety data were available.

2) COMPARISON: MONTELUKAST + 2ND GENERATION H1-AH 1-FOLD vs. 2ND GENERATION H1-AH 1-FOLD
No new data added in 2020

Efficacy
Montelukast + 2nd generation H1-AH 1-fold was superior to 2nd generation H1-AH 1-fold for the outcome*:* 'excellent response' (low quality).

No difference was found for the outcome: 'mean difference in TSS' (low quality).

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

3) COMPARISON: MONTELUKAST + LEVOCETIRIZIN 1-FOLD vs. LEVOCETIRIZIN 2-FOLD
Data added in 2020 update from 1 new study

Efficacy
Montelukast + levocetirizine 1-fold was superior to levocetirizine 2-fold for the outcome: 'DLQI' (very low quality).

No difference was found for the outcome: 'good or excellent response' (low quality) or 'UAS' (very low to low quality).

Safety

No safety data were available.

Should oral corticosteroids be used as add-on treatment in the treatment of urticaria?

No evidence identified

NB-UVB versus PUVA

POPULATION:	patients with chronic spontanious urticaria
INTERVENTION:	NB-UVB
COMPARISON:	PUVA
BIBLIOGRAPHY	Bishnoi 2017*, Khafagy 2013, * studies added in the update 2020

Assessment

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT: RESEARCH EVIDENCE

- ● Trivial
- ○ Small
- ○ Moderate
- ○ Large
- ○ Varies
- ○ Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with PUVA	Risk difference with NB-UVB
complete suppression - 90d*	50 (1 RCT)	⨁⨁◯◯ LOW[a,b]	**RR 3.00** (0.13 to 70.30)	Study population	
				0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
good or excellent response -90d*	50 (1 RCT)	⨁⨁⨁◯ MODERATE[a]	**RR 1.04** (0.91 to 1.20)	Study population	
				920 per 1.000	**37 more per 1.000** (83 fewer to 184 more)
mean change in TSS - w3	24 (1 RCT)	⨁⨁◯◯ LOW[b,c]	-		MD **0.75 lower** (5.09 lower to 3.59 higher)
UAS7 - d90*	50 (1 RCT)	⨁⨁◯◯ LOW[a, d]	-		MD **0.5 lower** (0.89 lower to 0.11 lower)

a. concomitant treatment: levocetirizine 10mg QD (Bishnoi 2017)
b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
c. unclear/high risk of bias
d. patients not blinded

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT: RESEARCH EVIDENCE

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with PUVA	Risk difference with NB-UVB
patients with at least 1 AE - w3	24 (1 RCT)	⨁⨁◯◯ LOW[b,c]	**RR 2.67** (0.93 to 7.69)	Study population	
				250 per 1.000	**418 more per 1.000** (17 fewer to 1.673 more)
withdrawal due to AE *	74 (2 RCTs)	⨁⨁⨁◯ MODERATE[a]	not pooled *(zero in both groups)*	Study population	
				not pooled	not pooled
relapse (back to baseline UAS)*	50 (1 RCT)	⨁⨁◯◯ LOW[a]	**RR 3.00** (0.13 to 70.30)	Study population	
				0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

a. concomitant treatment: levocetirizine 10mg QD (Bishnoi 2017)
b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
c. unclear/high risk of bias
d. wide CI

Values and overall certainty of the evidence

JUDGEMENT	RESEARCH EVIDENCE
● Low	**The relative importance or values of the main outcomes of interest:**

Outcome	Relative importance	Certainty of the evidence (GRADE)
complete suppression – 90d	critical	⨁⨁◯◯ LOW
good or excellent response -90d	critical	⨁⨁⨁◯ MODERATE
mean change in TSS –w3	critical	⨁⨁◯◯ LOW
UAS7- 90d	critical	⨁⨁◯◯ LOW
Patients with at least 1 AE -w3	critical	⨁⨁◯◯ LOW
withdrawal due to AE - w2	critical	⨁⨁⨁◯ MODERATE
relapse	important	⨁⨁◯◯ LOW

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE

	Outcomes	With PUVA	With NB-UVB	Difference	Relative effect (95% CI)
○ 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	complete suppression - 90d*	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer per 1.000** (0 fewer to 0 fewer)	**RR 3.00** (0.13 to 70.30)
	good or excellent response -90d*	920 per 1.000	**957 per 1.000** (837 to 1.000)	**37 more per 1.000** (83 fewer to 184 more)	**RR 1.04** (0.91 to 1.20)
	mean change in TSS - w3		The mean mean change in TSS - in the intervention group was 0,75 points lower (5,09 lower to 3,59 higher)	MD **0.75 points lower** (5.09 lower to 3.59 higher)	-
	UAS7 - d90*		The mean UAS7 in the intervention group was 0,5 points lower (0,89 lower to 0,11 lower)	MD **0.5 lower** (0.89 lower to 0.11 lower)	-
	withdrawal due to AE - w3	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer per 1.000** (0 fewer to 0 fewer)	not estimable
	patients with at least 1 AE - w3	250 per 1.000	**668 per 1.000** (233 to 1.000)	**418 more per 1.000** (17 fewer to 1.673 more)	**RR 2.67** (0.93 to 7.69)
	withdrawal due to AE - during treatment*	not pooled	not pooled	not pooled	not pooled
	relapse (back to baseline UAS)*	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer per 1.000** (0 fewer to 0 fewer)	**RR 3.00** (0.13 to 70.30)

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary:

COMPARISON: NB-UVB vs. PUVA

Data added in 2020 update from 1 new study (differences to 2016 marked in purple)

Efficacy

NB-UVB was superior to PUVA for the outcome: 'UAS7' (low quality).

No difference was found for the outcomes: 'complete supression' (low quality), 'good/excellent response' (moderate quality), 'mean change in TSS' (low quality) and relapse (low quality).

Safety

No difference was found for the outcomes: 'withdrawal due to adverse event' (moderate quality) and 'patients with at least one adverse event' (low quality).

NB-UVB versus 2nd gen H1-AH

POPULATION:	patients with chronic spontaneous urticaria
INTERVENTION:	2nd gen H1-AH + NB-UVB (2 or 3 times per week)
COMPARISON:	2nd gen H1-Ah (1 or 2-fold)
BIBLIOGRAPHY	**Sheikh 2019*** **Engin 2008b** **Zuo 2011** *- studies added in the 2020 update

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

- ● Trivial
- ○ Small
- ○ Moderate
- ○ Large
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

1) UB UVB BIW + loratadine 19mg QD compared to loratadine 10mg QD

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with loratadine 10mg QD	Risk difference with UB-NBV + loratadine 10mg QD
urticaria activity score - w 4	72 (1 observational study)	⨁◯◯◯ VERY LOW[a,b]	-		MD 10.36 lower (13.57 lower to 7.15 lower)
urticaria activity score – w8	72 (1 observational study)	⨁◯◯◯ VERY LOW[a]	-		MD 14.74 lower (18.65 lower to 10.83 lower)

a. ROBINS-I evaluation: critical
b. CI crosses MID threshold: statistically significant of unclear clinical importance
c. CI interval crossed line of no effect and MID threshold: uncertain whether there is any difference

2) NB UVB TIW + levocetirizine 10mg QD compared to levocetirizine 10mg QD

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with levocetirizine	Risk difference with levocetirizine + NB-UVB
mean change in UAS7 - w3	78 (1 RCT)	⨁⨁⨁◯ MODERATE a	-		MD **5.49 lower** (8.03 lower to 2.95 lower)

mean change in UAS7 - w7	78 (1 RCT)	⊕⊕⊕◯ MODERATE a			MD 4.02 lower (7.22 lower to 0.82 lower

a. unclear/high risk of bias

3) NB UVB TIW + mizolastine 10mg QD compared to mizolastine 10mg QD

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with minolastine alone	Risk difference with mizolastine + NB-UVB
change in mean total symptom score (MTSS) - w4	81 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	-		MD **3.46 lower** (4.14 lower to 2.78 lower)
change in mean total symptom score (MTSS) - w8	81 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	-		MD **3.73 lower** (4.23 lower to 3.23 lower)

a. unclear risk of bias

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

RESEARCH EVIDENCE

1) UB UVB BIW + loratadine 19mg QD compared to loratadine 10mg QD

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with loratadine 10mg QD	Risk difference with UB-NBV + loratadine 10mg QD
patients with at least 1 AE	72 (1 observational study)	⊕◯◯◯ VERY LOW[a,c]	**RR 2.84** (0.12 to 67.53)	Study population	
				0 per 1.000	0 fewer per 1.000 (0 fewer to 0 fewer)
relapse (change in UAS7 4w after treatment was finished)	72 (1 observational study)	⊕◯◯◯ VERY LOW[a]	-		MD 23.84 lower (27.6 lower to 20.08 lower)

a. ROBINS-I evaluation: critical
b. CI crosses MID threshold: statistically significant of unclear clinical importance
c. CI interval crossed line of no effect and MID threshold: uncertain whether there is any difference

2) NB UVB TIW + levocetirizine 10mg QD compared to levocetirizine 10mg QD

No evidence

3) NB UVB TIW + mizolastine 10mg QD compared to mizolastine 10mg QD

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with minolastine alone	Risk difference with mizolastine + NB-UVB
withdrawal due to AE - w8	81 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	not estimable *(zero events in both groups)*	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

a. unclear risk of bias

Values and overall certainty of evidence

JUDGEMENT	RESEARCH EVIDENCE

● Very low
○ Low
○ Moderate
○ High
○ No included studies

1) UB UVB BIW + loratadine 19mg QD compared to loratadine 10mg QD

Outcome	Relative importance	Certainty of the evidence (GRADE)
UAS – w4	critical	⨁◯◯◯ VERY LOW[a]
UAS – w8	critical	⨁◯◯◯ VERY LOW[a]
patients with at least 1 AE	important	⨁◯◯◯ VERY LOW[a]
relapse	imporant	⨁◯◯◯ VERY LOW[a]

2) NB UVB TIW + levocetirizine 10mg QD compared to levocetirizine 10mg QD

Outcome	Relative importance	Certainty of the evidence (GRADE)
mean change in UAS7 w3	critical	⨁⨁⨁◯ MODERATE
mean change in UAS7 - w7	critical	⨁⨁⨁◯ MODERATE

3) NB UVB TIW + mizolastine 10mg QD compared to mizolastine 10mg QD

Outcome	Relative importance	Certainty of the evidence (GRADE)
change in mean total symptom score (MTSS) -w4	critical	⨁⨁⨁◯ MODERATE
change in mean total symptom score (MTSS) - w8	critical	⨁⨁⨁◯ MODERATE
withdrawal due to AE - w8	critical	⨁⨁⨁◯ MODERATE

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE

○ 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

Summary of finding:

1) UB UVB BIW + loratadine 19mg QD compared to loratadine 10mg QD

Outcomes	With loratadine 10mg QD	With UB-NBV + loratadine 10mg QD	Difference	Relative effect (95% CI)
urticaria activity score – w4		The mean urticaria activity score in the intervention group was 10,36 points lower (13,57 lower to 7,15 lower)	MD 10.36 lower (13.57 lower to 7.15 lower)	-
urticaria activity score – w8		The mean urticaria activity score in the intervention group was 14,74 points lower (18,65 lower to 10,83 lower)	MD 14.74 lower (18.65 lower to 10.83 lower)	-
patients with at least 1 AE	0 per 1.000	0 per 1.000 (0 to 0)	0 fewer per 1.000 (0 fewer to 0 fewer)	**RR 2.84** (0.12 to 67.53)
relapse (change in UAS7 4w after treatment was finished)		The mean change in UAS7 4w after treatment relapse) in the intervention group was 23,84 points lower (27,6 lower to 20,08 lower)	MD 23.84 lower (27.6 lower to 20.08 lower)	-

2) NB UVB TIW + levocetirizine 10mg QD compared to levocetirizine 10mg QD

Outcome	With levocetirizine	With levocetirizine + NB-UVB	Difference (95% CI)	Relative effect (RR) (95% CI)
mean change in UAS7 - w3		The mean change in UAS7 in the intervention group was 4,68 points lower (7,22 lower to 2,14 lower)	MD **4.49 lower** (8.03 lower to 2.95 lower)	-
mean change in UAS7 - w7		The mean change in UAS7 in the intervention group was 4,02 points lower (7,22 lower to 0,82 lower)	MD **4.02 lower** (7.22 lower to 0.82 lower)	-

3) NB UVB TIW + mizolastine 10mg QD compared to mizolastine 10mg QD

Outcome	With minolastine alone	With mizolastine + NB-UVB	Difference (95% CI)	Relative effect (RR) (95% CI)
change in mean total symptom score (MTSS) - w4		The change in mean total symptom score (MTSS) in the intervention group was 3,46 points lower (4,13 lower to 2,79 lower)	MD **3.46 lower** (4.14 lower to 2.78 lower)	-

	change in mean total symptom score (MTSS) - w8		The change in mean total symptom score (MTSS) in the intervention group was 3,73 points lower (4,22 lower to 3,24 lower)	MD **3.73 lower** (4.23 lower to 3.23 lower)	-
	withdrawal due to AE - w8	0 per 1.000	**0 per 1.000** (0 to 0)		not estimable

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary

(Differences to 2016 marked in purple)

1) COMPARISON: NB-UVB BIW + LORATADINE 10MG QD vs. LORATADINE 10MG QD
Data added in 2020 update from 1 new study

Efficacy
Safety

2) COMPARISON: NB-UVB TIW + LEVOCETIRIZINE 10MG (2-FOLD) QD vs. LEVOCETIRIZINE 10MG (2-FOLD) QD
No new data added in 2020

NB-UVB TIW + levocetirizine 10mg (2-fold) QD was superior to levocetirizine 10mg (2-fold) for the outcome: 'mean change in USS7' (moderate quality, but of uncertain clinical importance).

No further evidence could be identified.

Autologeous whole blood injections versus placebo

Should AWB injection vs. placebo be used for urticaria - KQ19* update 2020?	
POPULATION:	patients with CSU
INTERVENTION:	AWB injection
COMPARISON:	placebo
BIBLIOGRAPHY	Staubach 2006, Adolnezhadaian 2016* *- studies added in 2020 update

Assessment

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT

- ● Trivial
- ○ Small
- ○ Moderate
- ○ Large
- ○ Varies
- ○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with AWB injection
clear*	51 (1 RCT)	⨁⨁◯◯ LOW[a,b]	not estimable *(zero in both groups)*	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
good or excellent response-w9*	51 (1 RCT)	⨁⨁◯◯ LOW[a,b]	RR 3.89 (0.22 to 68.11)	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
good or excellent response - w12	56 (1 RCT)	⨁⨁⨁◯ MODERATE[c]	RR 0.64 (0.33 to 1.24)	Study population	
				500 per 1,000	**180 fewer per 1,000** (335 fewer to 120 more)
TSS - w9*	50 (1 RCT)	⨁⨁◯◯ LOW[a,b]	-		MD **0.73 lower** (2.62 lower to 1.16 higher)

a. unclear risk of bias
b. H1-AH non-responders
c. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	no evidence

Values and overall certainty of evidence

JUDGEMENT	RESEARCH EVIDENCE	ADDITIONAL CONSIDERATIONS
○ Very low ● Low ○ Moderate ○ High ○ No included studies	**The relative importance or values of the main outcomes of interest:**	

Outcome	Relative importance	Certainty of the evidence (GRADE)
Clear	critical	⨁⨁◯◯ LOW
good or excellent response - w19	critical	⨁⨁◯◯ LOW
good or excellent response - w12	critical	⨁⨁⨁◯ MODERATE
TSS – w9	critical	⨁⨁◯◯ LOW

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention ○ Varies	**Summary of findings**:

Outcomes	With placebo	With AWB injection	Difference	Relative effect (95% CI)
clear*	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	not estimable
good or excellent response-w9*	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	RR 3.89 (0.22 to 68.11)

● Don't know	good or excellent response - w12	500 per 1,000	**320 per 1,000** (165 to 620)	**180 fewer per 1,000** (335 fewer to 120 more)	RR 0.64 (0.33 to 1.24)
	TSS - w9*		The mean TSS - w9* in the intervention group was MD **0.73 lower** (2.62 lower to 1.16 higher)	MD **0.73 lower** (2.62 lower to 1.16 higher)	-

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary

Data added in 2020 update from 1 new study (differences to 2016 marked in purple)

Efficacy

No difference was found for the outcome: 'clear' (low quality), 'good or excellent response' (low/moderate quality) or 'total symptom score' (low quality).

No further evidence could be identified.

Hydroxychloroquine versus placebo

Should hydroxychloroquine + H1-AH vs. placebo + H1-AH be used for chronic urticaria - KQ19?	
POPULATION:	patients with CSU unresponsive to H1-AH
INTERVENTION:	hydroxychloroquine + H1-AH
COMPARISON:	placebo + H1-AH
BIBLIOGRAPHY	Boonpiyathad 2017* *additional data added in 2020 update/ outcome with new data added 2020

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

● Trivial
○ Small
○ Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo + H1-AH	Risk difference with hydroxychloroquine + H1-AH
mean change in USS - w12*	39 (1 RCT)	⨁◯◯◯ VERY LOW[a,c]	-	The mean mean change in USS - w12* was 0	MD 24.57 lower (33.85 lower to 15.29 lower)
mean change in DLQI - w12*	39 (1 RCT)	⨁◯◯◯ VERY LOW[a,c]	-	The mean mean change in DLQI - w12* was 0	MD 5.83 lower (9.31 lower to 2.35 lower)

a. high risk of bias
b. CI crosses MID threshold and line of no effect: uncertain whether there is any difference
c. reporting of errors bars unclear (assumption made that these are SDs)

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
○ Moderate
○ Small
○ Trivial
○ Varies
● Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo + H1-AH	Risk difference with hydroxychloroquine + H1-AH
				Study population	

patients with at least 1 AE*	55 (1 RCT)	⨁◯◯◯ VERY LOW[a,b]	**RR 1.61** (0.42 to 6.08)	111 per 1.000	68 more per 1.000 (64 fewer to 564 more)

a. high risk of bias
b. CI crosses MID threshold and line of no effect: uncertain whether there is any difference
c. reporting of errors bars unclear (assumption made that these are SDs)

Values and overall certainty of evidence

JUDGEMENT | **RESEARCH EVIDENCE**

● Very low
○ Low
○ Moderate
○ High
○ No included studies

The relative importance or values of the main outcomes of interest:

Outcomes	Importance	Certainty of the evidence (GRADE)
USS	critical	⨁◯◯◯ VERY LOW
DLQI	critical	⨁◯◯◯ VERY LOW
Patients with at least 1 AE	important	⨁◯◯◯ VERY LOW

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT | **RESEARCH EVIDENCE**

○ 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

Summary of findings:

Outcomes	With placebo + H1-AH	With hydroxychloroquine + H1-AH	Difference	Relative effect (95% CI)
patients with at least 1 AE*	111 per 1.000	179 per 1.000 (47 to 676)	68 more per 1.000 (64 fewer to 564 more)	**RR 1.61** (0.42 to 6.08)
mean change in USS - w12*		The mean mean change in USS in the intervention group was 24,57 points lower (33,85 lower to 15,29 lower)	MD 24.57 lower (33.85 lower to 15.29 lower)	-
mean change in DLQI - w12*	The mean mean change in DLQI - w12* was 0	The mean mean change in DLQI in the intervention group was 5,83 points lower (9,31 lower to 2,35 lower)	MD 5.83 lower (9.31 lower to 2.35 lower)	-

Feasibility

Is the intervention feasible to implement?	
JUDGEMENT	**RESEARCH EVIDENCE**
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary:

COMPARISON: HYDROXYCHLOROQUINE AS ADD-ON TO H1-AH vs. PLACEBO + H1-AH
Data added in 2020 update from 1 new study (an extension of study included in 2016)

Efficacy

Hydroxychloroquine as add-on to H1-AH was superior to placebo + H1-AH for the outcome: 'mean change in USS' (very low quality).
No difference was found for: 'mean change in DLQI' (very low quality).

Safety

No difference was found for: 'patients with at least one AE' (very low quality).

Methotrexate versus placebo

Should MTX + H1-AH vs. placebo + H1-AH be used for chronic urticaria - KQ19?	
POPULATION:	patients with CSU unresponsive to standard or two-fold H1-AH
INTERVENTION:	MTX + H1-AH
COMPARISON:	placebo + H1-AH
BIBLIOGRAPHY	Leducq 2019* *additional data added in 2020 update/ outcome with new data added 2020

Assessment

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
● Trivial ○ Small ○ Moderate ○ Large ○ Varies ○ Don't know	

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Median change from baseline (IQR) with MTX+H1-AH	Median change from baseline (IQR) with H1-AH
median change in DLQI w8*	72 (1 RCT)	⨁◯◯◯ VERY LOW[a,c]	-	8.5 (4.8, 12.3)	5.7 (2.9, 11.9)

a. unclear risk of bias due to incomplete outcome data for w8
b. no mean and no SD reported

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	No data available

Values and overall certainty of evidence

JUDGEMENT	RESEARCH EVIDENCE

● Very low
○ Low
○ Moderate
○ High
○ No included studies

The relative importance or values of the main outcomes of interest:

Outcomes	Importance	Certainty of the evidence (GRADE)
DLQI	critical	⨁◯◯◯ VERY LOW

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT

○ 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

RESEARCH EVIDENCE

Summary of findings:

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Median change from baseline (IQR) with MTX+H1-AH	Median change from baseline (IQR) with H1-AH
median change in DLQI w8*	72 (1 RCT)	⨁◯◯◯ VERY LOW[a,c]	-	8.5 (4.8, 12.3)	5.7 (2.9, 11.9)

Feasibility
Is the intervention feasible to implement?

JUDGEMENT

○ No
○ Probably no
○ Probably yes
○ Yes
● Varies
○ Don't know

RESEARCH EVIDENCE

Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary:

COMPARISON: METHOTREXATE AS ADD-ON TO H1-AH vs. PLACEBO + H1-AH
Data added in 2020 update from 1 new study (differences to 2016 marked in purple)

Efficacy

No difference was found for the outcome: 'median change in DLQI' (very low quality).

Dapsone

POPULATION:	patients with chronic spontanious urticaria
INTERVENTION:	dapsone 100mg QD + existing therapy
COMPARISON:	placebo QD + existing therapy
BIBLIOGRAPHY	Morgan 2014 Engine 2008a

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Trivial ○ Small ○Moderate ○ Large ○ Varies ● Don't know	**1) Dapsone 100mg QD + existing therapy vs existing therapy alone**

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo QD + existing therapy	Risk difference with dapsone 100mg QD + existing therapy
complete suppression - w6	22 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 8.27** (0.48 to 143.35)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

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

2) Desloratadine + dapsone compared to desloratadine

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with desloratadine	Risk difference with desloratadine + dapsone
complete suppression - w4	65 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	**RR 6.46** (0.36 to 115.24)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
mean change in UAS7 - w4	62 (1 RCT)	⨁⨁⨁◯ MODERATE [a]	-		MD **1.23 lower** (1.54 lower to 0.92 lower)

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

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE

○ Trivial
○ Small

○Moderate
○ Large
○ Varies
● Don't know

1) Dapsone 100mg QD + existing therapy vs existing therapy alone

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo QD + existing therapy	Risk difference with dapsone 100mg QD + existing therapy
withdrawal due to AE - w6	22 (1 RCT)	⊕⊕⊕⊕ HIGH	not estimable	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)
patients with at least 1 AE - w6	21 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	**RR 1.47** (0.43 to 5.01)	273 per 1.000	**128 more per 1.000** (155 fewer to 1.094 more)

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

2) Desloratadine + dapsone compared to desloratadine

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with desloratadine	Risk difference with desloratadine + dapsone
withdrawal due to AE - w4	65 (1 RCT)	⊕◯◯◯ VERY LOW [1,2,3]	**RR 3.59** (0.18 to 71.91)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

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

Values and overall certainty of the evidence

JUDGEMENT	RESEARCH EVIDENCE
● Low/Very Low	**The relative importance or values of the main outcomes of interest:**

1) Dapsone 100mg QD + existing therapy vs existing therapy alone

Outcome	Relative importance	Certainty of the evidence (GRADE)
complete suppression – w6	critical	⊕⊕◯◯ LOW
withdrawal due to AE - w6	critical	⊕⊕⊕⊕ HIGH
patients with at least 1 AE – w6	important	⊕⊕⊕◯ MODERATE

2) Desloratadine + dapsone compared to desloratadine

Outcome	Relative importance	Certainty of the evidence (GRADE)
complete suppression - w4	critical	⊕◯◯◯ VERY LOW

mean change in UAS7 - - w4	critical	⊕⊕⊕◯ MODERATE
withdrawal due to AE - - w4	critical	⊕◯◯◯ VERY LOW

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT

○ 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

RESEARCH EVIDENCE

Summary of findings:

1) Dapsone 100mg QD + existing therapy vs existing therapy alone

Outcome	With placebo QD + existing therapy	With dapsone 100mg QD + existing therapy	Difference (95% CI)	Relative effect (RR) (95% CI)
complete suppression - w6	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	**RR 8.27** (0.48 to 143.35)
withdrawal due to AE -w6	0 per 1.000	**0 per 1.000** (0 to 0)		not estimable
patients with at least 1 AE -w6	273 per 1.000	**401 per 1.000** (117 to 1.000)	**128 more per 1.000** (from 155 fewer to 1.000 more)	**RR 1.47** (0.43 to 5.01)

2) Desloratadine + dapsone compared to desloratadine

Outcome	With desloratadine	With desloratadine + dapsone	Difference (95% CI)	Relative effect (RR) (95% CI)
complete suppression - w4	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	**RR 6.46** (0.36 to 115.24)
mean change in UAS7 - w4		The mean change in UAS7 in the intervention group was 1,23 points lower (1,54 lower to 0,92 lower)	MD **1.23 lower** (1.54 lower to 0.92 lower)	-
withdrawal due to AE - w4	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	**RR 3.59** (0.18 to 71.91)

Feasibility

Is the intervention feasible to implement?

JUDGEMENT

○ No
○ Probably no
○ Probably yes
○ Yes
● Varies
○ Don't know

RESEARCH EVIDENCE

Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary:

1) Dapsone 100mg Qd + existing therapy vs existing therapy alone

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

2) Desloratadine + dapsone compared to desloratadine

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' (very low quality) and 'withdrawal due to AE' (very low quality).

Motelukast versus montelukast + desloratadine

POPULATION:	patients with chronic spontanious urticaria
INTERVENTION:	Montelukast (+ placebo)
COMPARISON:	Montelukast + desloratadine,
BIBLIOGRAPHY	DiLorenzo 2004

Assessment

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
● Trivial ○ Small ○Moderate ○ Large ○ Varies ○ Don't know	Montelukast (+placebo) vs. montelukast + desloratadine

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with montelukast 10mg QD + desloratadine 5mg QD	Risk difference with montelukast 10mg QD + placebo
mean difference (mean change in TSS)	80 (1 RCT)	⊕⊕⊕◯ MODERATE [a]	-	0	MD **1.14 points higher** (1.03 higher to 1.26 higher)

a. unclear method of randomization and allocation concealment

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Trivial ○ Small ○Moderate ○ Large ○ Varies ● Don't know	Montelukast (+placebo) vs. montelukast + desloratadine No data available

Values and overall certainty of the evidence

JUDGEMENT	RESEARCH EVIDENCE
● Moderate	**The relative importance or values of the main outcomes of interest:** Montelukast (+placebo) vs. montelukast + desloratadine

Outcome	Relative importance	Certainty of the evidence (GRADE)
mean difference (mean change in TSS)	critical	⊕⊕⊕◯ MODERATE

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ 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	**Summary of findings**: Montelukast (+placebo) vs. montelukast + desloratadine

Outcome	With desloratadine 5mg QD + montelukast 10mg QD	With placebo + montelukast 10mg QD	Difference (95% CI)	Relative effect (RR) (95% CI)
mean difference (mean change in TSS)		The(mean change in TSS in the intervention group was 1,14 points higher (1,03 higher to 1,26 higher)	MD **1.14 points higher** (1.03 higher to 1.26 higher)	-

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary:

Montelukast (+placebo) vs. montelukast + desloratadine

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.

PART II: CINDU

Symptomatic dermographism (3 comparisons in total)

1) BETAMETHASONE 2MG + CETIRIZINE HCl 10MG QD vs. CETIRIZINE HCl 10MG QD *(No new data added in 2020)*

POPULATION:	patients with symptomatic dermographism
INTERVENTION(S):	betamethasone 2mg + cetirizine HCl 10mg QD
COMPARISON:	cetirizine HCl 10mg QD
BIBLIOGRAPHY	Kumar 2002

Assessment

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with betamethasone 2mg + cetirizine HCl 10mg QD	Risk difference with cetirizine HCl 10mg QD
complete remission w4	16 (1 RCT)	⨁◯◯◯ VERY LOW[a,b]	**RR 1.44** (0.88 to 2.35)	Study population	
				667 per 1,000	**293 more per 1,000** (80 fewer to 900 more)
≥90% relief w4	16 (1 RCT)	⨁◯◯◯ VERY LOW[a,b]	**RR 1.25** (0.84 to 1.86)	Study population	
				778 per 1,000	**194 more per 1,000** (124 fewer to 669 more)

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

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT: RESEARCH EVIDENCE

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with betamethasone 2mg + cetirizine HCl 10mg QD	Risk difference with cetirizine HCl 10mg QD
withdrawal due to AE w4	16 (1 RCT)	⨁⨁◯◯ LOW[a]	not estimable	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

a. CCT

Values and overall certainty of the evidence

JUDGEMENT | **RESEARCH EVIDENCE**

● Very low
○ Low
○ Moderate
○ High
○ No included studies

The relative importance or values of the main outcomes of interest:

Outcomes	Importance	Certainty of the evidence (GRADE)
complete remission w4	critical	⨁◯◯◯ VERY LOW[a,b]
≥90% relief w4	critical	⨁◯◯◯ VERY LOW[a,b]
withdrawal due to AE w4	critical	⨁⨁◯◯ LOW[a]

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

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT | **RESEARCH EVIDENCE**

	Outcomes	With betamethasone 2mg + cetirizine HCl 10mg QD	With cetirizine HCl 10mg QD	Difference	Relative effect (95% CI)
○ 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	complete remission w4	667 per 1,000	**960 per 1,000** (587 to 1,000)	**293 more per 1,000** (80 fewer to 900 more)	**RR 1.44** (0.88 to 2.35)
	≥90% relief w4	778 per 1,000	**972 per 1,000** (653 to 1,000)	**194 more per 1,000** (124 fewer to 669 more)	**RR 1.25** (0.84 to 1.86)
	withdrawal due to AE w4	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	not estimable

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary:

1) COMPARISON: BETAMETHASONE 2MG + CETIRIZINE HCl 10MG QD vs. CETIRIZINE HCl 10MG QD FOR DERMOGRAPHISM
No new data added in 2020

Efficacy
No difference was found for the outcomes: 'complete remission' (very low quality) and '>=90% relief' (very low quality).

Safety
No difference was found for the outcome: 'withdrawal due to adverse event' (low quality).

2) COMPARISON: omalizumab 300MG vs. placebo

3) COMPARISON: omalizumab 150mg vs. placebo

POPULATION:	patients with symptomatic dermographism
INTERVENTION(S):	2) omalizumab 300mg every 4w, 3) omalizumab 150mg every 4w
COMPARISON:	placebo
BIBLIOGRAPHY	Maurer 2017* *New study in 2020 update

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE

2) omalizumab 300mg every 4w vs. placebo

○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know

2) omalizumab 300mg every 4w compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with omalizumab 300mg every 4w
complete response w10	42 (1 RCT)	⨁⨁◯◯ LOW[a,b]	**RR 5.00** (1.24 to 20.12)	Study population	
				95 per 1,000	**381 more per 1,000** (23 more to 1,821 more)
change in trigger threshold from baseline w10	42 (1 RCT)	⨁◯◯◯ VERY LOW[b,d]	-		MD **1.4 lower** (2.38 lower to 0.42 lower)
DLQI w10	38 (1 RCT)	⨁◯◯◯ VERY LOW[c,d]	-		MD **3.25 lower** (6.73 lower to 0.23 higher)

a. Several risk-of-bias items unclear
b. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
c. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
d. High risk of bias due to incomplete outcome data

3) omalizumab

150mg every 4w vs. placebo

○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know

3) omalizumab 150mg every 4w compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with omalizumab 150mg every 4w
complete response w10	40 (1 RCT)	⨁⨁◯◯ LOW[a,b]	**RR 4.42** (1.07 to 18.29)	Study population	
				95 per 1,000	**326 more per 1,000** (7 more to 1,647 more)
change in trigger threshold from baseline w10	40 (1 RCT)	⨁◯◯◯ VERY LOW[b,d]	-		MD **1.2 lower** (2.17 lower to 0.23 lower)
DLQI w10	37 (1 RCT)	⨁⨁◯◯ LOW[,d]	-		MD **4.27 lower** (8.16 lower to 0.38 lower)

a. Several risk-of-bias items unclear
b. CI crosses MID threshold: statistically significant difference of uncertain clinical importance
c. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
d. High risk of bias due to incomplete outcome data

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT | RESEARCH EVIDENCE

2) omalizumab 300mg every 4w vs. placebo

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

2) omalizumab 300mg every 4w compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with omalizumab 300mg every 4w
withdrawal due to AE w10	42 (1 RCT)	⨁⨁⨁◯ MODERATE[a]	not estimable *(zero in both groups)*	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
patients with at least 1 AE w10	42 (1 RCT)	⨁⨁◯◯ LOW[a,b]	**RR 0.89** (0.70 to 1.15)	Study population	
				905 per 1,000	**100 fewer per 1,000** (271 fewer to 136 more)

a. Several risk-of-bias items unclear

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

3) omalizumab 150mg vs. placebo

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

3) omalizumab 150mg every 4w compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with omalizumab 150mg every 4w
withdrawal due to AE w10	40 (1 RCT)	⨁⨁⨁◯ MODERATE[a]	not estimable *(zero in both groups)*	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
patients with at least 1 AE w10	40 (1 RCT)	⨁⨁◯◯ LOW[a,b]	**RR 0.99** (0.80 to 1.22)	Study population	
				905 per 1,000	**9 fewer per 1,000** (181 fewer to 199 more)

a. Several risk-of-bias items unclear
b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Values and overall certainty of the evidence

JUDGEMENT	RESEARCH EVIDENCE

2) & 3) omalizumab 300mg or 150mg every 4w vs. placebo

○ Very low
● Low
○ Moderate
○ High
○ No included studies

The relative importance or values of the main outcomes of interest:

2) omalizumab 300mg every 4w compared to placebo

Outcomes	Importance	Certainty of the evidence (GRADE)
complete response w10	critical	⨁⨁◯◯ LOW
change in trigger threshold from baseline w10	critical	⨁◯◯◯ VERY LOW
DLQI w10	critical	⨁◯◯◯ VERY LOW
withdrawal due to AE w10	critical	⨁⨁⨁◯ MODERATE

patients with at least 1 AE w10	important	⨁⨁◯◯ LOW

3) omalizumab 150mg every 4w compared to placebo

Outcomes	Importance	Certainty of the evidence (GRADE)
complete response w10	critical	⨁⨁◯◯ LOW
change in trigger threshold from baseline w10	critical	⨁◯◯◯ VERY LOW
DLQI w10	critical	⨁◯◯◯ VERY LOW
withdrawal due to AE w10	critical	⨁⨁⨁◯ MODERATE
patients with at least 1 AE w10	important	⨁⨁◯◯ LOW

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
2) omalizumab 300mg every 4w vs. placebo ○ Favors the comparison ○ Probably favors the comparison ○ Does not favor either the intervention or the comparison ○ Probably favors the intervention ○ Favors the intervention	**2) omalizumab 300mg every 4w compared to placebo**

Outcomes	With placebo	With omalizumab 300mg every 4w	Difference	Relative effect (95% CI)
complete response - w10	95 per 1,000	**476 per 1,000** (118 to 1,000)	**381 more per 1,000** (23 more to 1,821 more)	**RR 5.00** (1.24 to 20.12)
change in trigger threshold from baseline - w10		The mean change in trigger threshold from baseline - w10 in the intervention group was 1.4 points lower (2.38 lower to 0.42 lower)	MD **1.4 lower** (2.38 lower to 0.42 lower)	-

○ Varies
● Don't know

DLQI - w10		The mean DLQI - w10 in the intervention group was 3.25 points lower (18.42 lower to 11.92 higher)	MD **3.25 lower** (18.42 lower to 11.92 higher)	-
withdrawal due to AE - w10	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	not estimable
patients with at least 1 AE - w10	905 per 1,000	**805 per 1,000** (633 to 1,000)	**100 fewer per 1,000** (271 fewer to 136 more)	**RR 0.89** (0.70 to 1.15)

3) omalizumab 150mg every 4w compared to placebo

3) omalizumab 150mg every 4w vs. placebo

○ 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

Outcomes	With placebo	With omalizumab 150mg every 4w	Difference	Relative effect (95% CI)
complete response w10	95 per 1,000	**421 per 1,000** (102 to 1,000)	**326 more per 1,000** (7 more to 1,647 more)	**RR 4.42** (1.07 to 18.29)
change in trigger threshold from baseline w10		The mean change in trigger threshold from baseline w10 in the intervention group was 1.2 points lower (2.17 lower to 0.23 lower)	MD **1.2 lower** (2.17 lower to 0.23 lower)	-
DLQI w10		The mean DLQI w10 in the intervention group was 4.27 points lower (20.86 lower to 12.32 higher)	MD **4.27 lower** (20.86 lower to 12.32 higher)	-
withdrawal due to AE w10	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	not estimable
patients with at least 1 AE w10	905 per 1,000	**896 per 1,000** (724 to 1,000)	**9 fewer per 1,000** (181 fewer to 199 more)	**RR 0.99** (0.80 to 1.22)

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
2) & 3) omalizumab 300mg or 150mg every 4w vs. placebo ○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	**2) & 3) omalizumab 300mg or 150mg every 4w vs. placebo** Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary:

(Differences to 2016 marked in purple.)

2) COMPARISON: OMALIZUMAB 300MG EVERY 4 WEEKS vs. PLACEBO FOR DERMOGRAPHISM
Data added in 2020 update from 1 new study

Efficacy
Omalizumab 300mg every 4 weeks was superior to placebo for the outcomes: 'complete response' (low quality) and 'change in trigger threshhold from baseline' (very low quality).

No difference was found for the outcome: 'DLQI' (very low quality).

Safety
No difference was found for the outcome: 'withdrawal due to adverse event' (moderate quality) and 'patients with at least one adverse event' (low quality).

3) COMPARISON: OMALIZUMAB 150MG EVERY 4 WEEKS vs. PLACEBO FOR DERMOGRAPHISM
Data added in 2020 update from 1 new study

Efficacy
Omalizumab 150mg every 4 weeks was superior to placebo for the outcomes: 'complete response' (low quality) and 'change in trigger threshhold from baseline' (very low quality).

No difference was found for the outcome: 'DLQI' (very low quality).

Safety
No difference was found for the outcomes: 'withdrawal due to adverse event' (moderate quality) and 'patients with at least one adverse event' (low quality).

Cold urticaria (8 comparisons in total)

1) Comparison: 2nd gen H1-AH: high dose vs. low dose (No new data added in 2020)

Are 2nd gen H1-AH (high dose) more effective and safer than 2nd gen H1-AH (low dose) in patients with cold urticaria?	
POPULATION:	patients with cold urticaria
INTERVENTION:	2nd gen H1-AH (high dose)
COMPARISON:	2nd gen H1-AH (low dose)
BIBLIOGRAPHY	Krause 2013, Magerl 2012, Kaplan2010/Siebenhaar 2009, Abajian 2016

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

2nd gen AH 2-fold compared to 2nd gen AH 1-2-fold for cold urticaria

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 2nd gen AH (different dosage)	Risk difference with 2nd gen AH
symptom free - 2nd gen AH 2-fold vs. 1-fold (1w)	40 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 1.57** (0.77 to 3.22)	350 per 1.000	**200 more per 1.000** (80 fewer to 777 more)
symptom free - 2nd gen AH 1 to 2-fold increase vs. 1-fold (4w)	27 (1 RCT)	⨁⨁◯◯ LOW [b,c]	**RR 4.06** (0.21 to 77.37)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

2nd gen AH 4-fold compared to 2nd gen AH 1-fold for cold urticaria

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 2nd gen AH (different dosage)	Risk difference with 2nd gen AH
symptom free - 2nd gen AH 4-fold vs. 1-fold (1w)	100 (2 RCTs)	⨁⨁◯◯ LOW [a,c]	**RR 1.90** (1.15 to 3.16)	280 per 1.000	**252 more per 1.000** (42 more to 605 more)

2nd gen AH 4-fold compared to 2nd gen AH 2-fold for cold urticaria

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 2nd gen AH (different dosage)	Risk difference with 2nd gen AH
symptom free - 2nd gen AH 4-fold vs. 2-fold (1w)	85 (2 RCTs)	⨁⨁◯◯ LOW [a,c]	**RR 1.16** (0.77 to 1.76)	465 per 1.000	**74 more per 1.000** (107 fewer to 353 more)

a. unclear risk of bias
b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
c. wide CI
d. CI crosses MID threshold: statistically significant difference of uncertain clinical importance

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Large ○ Moderate ● Small ○ Trivial ○ Varies ○ Don't know	

2nd gen AH 2-fold compared to 2nd gen AH 1-2-fold for cold urticaria

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 2nd gen AH (different dosage)	Risk difference with 2nd gen AH
patients with at least 1 AE - 2nd gen AH 2-fold vs. 1-fold (w1)	40 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 1.40** (0.53 to 3.68)	250 per 1.000	**100 more per 1.000** (118 fewer to 670 more)

2nd gen AH 4-fold compared to 2nd gen AH 1-fold for cold urticaria

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 2nd gen AH (different dosage)	Risk difference with 2nd gen AH
patients with at least 1 AE - 2nd gen AH 4-fold vs. 1-fold (1w)	40 (1 RCT)	⨁⨁◯◯ LOW [a,b]	**RR 0.80** (0.25 to 2.55)	250 per 1.000	**50 fewer per 1.000** (188 fewer to 387 more)

2nd gen AH 4-fold compared to 2nd gen AH 2-fold for cold urticaria

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 2nd gen AH (different dosage)	Risk difference with 2nd gen AH
withdrawal due to AE - 2nd gen AH 1 to 4-fold increase vs. 2-fold (6w)	28 (1 RCT)	⨁⨁⨁⨁ HIGH	not estimable	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

patients with at least 1 AE - 2nd gen AH 4-fold vs. 2-fold (1w)	86 (2 RCTs)	⨁⨁◯◯ LOW [a,b]	**RR 1.02** (0.38 to 2.73)	326 per 1.000	**7 more per 1.000** (202 fewer to 563 more)

a. unclear risk of bias
b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
c. wide CI
d. CI crosses MID threshold: statistically significant difference of uncertain clinical importance

Values and overall certainty of evidence

JUDGEMENT | **RESEARCH EVIDENCE**

○ Very low
● Low
○ Moderate
○ High
○ No included studies

The relative importance or values of the main outcomes of interest:

Outcome	Relative importance	Certainty of the evidence (GRADE)
symptom free - 2nd gen AH 2-fold vs. 1-fold (1w)	critical	⨁⨁◯◯ LOW
symptom free - 2nd gen AH 1 to 2-fold increase vs. 1-fold (4w)	critical	⨁⨁◯◯ LOW
symptom free - 2nd gen AH 4-fold vs. 1-fold (1w)	critical	⨁⨁◯◯ LOW
symptom free - 2nd gen AH 4-fold vs. 2-fold (1w)	critical	⨁⨁◯◯ LOW
withdrawal due to AE - 2nd gen AH 1 to 4-fold increase vs. 2-fold (6w)	critical	⨁⨁⨁⨁ HIGH
patients with at least 1 AE - 2nd gen AH 2-fold vs. 1-fold (w1)	important	⨁⨁◯◯ LOW
patients with at least 1 AE - 2nd gen AH 4-fold vs. 1-fold (1w)	important	⨁⨁◯◯ LOW
patients with at least 1 AE - 2nd gen AH 4-fold vs. 2-fold (1w)	important	⨁⨁◯◯ LOW

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT | **RESEARCH EVIDENCE**

○ 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

Summary of findings:

Outcome	With 2nd gen AH (different dosage)	With 2nd gen AH	Difference (95% CI)	Relative effect (RR) (95% CI)
symptom free - 2nd gen AH 2-fold vs. 1-fold (1w)	350 per 1.000	**550 per 1.000** (269 to 1.000)	**200 more per 1.000** (from 80 fewer to 777 more)	**RR 1.57** (0.77 to 3.22)
symptom free - 2nd gen AH 1 to 2-fold increase vs. 1-fold (4w)	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	**RR 4.06** (0.21 to 77.37)
symptom free - 2nd gen AH 4-fold vs. 1-fold (1w)	280 per 1.000	**532 per 1.000** (322 to 885)	**252 more per 1.000** (from 42 more to 605 more)	**RR 1.90** (1.15 to 3.16)

know	symptom free - 2nd gen AH 4-fold vs. 2-fold (1w)	465 per 1.000	**540 per 1.000** (358 to 819)	**74 more per 1.000** (from 107 fewer to 353 more)	**RR 1.16** (0.77 to 1.76)
	withdrawal due to AE - 2nd gen AH 1 to 4-fold increase vs. 2-fold (6w)	0 per 1.000	**0 per 1.000** (0 to 0)		not estimable
	patients with at least 1 AE - 2nd gen AH 2-fold vs. 1-fold (w1)	250 per 1.000	**350 per 1.000** (133 to 920)	**100 more per 1.000** (from 118 fewer to 670 more)	**RR 1.40** (0.53 to 3.68)
	patients with at least 1 AE - 2nd gen AH 4-fold vs. 1-fold (1w)	250 per 1.000	**200 per 1.000** (63 to 638)	**50 fewer per 1.000** (from 188 fewer to 387 more)	**RR 0.80** (0.25 to 2.55)
	patients with at least 1 AE - 2nd gen AH 4-fold vs. 2-fold (1w)	326 per 1.000	**332 per 1.000** (124 to 889)	**7 more per 1.000** (from 202 fewer to 563 more)	**RR 1.02** (0.38 to 2.73)

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary:

1) COMPARISON: 2ND GENERATION H1-AH (HIGH DOSE) vs. 2ND GENERATION H1-AH (LOW DOSE) FOR COLD URTICARIA
No new data added in 2020

Efficacy

2nd generation H1-AH (high dose) was superior to 2nd generation H1-AH (low dose) for the outcome: 'symptom free' (low quality).

Safety

No difference was found for the outcomes: 'patients with at least one adverse event' (low quality) and (for 4-fold vs. 2-fold only) 'withdrawal due to adverse event' (high).

2) COMPARISON: 2ND GENERATION H1-AH vs. 1ST GENERATION H1-AH

(No new data added in 2020)

Are 2nd gen H1-AH more effective and safer than 1st gen H1-AH in patients with cold urticaria?	
POPULATION:	patients with cold urticaria
INTERVENTION:	2nd gen H1-AH
COMPARISON:	1st gen H1-AH
BIBLIOGRAPHY	Villas Martinez 1992

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT

○ Trivial
● Small
○ Moderate
○ Large
○ Varies
○ Don't know

RESEARCH EVIDENCE

2nd gen AH compared to 1st gen AH for cold urticaria

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 1st gen AH	Risk difference with 2nd gen AH
symptom free (2w)	20 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	**RR 0.86** (0.30 to 2.49)	667 per 1.000	**93 fewer per 1.000** (467 fewer to 993 more)

a. unclear risk of bias
b. statistical heterogeneity (I^2 = 40%) maybe due to methodological differences
c. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
d. wide CI

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT

○ Large
● Moderate
○ Small
○ Trivial
○ Varies
○ Don't know

RESEARCH EVIDENCE

2nd gen AH compared to 1st gen AH for cold urticaria

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with 1st gen AH	Risk difference with 2nd gen AH
patients with at least one AE (time unclear)	19 (1 RCT)	⨁◯◯◯ VERY LOW [a,d]	**RR 0.37** (0.10 to 1.39)	600 per 1.000	**378 fewer per 1.000** (540 fewer to 234 more)

drowsiness (time unclear)	19 (1 RCT)	⊕◯◯◯ VERY LOW [a,c,d]	**RR 0.32** (0.06 to 1.80)	600 per 1.000	**408 fewer per 1.000** (564 fewer to 480 more)

a. unclear risk of bias
b. statistical heterogeneity (I^2 = 40%) maybe due to methodological differences
c. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
d. wide CI

Values and overall certainty of evidence

JUDGEMENT | **RESEARCH EVIDENCE**

● Very low
○ Low
○ Moderate
○ High
○ No included studies

The relative importance or values of the main outcomes of interest:

Outcome	Relative importance	Certainty of the evidence (GRADE)
symptom free (2w)	critical	⊕◯◯◯ VERY LOW
patients with at least one AE (time unclear)	important	⊕◯◯◯ VERY LOW
drowsiness (time unclear)	important	⊕◯◯◯ VERY LOW

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT | **RESEARCH EVIDENCE**

○ 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

Summary of findings:

Outcome	With 1st gen AH	With 2nd gen AH	Difference (95% CI)	Relative effect (RR) (95% CI)
symptom free (2w)	667 per 1.000	**573 per 1.000** (200 to 1.000)	**93 fewer per 1.000** (from 467 fewer to 993 more)	**RR 0.86** (0.30 to 2.49)
patients with at least one AE (time unclear)	600 per 1.000	**222 per 1.000** (60 to 834)	**378 fewer per 1.000** (from 234 more to 540 fewer)	**RR 0.37** (0.10 to 1.39)
drowsiness (time unclear)	600 per 1.000	**192 per 1.000** (36 to 1.000)	**408 fewer per 1.000** (from 480 more to 564 fewer)	**RR 0.32** (0.06 to 1.80)

Feasibility

Is the intervention feasible to implement?

JUDGEMENT | **RESEARCH EVIDENCE**

○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary:

2) COMPARISON: 2ND GENERATION H1-AH vs. 1ST GENERATION H1-AH FOR COLD URTICARIA

No new data added in 2020

Efficacy

No difference was found for the outcome: 'symptom free' (very low quality).

Safety

No difference was found for the outcomes: 'patients with at least one adverse event' (very low quality) and 'drowsiness' (very low quality).

3) COMPARISON: 2ND GENERATION H1-AH 1-4 FOLD vs. PLACEBO

(No new data added in 2020)

Are 2nd gen H1-AH more effective and safer than 1st gen H1-AH in patients with cold urticaria?	
POPULATION:	patients with cold urticaria
INTERVENTION:	2nd gen H1-AH 1-4 fold
COMPARISON:	placebo
BIBLIOGRAPHY	Krause 2013, Dubertret 2003, Kaplan2010/Siebenhaar 2009, Metz 2010, Abajian 2016

Assessment

Desirable Effects How substantial are the desirable anticipated effects?	
JUDGEMENT	**RESEARCH EVIDENCE**

○ Trivial
○ Small
● Moderate
○ Large
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with 2nd gen H1-AH 1-4 fold
symptom free	268 (4 RCTs)	⊕⊕⊕◯ MODERATE [a]	**RR 4.33** (2.11 to 8.85)	61 per 1.000	**202 more per 1.000** (67 more to 476 more)

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

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT | **RESEARCH EVIDENCE**

○ Large
○ Moderate
● Small
○ Trivial
○ Varies
○ Don't know

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with 2nd gen H1-AH 1-4 fold
withdrawal due to AE	96 (2 RCTs)	⊕⊕⊕◯ MODERATE [a]	not pooled	not pooled	not pooled
patients with at least 1AE	199 (3 RCTs)	⊕⊕◯◯ LOW [a,b]	**RR 1.63** (0.92 to 2.89)	162 per 1.000	**102 more per 1.000** (13 fewer to 306 more)

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

Values and overall certainty of evidence

JUDGEMENT | **RESEARCH EVIDENCE**

○ Very low
○ Low
● Moderate
○ High
○ No included studies

The relative importance or values of the main outcomes of interest:

Outcome	Relative importance	Certainty of the evidence (GRADE)
symptom free	critical	⊕⊕⊕◯ MODERATE
withdrawal due to AE	critical	⊕⊕⊕◯ MODERATE
patients with at least 1AE	important	⊕⊕◯◯ LOW

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT | **RESEARCH EVIDENCE**

○ 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	Summary of findings: **Outcome** | **With placebo** | **With 2nd gen AH (1-4 fold)** | **Difference (95% CI)** | **Relative effect (RR) (95% CI)** symptom free | 61 per 1.000 | **262 per 1.000** (128 to 536) | **202 more per 1.000** (from 67 more to 476 more) | **RR 4.33** (2.11 to 8.85) withdrawal due to AE | 0 per 1.000 | **0 per 1.000** (0 to 0) | | not pooled patients with at least 1AE | 162 per 1.000 | **264 per 1.000** (149 to 468) | **102 more per 1.000** (from 13 fewer to 306 more) | **RR 1.63** (0.92 to 2.89)

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary:

3) COMPARISON: 2ND GENERATION H1-AH 1-4 FOLD vs. PLACEBO FOR COLD URTICARIA
No new data added in 2020

Efficacy
2nd generation H1-AH 1-4 fold were superior to placebo based on the outcome: 'symptom free' (moderate quality).

Safety
No difference was found for the outcomes: 'patients with at least one adverse event' (low quality) and 'withdrawal due to adverse event' (moderate quality).

4) COMPARISON: DOXEPINE vs. PLACEBO

(No new data added in 2020)

Evidence Report *The International EAACI/GA²LEN/EuroGuiDerm/APAAACI Guideline for the Definition, Classification, Diagnosis and Management of Urticaria*	**EuroGuiDerm** Centre for Guideline Development

Is doxepine more effective and safer than placebo in patients with cold urticaria?	
POPULATION:	patients with cold urticaria
INTERVENTION:	doxepine
COMPARISON:	placebo
BIBLIOGRAPHY	Neittaanmäki 1984, Neittaanmäki 1984

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Trivial ○ Small ● Moderate ○ Large ○ Varies ○ Don't know	**Doxepine compared to placebo for cold urticaria**

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with doxepine
very effective- 1w	44 (2 RCTs)	⨁⨁◯◯ LOW [a,b]	**RR 14.90** (2.13 to 104.08)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

a. unclear risk of bias
b. wide CI

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	No evidence

Values and overall certainty of evidence

JUDGEMENT	RESEARCH EVIDENCE
○ Very low ● Low ○ Moderate ○ High ○ No included studies	**The relative importance or values of the main outcomes of interest:**

Outcome	Relative importance	Certainty of the evidence (GRADE)
very effective- 1w	critical	⨁⨁◯◯ LOW

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ 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	**Summary of findings:**

Outcome	With placebo	With doxepine	Difference (95% CI)	Relative effect (RR) (95% CI)
very effective-1w	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	**RR 14.90** (2.13 to 104.08)

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary:

4) COMPARISON: DOXEPINE vs. PLACEBO FOR COLD URTICARIA

No new data added in 2020

Efficacy

Doxepine was superior to placebo based on the outcome: 'very effective' (low quality).

Safety

No safety data were available.

5) COMPARISON: HYDROXYZINE vs. DOXEPINE

(No new data added in 2020)

Is hydroxyzine more effective and safer than doxepine in patients with cold urticaria?	
POPULATION:	patients with cold urticaria
INTERVENTION:	hydroxyzine
COMPARISON:	doxepine
BIBLIOGRAPHY	Neittaanmäki 1984

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	**Hydroxyzine compared to doxepine for cold urticaria**

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with doxepine	Risk difference with hydroxyzine
very effective	24 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	**RR 0.33** (0.08 to 1.33)	500 per 1.000	**335 fewer per 1.000** (460 fewer to 165 more)

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

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies ● Don't know	No evidence

Values and overall certainty of evidence

JUDGEMENT	RESEARCH EVIDENCE

● Very low ○ Low ○ Moderate ○ High ○ No included studies	**The relative importance or values of the main outcomes of interest:** **Outcome** | **Relative importance** | **Certainty of the evidence (GRADE)** very effective | critical | ⊕◯◯◯ VERY LOW

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ 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	**Summary of findings**: **Outcome** | **With doxepine** | **With hydroxyzine** | **Difference (95% CI)** | **Relative effect (RR) (95% CI)** very effective | 500 per 1.000 | **165 per 1.000** (40 to 665) | **335 fewer per 1.000** (from 165 more to 460 fewer) | **RR 0.33**

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary:

5) COMPARISON: HYDROXYZINE vs. DOXEPINE FOR COLD URTICARIA

No new data added in 2020

Efficacy

No difference was found for the outcome: 'very effective' (very low quality).

Safety

No safety data were available.

6) COMPARISON: HYDROXYZINE vs. PLACEBO

(No new data added in 2020)

Is hydroxyzine more effective and safer than placebo in patients with cold urticaria?	
POPULATION:	patients with cold urticaria
INTERVENTION:	hydroxyzine
COMPARISON:	placebo
BIBLIOGRAPHY	Neittaanmäki 1984

Assessment

Desirable Effects

How substantial are the desirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Trivial ○ Small ○ Moderate ○ Large ○ Varies ● Don't know	**Hydroxyzine compared to placebo for cold urticaria**

Outcomes	№ of participants (studies) Follow-up	Quality of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects	
				Risk with placebo	Risk difference with hydroxyzine
very effective	24 (1 RCT)	⨁◯◯◯ VERY LOW [a,b,c]	**RR 5.00** (0.27 to 94.34)	0 per 1.000	**0 fewer per 1.000** (0 fewer to 0 fewer)

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

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
○ Large ○ Moderate ○ Small ○ Trivial ○ Varies	No evidence

● Don't know	

Values and overall certainty of evidence
What is the overall certainty of the evidence of effects?

JUDGEMENT	RESEARCH EVIDENCE
● Very low ○ Low ○ Moderate ○ High ○ No included studies	**The relative importance or values of the main outcomes of interest:**

Outcome	Relative importance	Certainty of the evidence (GRADE)
very effective	critical	⊕◯◯◯ VERY LOW

Balance of effects
Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT	RESEARCH EVIDENCE
○ 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	**Summary of findings:**

Outcome	With placebo	With hydroxyzine	Difference (95% CI)	Relative effect (RR) (95% CI)
very effective	0 per 1.000	**0 per 1.000** (0 to 0)	**0 fewer per 1.000** (from 0 fewer to 0 fewer)	**RR 5.00** (0.27 to 94.34)

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

know	

Summary:

6) COMPARISON: HYDROXYZINE vs. PLACEBO FOR COLD URTICARIA
No new data added in 2020

Efficacy
No difference was found for the outcome: 'very effective' (very low quality).

Safety
No safety data were available.

7) COMPARISON: OMALIZUMAB 300mg EVERY 4 WEEKS vs. PLACEBO

8) COMPARISON: OMALIZUMAB 150mg EVERY 4 WEEKS vs. PLACEBO

POPULATION:	patients with cold urticaria
INTERVENTION(S):	omalizumab 300mg every 4w, omalizumab 150mg every 4w
COMPARISON:	placebo
BIBLIOGRAPHY	Metz 2017* *New study in 2020 update

Assessment

Desirable Effects How substantial are the desirable anticipated effects?	
JUDGEMENT	RESEARCH EVIDENCE
7) omalizumab 300mg every 4w vs. placebo ○ Trivial ○ Small ○ Moderate ○ Large	**7) omalizumab 300mg every 4w compared to placebo**

● Varies
○ Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with omalizumab 300mg every 4w
complete response w10	21 (1 RCT)	⨁⨁⨁◯ MODERATE[a,b]	**RR 11.70** (0.71 to 192.98)	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
change in trigger threshold from baseline w10	21 (1 RCT)	⨁⨁⨁⨁ HIGH	-		MD **10.1 lower** (16.63 lower to 3.57 lower)

8) omalizumab 150mg every 4w vs. placebo

○ Trivial
○ Small
○ Moderate
○ Large
● Varies
○ Don't know

a. Wide confidence interval
b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

8) omalizumab 150mg every 4w compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with omalizumab 150mg every 4w
complete response w10	22 (1 RCT)	⨁⨁⨁◯ MODERATE[a,b]	**RR 10.64** (0.64 to 176.54)	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
change in trigger threshold from baseline w10	22 (1 RCT)	⨁⨁⨁⨁ HIGH	-		MD **10.3 lower** (15.5 lower to 5.1 lower)

a. Wide confidence interval
b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Undesirable Effects

How substantial are the undesirable anticipated effects?

JUDGEMENT	RESEARCH EVIDENCE
7) omalizumab 300mg every 4w vs. placebo ○ Large ○ Moderate ○ Small ● Trivial	**7) omalizumab 300mg every 4w compared to placebo**

○ Varies
○ Don't know

8) omalizumab 150mg every 4w vs. placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with omalizumab 300mg every 4w
withdrawal due to AE w10	21 (1 RCT)	⨁⨁⨁⨁ HIGH	not estimable *(zero in both groups)*	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
patients with at least 1 AE w10	21 (1 RCT)	⨁⨁⨁◯ MODERATE[a]	**RR 1.04** (0.64 to 1.67)	Study population	
				750 per 1,000	**30 more per 1,000** (270 fewer to 502 more)

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

○ Large
○ Moderate
○ Small
● Trivial
○ Varies
○ Don't know

8) omalizumab 150mg every 4w compared to placebo

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with omalizumab 150mg every 4w
withdrawal due to AE w10	22 (1 RCT)	⨁⨁⨁⨁ HIGH	not estimable *(zero in both groups)*	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)
patients with at least 1 AE w10	22 (1 RCT)	⨁⨁⨁◯ MODERATE[b]	**RR 0.93** (0.55 to 1.57)	Study population	
				750 per 1,000	**52 fewer per 1,000** (337 fewer to 428 more)

a. Wide confidence interval
b. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference

Values and overall certainty of the evidence

JUDGEMENT	RESEARCH EVIDENCE
7) & 8) omalizumab 300mg or 150mg every 4w vs. placebo	**The relative importance or values of the main outcomes of interest:** **7) omalizumab 300mg every 4w compared to placebo**

○ Very low
○ Low
● Moderate
○ High
○ No included studies

Outcomes	Importance	Certainty of the evidence (GRADE)
complete response w10	critical	⊕⊕⊕◯ MODERATE
change in trigger threshold from baseline w10	critical	⊕⊕⊕⊕ HIGH
withdrawal due to AE w10	critical	⊕⊕⊕⊕ HIGH
patients with at least 1 AE w10	important	⊕⊕⊕◯ MODERATE

8) omalizumab 150mg every 4w compared to placebo

Outcomes	Importance	Certainty of the evidence (GRADE)
complete response w10	critical	⊕⊕⊕◯ MODERATE
withdrawal due to AE w10	critical	⊕⊕⊕⊕ HIGH
patients with at least 1 AE w10	critical	⊕⊕⊕◯ MODERATE
change in trigger threshold from baseline w10	important	⊕⊕⊕⊕ HIGH

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT

7) omalizumab 300mg every 4w vs. placebo

○ Favors the comparison
○ Probably favors the comparison
○ Does not favor either the intervention or the comparison
○ Probably favors the intervention
○ Favors the intervention

RESEARCH EVIDENCE

7) omalizumab 300mg every 4w compared to placebo

Outcomes	With placebo	With omalizumab 300mg every 4w	Difference	Relative effect (95% CI)
complete response w10	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 11.70** (0.71 to 192.98)
change in trigger threshold from baseline w10		The mean change in trigger threshold from baseline w10 in the intervention group was 10.1 points lower (16.63 lower to 3.57 lower)	MD **10.1 lower** (16.63 lower to 3.57 lower)	-
withdrawal due to AE w10	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000**	not estimable

○ Varies ● Don't know				(0 fewer to 0 fewer)	
	patients with at least 1 AE w10	750 per 1,000	**780 per 1,000** (480 to 1,000)	**30 more per 1,000** (270 fewer to 502 more)	**RR 1.04** (0.64 to 1.67)

8) omalizumab 150mg every 4w compared to placebo

8) omalizumab 150mg every 4w vs. placebo ○ 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	**Outcomes**	**With placebo**	**With omalizumab 150mg every 4w**	**Difference**	**Relative effect (95% CI)**
	complete response w10	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	**RR 10.64** (0.64 to 176.54)
	withdrawal due to AE w10	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	not estimable
	patients with at least 1 AE w10	750 per 1,000	**698 per 1,000** (413 to 1,000)	**52 fewer per 1,000** (337 fewer to 428 more)	**RR 0.93** (0.55 to 1.57)
	change in trigger threshold from baseline w10		The mean change in trigger threshold from baseline w10 in the intervention group was 10.3 points lower (15.5 lower to 5.1 lower)	MD **10.3 lower** (15.5 lower to 5.1 lower)	-

Feasibility

Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
7) & 8) omalizumab 300mg or 150mg every 4w vs. placebo ○ No ○ Probably no ○ Probably yes ○ Yes	**7) & 8) omalizumab 300mg or 150mg every 4w vs. placebo** Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

● Varies ○ Don't know	

Summary:

(Differences to 2016 marked in purple.)

7) & 8) COMPARISON: OMALIZUMAB 300mg OR 150mg EVERY 4 WEEKS vs. PLACEBO FOR COLD URTICARIA

Data added in 2020 update from 1 new study

Efficacy

Omalizumab 300mg or 150mg every 4 weeks was superior to placebo for the outcome: 'change in trigger threshhold from baseline' (high quality).

No difference was found for the outcome: 'complete response' (moderate quality).

Safety

No difference was found for the outcomes: 'withdrawal due to adverse event' (high quality) or 'patients with at least one adverse event' (moderate quality).

Cholinergic urticaria (1 comparison)

1) Comparison: OMALIZUMAB 300mg vs. PLACEBO

POPULATION:	patients with cholinergic urticaria
INTERVENTION(S):	omalizumab 300mg every 4w
COMPARISON:	placebo
BIBLIOGRAPHY	Gastaminza 2019* *New study in 2020 update

Assessment

Desirable Effects
How substantial are the desirable anticipated effects?

JUDGEMENT: RESEARCH EVIDENCE

- ● Trivial
- ○ Small
- ○ Moderate
- ○ Large
- ○ Varies
- ○ Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with omalizumab 300mg every 4w
symptom free with UCOL exercise challenge	23 (1 RCT)	⨁⨁⨁◯ MODERATE[a]	**RR 0.38** (0.04 to 3.67)	Study population	
				200 per 1,000	**124 fewer per 1,000** (192 fewer to 534 more)
CU2QoL	22 (1 RCT)	⨁⨁◯◯ LOW[a,b]	-		MD **7 lower** (19.52 lower to 5.52 higher)

a. CI crossed line of no effect and MID threshold(s): uncertain whether there is any difference
b. Mean and SD were estimated based on median and 25th and 75th quartile values according to Wan 2014

Undesirable Effects
How substantial are the undesirable anticipated effects?

JUDGEMENT: RESEARCH EVIDENCE

- ● Trivial
- ○ Small
- ○ Moderate
- ○ Large
- ○ Varies
- ○ Don't know

Outcomes	№ of participants (studies) Follow up	Certainty of the evidence (GRADE)	Relative effect (95% CI)	Anticipated absolute effects* (95% CI)	
				Risk with placebo	Risk difference with omalizumab 300mg every 4w
patients with at least 1 AE	22 (1 RCT)	⊕⊕⊕◯ MODERATE[a]	**RR 1.56** (0.69 to 3.52)	Study population	
				444 per 1,000	**249 more per 1,000** (138 fewer to 1,120 more)
withdrawal due to AE	23 (1 RCT)	⊕⊕⊕⊕ HIGH	not estimable *(zero in both groups)*	Study population	
				0 per 1,000	**0 fewer per 1,000** (0 fewer to 0 fewer)

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

Values and overall certainty of the evidence

JUDGEMENT | **RESEARCH EVIDENCE**

- ○ Very low
- ○ Low
- ● Moderate
- ○ High
- ○ No included studies

The relative importance or values of the main outcomes of interest:

Outcomes	Importance	Certainty of the evidence (GRADE)
symptom free with UCOL exercise challenge	critical	⊕⊕⊕◯ MODERATE
CU2QoL	critical	⊕⊕◯◯ LOW
withdrawal due to AE	critical	⊕⊕⊕⊕ HIGH
patients with at least 1 AE	important	⊕⊕⊕◯ MODERATE

Balance of effects

Does the balance between desirable and undesirable effects favor the intervention or the comparison?

JUDGEMENT | **RESEARCH EVIDENCE**

- ○ Favors the comparison
- ○ Probably favors the comparison
- ● Does not favor either the intervention or the comparison

Outcomes	With placebo	With omalizumab 300mg every 4w	Difference	Relative effect (95% CI)
symptom free with UCOL exercise challenge	200 per 1,000	**76 per 1,000** (8 to 734)	**124 fewer per 1,000** (192 fewer to 534 more)	**RR 0.38** (0.04 to 3.67)

○ Probably favors the intervention ○ Favors the intervention ○ Varies ○ Don't know	patients with at least 1 AE	444 per 1,000	**693 per 1,000** (307 to 1,000)	**249 more per 1,000** (138 fewer to 1,120 more)	**RR 1.56** (0.69 to 3.52)
	withdrawal due to AE	0 per 1,000	**0 per 1,000** (0 to 0)	**0 fewer per 1,000** (0 fewer to 0 fewer)	not estimable
	CU2QoL		The mean cU2QoL in the intervention group was 7 points lower (19.52 lower to 5.52 higher)	MD **7 lower** (19.52 lower to 5.52 higher)	-

Feasibility
Is the intervention feasible to implement?

JUDGEMENT	RESEARCH EVIDENCE
○ No ○ Probably no ○ Probably yes ○ Yes ● Varies ○ Don't know	Feasibility, costs, equity and acceptability of the intervention need to be considered in the context of the local health care systems.

Summary:

(Differences to 2016 marked in purple.)

COMPARISON: OMALIZUMAB 300mg EVERY 4 WEEKS vs. PLACEBO FOR CHOLINERGIC URTICARIA

Data added in 2020 update from 1 new study

Efficacy

No difference was found for the outcomes: 'symptom free with UCOL exercise challenge' (moderate quality) and 'CU2QoL' (low quality)

Safety

No difference was found for the outcomes: 'withdrawal due to adverse event' (high quality) and 'patients with at least one adverse event' (moderate quality).

Solar urticaria/vibratory AE/aquagenic urticaria/contact urticaria

No evidence identified