Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: 2015-06-01-D-170 Ivermectin

Stand: August 2015

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Ivermectin **zur topischen Behandlung entzündlicher Läsionen der (papulopustulösen) Rosazea**	
Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*siehe Übersicht II* Zugelassene Arzneimittel im Anwendungsgebiet:
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	*nicht angezeigt*
Als Vergleichstherapie sollen bevorzugt Arzneimittelanwendungen oder nicht-medikamentöse Behandlungen herangezogen werden, deren patientenrelevanter Nutzen durch den Gemeinsamen Bundesausschuss bereits festgestellt ist.	*es liegen keine Beschlüsse vor*
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	
Zu prüfendes Arzneimittel:	
Soolantra®	Soolantra wird angewendet bei erwachsenen Patienten zur topischen Behandlung von entzündlichen Läsionen der (papulopustulösen) Rosazea.
topisch	
Metronidazol D06BX01 z.B. Metrocreme®	Zur Anwendung auf der Haut bei mäßig ausgeprägter entzündlicher papulo-pustulöser Rosazea.
Azelainsäure D10AX03 z.B. Skinoren 15% Gel®	Zur Linderung bei leichter bis mittelschwerer, papulopustulöser Akne des Gesichtes. Zur äußerlichen Behandlung der papulopustulösen Rosazea.
systemisch	
Doxycyclin J01AA02 generisch	Hauterkrankungen, auch infizierte schwere Formen der Acne vulgaris und Rosacea.
Minocyclin J01AA08 generisch	Hauterkrankungen, auch infizierte schwere Formen der Akne vulgaris und Rosacea.
Tetracyclin J01AA07 generisch	Infizierte schwere Formen der Akne vulgaris sowie Rosacea, wenn eine systemische antibiotische Therapie erforderlich ist.
Azithromycin J01FA10 generisch	[…] leichte bis mittelschwere Infektionen der Haut….
Clarithromycin J01FA09	[…] leichte bis mittelschwere Infektionen der Haut

generisch	
Clindamycin J01FF01 generisch	Infektionen der Haut…
Ichthyol®-Natrium D11AX z.B. Ichtraletten	Rosacea, auch mit Seborrhoe

Quellen: AMIS-Datenbank, Fachinformatione

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Systematische Recherche:

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen, HTA-Berichten und Evidenz-basierten systematischen Leitlinien zur Indikation ***„Rosazea“*** durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am ***06.07.2015*** abgeschlossen. Die Suche erfolgte in folgenden Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database), MEDLINE (PubMed), arztbibliothek.de (ÄZQ), AWMF, Clinical Evidence, DAHTA, G-BA, GIN, IQWiG, NGC, NICE, TRIP. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Bei der Recherche wurde keine Sprachrestriktion vorgenommen. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

Die Recherche ergab **48** Quellen, die anschließend nach Themenrelevanz und methodischer Qualität gesichtet wurden. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Davon wurden **22** Quellen eingeschlossen. Insgesamt ergab dies **3** Quellen, die in die synoptische Evidenz-Übersicht aufgenommen wurden.

Abkürzungen

ÄZQ	Ärztliches Zentrum für Qualität in der Medizin
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
DAHTA	Deutsche Agentur für Health Technology Assessment
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
HRQOL	Health-related quality of life
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
NGC	National Guideline Clearinghouse
NHS CRD	National Health Services Center for Reviews and Dissemination
NICE	National Institute for Health and Care Excellence
TRIP	Turn Research into Practice Database
WHO	World Health Organization

IQWiG Berichte/ G-BA Beschlüsse

Es konnten keine IQWiG Berichte/ G-BA Beschlüsse identifiziert werden.

Cochrane Reviews

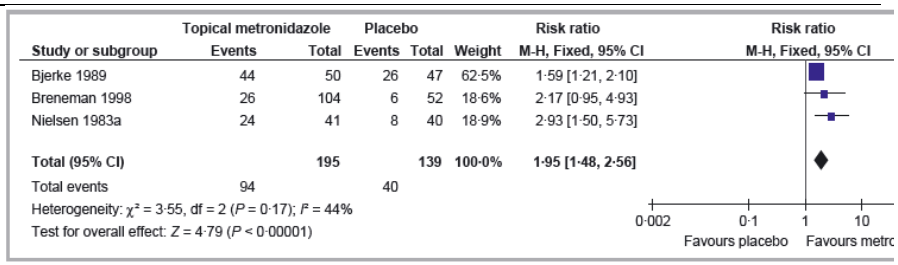
van Zuuren EJ, 2015: [3] Interventions for rosacea	1. Fragestellung To assess the efficacy and safety of treatments for rosacea. Review question: Which treatments are effective for rosacea?
	2. Methodik Population: People older than 19 years with moderate to severe rosacea (diagnosed clinically). Intervention: Any type of intervention used, either alone or in combination Komparator: placebo, no treatment or active treatment Endpunkte: *Primary outcomes:* Change in health-related quality of life (HRQOL) at end of study, Participant-assessed changes in rosacea severity at end of study, Proportion of participants who reported an adverse event throughout the study period; *Secondary outcomes:* Physician-assessed changes in rosacea severity (physician's global assessment of rosacea severity at end of study, assessment of erythema or telangiectasia, or both, at end of study, reduction in lesion counts (treatment success defined as greater than 50% reduction in lesion counts), time needed until improvement of the skin lesions, duration of remission), change in HRQOL, participant-reported improvement of rosacea, proportion of participants who reported an adverse event, physician's global assessment of improvement of rosacea, assessment of erythema or telangiectasia, or both, reduction in lesion counts, time needed until improvement of the skin lesions, duration of remission Suchzeitraum (Aktualität der Recherche): bis 07/2014 Anzahl eingeschlossene Studien/Patienten (Gesamt): 106 RCTs (n= 13,631) Qualitätsbewertung der Studien: Two review authors independently assessed risk of bias using the Cochrane Collaboration tool for assessing risk of bias as described in Chapter 8, section 8.5 in the *Cochrane Handbook for Systematic Reviews of Interventions*. Only 12 of the studies met all of the criteria across all of the domains in the Cochrane Collaboration's tool for assessing the risk of bias, and therefore these studies were considered to be at 'low risk of bias' (plausible bias unlikely to seriously alter the results). Almost half of the studies (57) were categorised as 'unclear risk of bias' (plausible bias that raised some doubt about the results) because one or more criteria were assessed as unclear, and the remaining 37 studies were assessed as 'high risk of bias' (plausible bias that seriously weakened confidence in the results) because one or more of the criteria were not met. **Quality of the evidence:** We rated the quality of the evidence for several outcomes as very low to high. There was high

	quality evidence for azelaic acid, topical ivermectin, brimonidine, doxycycline and isotretinoin. The lower quality evidence for other treatments was mostly because there were few people in the studies, making the results less precise, and the lack of blinding (people knew which treatments they were receiving).
	3. Ergebnisdarstellung (Summary of findings for the main comparison siehe Anhang) • 11 categories of interventions: topical metronidazole (n=15); topical azelaic acid (7); topical brimonidine (6); topical ivermectin (2); topical metronidazole, azelaic acid or other topical treatments, or both (35); oral antibiotics (10); oral antibiotics combined with topical treatments (6); oral antibiotics compared with topical antibiotics (5); other systemic treatments (10); laser and light-based therapies (7); and other treatments or combined treatments (3) **Key results** • Most of the treatments appeared to be effective in treating rosacea. • Only 11 assessed changes to quality of life. Almost all studies reported side effects, although this information was often limited. • Studies mostly evaluated changes in the number of pimples and pustules, and redness. • Only five studies included ocular rosacea. • None included the rare variant called 'granulomatous rosacea'. *Topical treatments:* • Two separate treatments, metronidazole and azelaic acid, were effective and safe in reducing rosacea symptoms. Improvements tended to appear after three to six weeks. With metronidazole, very few people experienced mild itching, skin irritation and dry skin. • For some, azelaic acid caused mild burning, stinging or irritation. Ivermectin, a new treatment, was more effective than placebo and slightly more effective than metronidazole. • Another newly registered treatment called brimonidine, especially for reducing redness, was shown to work up to 12 hours after being applied. *Oral treatments:* • Antibiotics such as tetracycline, a low dose of doxycycline or a low dose of minocycline reduced the number of pimples and pustules. • Low dose doxycycline (40mg) was likely as effective as 100 mg, but with much fewer side effects of diarrhoea and nausea. Azithromycin may be as effective as 100 mg doxycycline, but only one study addressed this treatment and better quality studies are needed to confirm this. • A low dose of isotretinoin (0.3 mg/kg), a vitamin A-related

	drug, appeared to be slightly more effective than 50-100 mg doxycycline for treating pimples and pustules. • However, extra precautions need to be taken regarding contraception in women of childbearing age as this drug is known to cause malformations in the foetus. *Light-based therapies:* • Laser therapy and intense pulsed light therapy were both effective for the treatment of telangiectasia, but the studies examining these treatments only reported limited data. *Rosacea of the eyes or eyelids, or both (ocular rosacea):* • Better quality studies are required on ocular rosacea, though ciclosporin 0.05% ophthalmic emulsion appeared to be more effective than artificial tears.
	4. Anmerkungen/Fazit der Autoren There was high quality evidence to support the effectiveness of topical azelaic acid, topical ivermectin, brimonidine, doxycycline and isotretinoin for rosacea. Moderate quality evidence was available for topical metronidazole and oral tetracycline. There was low quality evidence for low dose minocycline, laser and intense pulsed light therapy and ciclosporin ophthalmic emulsion for ocular rosacea. Time needed to response and response duration should be addressed more completely, with more rigorous reporting of adverse events. Further studies on treatment of ocular rosacea are warranted.

Systematische Reviews

van Zuuren EJ, 2011: [2] Effective and evidence-based management strategies for rosacea: summary of a Cochrane systematic review	1. Fragestellung The aim of this review was to assess the evidence for the efficacy and safety of treatments for rosacea.
	2. Methodik Population: people with moderate to severe rosacea Intervention: topical metronidazole, oral antibiotics, topical azelaic cream or gel, topical benzoyl peroxide and/or combined with topical antibiotics, sulphacetamide/sulphur, and others Komparator: placebo or active treatment Endpunkte: primary outcomes: impact on quality of life and participant-assessed changes in rosacea severity; Secondary outcomes: physician-assessed changes in rosacea severity, drop-out rates and adverse events Suchzeitraum (Aktualität der Recherche): bis 02/2011 Anzahl eingeschlossene Studien/Patienten (Gesamt): 58 (n= 6633 participants) Qualitätsbewertung der Studien: The review authors independently assessed risk of bias in the included studies using the Cochrane Collaboration's domain-based evaluation tool as described in Chapter 8, Section 8.5, in the Cochrane Handbook for Systematic Reviews of Interventions. Only three of the studies met all of the criteria across all of the domains in the Cochrane Collaboration's tool for assessing the risk of bias, and therefore these studies were considered to be at 'low risk of bias' (plausible bias unlikely to seriously alter the results).17,18 Thirty studies were categorized as 'unclear risk of bias' (plausible bias that raises some doubt about the results) because one or more criteria were assessed as unclear, while the remaining 25 studies were assessed as 'high risk of bias' (plausible bias that seriously weakens confidence in the results) because one or more of the criteria were not met.
	3. Ergebnisdarstellung *Studies with only topical metronidazole:* • Fourteen trials provided data on the effectiveness of topical metronidazole (three studies could be pooled) • Topical metronidazole was more effective than placebo and the results were both statistically significant [relative risk (RR) 1.95, 95% confidence interval (CI) 1.48–2.56] and clinically important. *Physician's Global Evaluation of improvement of rosacea:*

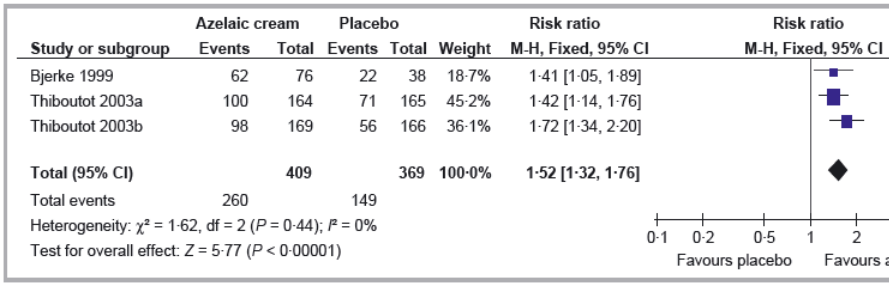


- no statistically significant differences between the two concentrations of topical metronidazole (0.75% and 1%), or comparisons using different vehicles and topical metronidazole was also shown to be effective in maintaining remission.
- no significant differences in the number of dropouts and adverse events across the intervention groups in these studies

Studies with only azelaic acid

- Six studies evaluated the effect of azelaic acid out of which three studies compared the effectiveness of azelaic acid vs. placebo
- Pooled participant-assessed data from these studies indicated an improvement in rosacea severity rate of complete remission or marked improvement of 70–80% in the azelaic acid group compared with 50–55% in the placebo group (RR 1.52, 95% CI 1.32–1.76)

Participant-assessed improvement of rosacea:



- no statistically significant difference during maintenance phase between the azelaic acid group and vehicle-only group

Studies comparing topical metronidazole and azelaic acid

- Three studies provided data for this comparison, one of which had a within-patient study design; therefore pooling of data with the other two studies was not possible.
- In two of the studies there was no statistically significant difference between the treatment groups in the patient-assessed outcomes

Studies with other topical treatments:

- most of these studies were judged to be at high risk of bias and had skewed or unusable data

Studies with laser- and/or light-based treatment

- one study the effectiveness of dual-wavelength 595-nm

	pulsed-dye laser (PDL) and 1064 nm Nd:YAG was investigated, but this was only on the nose • another study (PDL vs. intense pulsed light therapy vs. control) the data were limited and unusable
	4. Anmerkungen/Fazit der Autoren Although the majority of included studies were assessed as being at high or unclear risk of bias, there was some evidence to support the effectiveness of topical metronidazole, azelaic acid and doxycycline (40 mg) in the treatment of moderate to severe rosacea, and ciclosporin 0.05% ophthalmic emulsion for ocular rosacea. Further well-designed, adequately powered randomized controlled trials are required.
van Zuuren EJ, 2015: [1] Interventions for rosacea: abridged updated Cochrane systematic review including GRADE assessments	*Siehe Cochrane Review* ***van Zuuren, 2015***

Leitlinien

Es konnten keine adäquaten Leitlinien identifiziert werden.

Detaillierte Darstellung der Recherchestrategie:

Cochrane Library (Cochrane Database of Systematic Reviews, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database) **am 02.07.2015**

#	Suchfrage
#1	MeSH descriptor: [Rosacea] explode all trees
#2	rosacea* or rhinophyma* or (pyoderma next faciale):ti,ab,kw (Word variations have been searched)
#3	#1 or #2
#4	#1 or #2 Publication Year from 2010 to 2015, in Cochrane Reviews (Reviews only), Other Reviews and Technology Assessments

SR, HTAs in Medline (PubMed) am 02.07.2015

#	Suchfrage
#1	rosacea[MeSH Terms]
#2	((rosacea*[Title/Abstract]) OR rhinophyma*[Title/Abstract]) OR pyoderma faciale[Title/Abstract]
#3	(#1) OR #2
#4	(#3) AND (Meta-Analysis[ptyp] OR systematic[sb] OR Technical Report[ptyp])
#5	(#3) AND (((((trials[Title/Abstract] OR studies[Title/Abstract] OR database*[Title/Abstract] OR literature[Title/Abstract] OR publication*[Title/Abstract] OR Medline[Title/Abstract] OR Embase[Title/Abstract] OR Cochrane[Title/Abstract] OR Pubmed[Title/Abstract])) AND systematic*[Title/Abstract] AND (search*[Title/Abstract] OR research*[Title/Abstract]))) OR ((((((((((HTA[Title/Abstract]) OR technology assessment*[Title/Abstract]) OR technology report*[Title/Abstract]) OR (systematic*[Title/Abstract] AND review*[Title/Abstract])) OR (systematic*[Title/Abstract] AND overview*[Title/Abstract])) OR meta-analy*[Title/Abstract]) OR (meta[Title/Abstract] AND analyz*[Title/Abstract])) OR (meta[Title/Abstract] AND analys*[Title/Abstract])) OR (meta[Title/Abstract] AND analyt*[Title/Abstract]))) OR (((review*[Title/Abstract]) OR overview*[Title/Abstract]) AND ((evidence[Title/Abstract]) AND based[Title/Abstract]))))
#6	(#4) OR #5
#7	(#6) AND ("2010/07/01"[PDAT] : "2015/07/02"[PDAT])

Leitlinien in Medline (PubMed) am 02.07.2015

#	Suchfrage
#1	rosacea[MeSH Terms]
#2	((rosacea*[Title/Abstract]) OR rhinophyma*[Title/Abstract]) OR pyoderma faciale[Title/Abstract]
#3	(#1) OR #2
#4	(#3) AND (((((((Guideline[Publication Type]) OR Practice Guideline[Publication Type]) OR Consensus Development Conference[Publication Type]) OR Consensus Development Conference, NIH[Publication Type]) OR guideline*[Title]) OR recommendation*[Title]) OR consensus[Title])
#5	(#4) AND ("2010/07/01"[PDAT] : "2015/07/02"[PDAT])

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Anhang

Summary of findings for the main comparison

Summary of findings 1: *Metronidazole compared to placebo for rosacea*

Metronidazole compared to placebo for rosacea						
Patient or population: Participants with rosacea **Intervention:** Metronidazole **Comparison:** Placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo	**Metronidazole**				
HRQOL - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Participant-assessed improvement in rosacea severity	See comment	See comment	Not estimable	252 (3 studies[1])	⊕⊕⊕○ **moderate**[2]	Bjerke 1989 RR 1.68, 95% CI 1.25 to 2.28; P = 0.0007, Nielsen 1983a RR 3.05, 95% CI 1.57 to 5.94; P = 0.001, Bleicher 1987 (within-participant study) RR 7. These are clinically important improvements
Proportion of participants with adverse event	**161 per 1000**	**191 per 1000** (151 to 243)	**RR 1.19** (0.94 to 1.51)	1773 (6 studies[3])	⊕⊕⊕⊕ **high**	Most instances of these adverse events were mild and consisted of pruritus, skin irritation and dry skin
Physician-assessed improvement in rosacea severity	**288 per 1000**	**570 per 1000** (371 to 869)	**RR 1.98** (1.29 to 3.02)	334 (3 studies[4])	⊕⊕⊕○ **moderate**[2,5]	The results are both statistically significant and clinically important

Assessment of erythema or telangiectasia	See comment	See comment	Not estimable	602 (7 studies[6])	⊕⊕⊕◯ **moderate**[5,7]	In the separate studies (but not in Bitar 1990) there was a greater reduction of erythema in the groups treated with metronidazole, but data were inadequately reported. Except in Koçak 2002 data were adequately reported with a MD of -1.40 (95% CI -2.47 to -0.33; P = 0.01) in favour of metronidazole
Lesion count	See comment	See comment	Not estimable	1964 (8 studies[8])	⊕⊕⊕◯ **moderate**[7]	No SDs reported, data were skewed but appeared to support data of physician-assessed improvement
Time needed until improvement of the skin lesions	See comment	See comment	Not estimable	514 (5 studies[9])	⊕⊕⊕⊕ **high**	Based on interim data improvement started around four weeks
Duration of remission	**409 per 1000**	**205 per 1000** (102 to 405)	**RR 0.50** (0.25 to 0.99)	88 (1 study[10])	⊕⊕⊕◯ **moderate**[11,12]	9/44 in metronidazole group relapsed, versus 18/44 in vehicle group during six months follow-up

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Bjerke 1989, Nielsen 1983a, Bleicher 1987
[2] Downgraded one level due to serious imprecision (wide confidence intervals)
[3] Beutner 2005, Bitar 1990, Bjerke 1989, Breneman 1998, Koçak 2002, Nielsen 1983a
[4] Bjerke 1989, Breneman 1998, Nielsen 1983a
[5] Although for two studies the sequence generation and allocation concealment was unclear (Bjerke 1989 and Nielsen 1983a), the blinding was ensured for both Bleicher 1987 and Nielsen 1983a, and stated as double-blind for Bjerke 1989 and therefore we considered it unlikely that this would have an impact on this outcome assessment and decided only to downgrade for imprecision
[6] Bitar 1990, Bjerke 1989, Bleicher 1987, Breneman 1998, Dahl 1998, Koçak 2002, Nielsen 1983a
[7] Downgraded one level due to serious imprecision (small sample sizes in the individual studies, pooling not possible due to missing SDs)
[8] Beutner 2005, Bitar 1990, Bjerke 1989, Bleicher 1987, Breneman 1998, Dahl 1998, Koçak 2002, Nielsen 1983a
[9] Bitar 1990, Bjerke 1989, Bleicher 1987, Breneman 1998, Nielsen 1983a
[10] Dahl 1998
[11] Although we judged the domains for sequence generation, allocation concealment as unclear and the method of blinding of participants and physicians was not reported, there was no attrition bias nor selective reporting and therefore we concluded there was no serious risk of bias for this outcome assessment
12 Downgraded one level due to serious imprecision (low sample size, optimal sample size is not met)

Summary of findings 2: *Azelaic acid versus placebo for rosacea*

Azelaic acid compared to placebo for rosacea						
Patient or population: Participants with rosacea **Intervention:** Azelaic acid **Comparison:** Placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo	**Azelaic acid**				
HRQOL - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Participant-assessed improvement in rosacea severity Marked improvement to complete remission on Likert scale	**421 per 1000**	**636 per 1000** (552 to 733)	**RR 1.46** (1.30 to 1.63)	1179 (4 studies[1])	⊕⊕⊕⊕ **high**	This is a clinically important improvement in favour of azelaic acid
Proportion of participants with adverse event	See comment	See comment	Not estimable	1245 (5 studies[2])	⊕⊕⊕⊕ **high**	Bjerke 1999 RR 1.00, 95% CI 0.62 to 1.62; P = 0.02, Carmichael 1993 (within-participant) 24/33 on the azelaic acid side and 19/33 on placebo side, Draelos 2013a RR 2.39, 95% CI 1.12 to 5.09; P = 0.02, Thiboutot 2003a and Thiboutot 2003b 18% and 8% respectively for azelaic acid

						treated groups and limited to no data for the placebo groups
Physician-assessed improvement in rosacea severity	**497 per 1000**	**655 per 1000** (586 to 730)	**RR 1.32** (1.18 to 1.47)	1179 (4 studies[1])	⊕⊕⊕⊕ **high**	Data for these assessments from four studies illustrated that azelaic acid was more effective than placebo
Assessment of erythema or telangiectasia	See comment	See comment	Not estimable	1245 (5 studies[2])	⊕⊕⊕⊕ **high**	Decrease in erythema in groups treated with azelaic acid ranged from 44% to 47.9% and for placebo from 28% to 37.9%, telangiectasia minimal changes. SDs missing
Lesion count	The mean lesion count in the control group was **-9.5 inflammatory lesions**	The mean lesion count in the control group was **3.90 lower** (5.87 to 1.93 lower)		401 (1 study[3])	⊕⊕⊕◯ **moderate**[4]	No SDs were reported in (Bjerke 1999; Thiboutot 2003a; Thiboutot 2003b) and data were skewed in Carmichael 1993. All four studies showed a greater reduction in lesions in azelaic acid treated groups (see Analysis 2.3)
Time needed until improvement of the skin lesions	See comment	See comment	Not estimable	1245 (5 studies[2])	⊕⊕⊕⊕ **high**	This was not a pre-specified outcome, but all studies showed clear improvement after three to six weeks
Duration of remission - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Bjerke 1999, Draelos 2013a, Thiboutot 2003a, Thiboutot 2003b
[2] Bjerke 1999, Carmichael 1993, Draelos 2013a, Thiboutot 2003a, Thiboutot 2003b
[3] Draelos 2013a
[4] Downgraded one level due to serious imprecision (wide confidence interval)

Summary of findings 3: *Topical ivermectin compared to placebo for rosacea*

Topical ivermectin compared to placebo for rosacea						
Patient or population: Participants with rosacea **Intervention:** Topical ivermectin **Comparison:** Placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo	**Topical ivermectin**				
HRQOL DLQI and RosaQoL	See comment	See comment	Not estimable	1371 (2 studies[1])	⊕⊕⊕⊕ **high**	Although data were statistically significant in favour of ivermectin, the clinical importance is unclear as MID in reduction of DLQI score was not reached and the MID is not yet established for RosaQoL[2]
Participant-assessed improvement in rosacea severity Likert scale, good to excellent improvement	See comment	See comment	Not estimable	1371 (2 studies[1])	⊕⊕⊕⊕ **high**	RR 1.78, 95% CI 1.50 to 2.11 (Stein 2014a), RR 1.92, 95% CI 1.59 to 2.32 (Stein 2014b). Both studies showed a statistically significant and clinically important improvement in favour of topical ivermectin
Proportion of participants with adverse event	See comment	See comment	Not estimable	1371 (2 studies[1])	⊕⊕⊕⊕ **high**	RR 0.54, 95% CI 0.29 to 1.01 (Stein 2014a), RR 1.00, 95% CI 0.55 to 1.82 (Stein 2014b)

Physician-assessed improvement in rosacea severity Investigator's Global Assessment of clear or almost clear	See comment	See comment	Not estimable	1371 (2 studies[1])	⊕⊕⊕⊕ **high**	RR 3.30, 95% CI 2.27 to 4.79 (Stein 2014a), RR 2.10, 95% CI 1.57 to 2.81 (Stein 2014b). The results of both studies are in concordance with the assessments of the participants
Assessment of erythema or telangiectasia - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Lesion count	See comment	See comment	Not estimable	1371 (2 studies[1])	⊕⊕⊕⊕ **high**	MD -8.40, 95% CI -9.93 to -6.87 (Stein 2014a), MD -8.90, 95% CI -10.45 to -7.35 (Stein 2014b). Both of these differences are statistically significant and clinically important
Time needed until improvement of the skin lesions	See comment	See comment	Not estimable	1371 (2 studies[1])	⊕⊕⊕⊕ **high**	Improvement in both studies was seen after four weeks
Duration of remission - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Stein 2014a, Stein 2014b

Summary of findings 4: *Topical brimonidine compared to vehicle for rosacea*

Topical brimonidine compared to vehicle for rosacea						
Patient or population: Participants with rosacea **Intervention:** Topical brimonidine **Comparison:** Vehicle						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo	**Topical brimonidine**				
HRQOL - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Participant-assessed improvement in rosacea severity Patient Satisfaction Assessment - grade 2 improvement	See comment	See comment	Not estimable	553 (2 studies[1])	⊕⊕⊕⊕ **high**	At 3 hours RR 2.21, 95% CI 1.52 to 3.22 (Fowler 2013a) and RR 2.00, 95% CI 1.33 to 3.01 (Fowler 2013b). At each time point in both studies brimonidine was shown to be more effective than vehicle in an improvement which was statistically significant
Proportion of participants with adverse event	See comment	See comment	Not estimable	553 (2 studies[1])	⊕⊕⊕⊕ **high**	RR 1.17, 95% CI 0.79 to 1.74 (Fowler 2013a), RR 1.40, 95% CI 0.97 to 2.02 (Fowler 2013b). Adverse events were mild and transient

Physician-assessed improvement in rosacea severity - not reported	See comment	See comment	Not estimable	-	See comment	No reporting of data other than ' ' No aggravations in the severity of IGA were observed"
Assessment of erythema or telangiectasia Clinician Erythema Assessment - grade 2 improvement	See comment	See comment	Not estimable	553 (2 studies[1])	⊕⊕⊕⊕ **high**	At 3 hours RR 2.82, 95% CI 1.85 to 4.30 (Fowler 2013a), RR 1.78, 95% CI 1.25 to 2.55 (Fowler 2013b)
Lesion count - not reported	See comment	See comment	Not estimable	-	See comment	No reporting of data other than ' ' No aggravations in the severity of lesion counts were observed"
Time needed until improvement of the skin lesions	See comment	See comment	Not estimable	553 (2 studies[1])	⊕⊕⊕⊕ **high**	Improvement was seen within 30 min
Duration of remission - not measured	See comment	See comment	Not estimable	-	See comment	There was no rebound or worsening of erythema after treatment cessation in comparison to baseline assessments

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Fowler 2013a, Fowler 2013b

Summary of findings 5: *Topical azelaic acid compared to topical metronidazole for rosacea*

Topical azelaic acid compared to topical metronidazole for rosacea						
Patient or population: Participants with rosacea **Intervention:** Topical azelaic acid **Comparison:** Topical metronidazole						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Topical metronidazole	**Topical azelaic acid**				
HRQOL - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Participant-assessed improvement in rosacea severity	See comment	See comment	Not estimable	491 (3 studies[1])	⊕⊕◯◯ **low**[2,3]	RR 1.23, CI 95% 1.04 to 1.44; P = 0.01 (Elewski 2003), RR 1.00, 95% CI 0.83 to 1.21 (Wolf 2006) , Maddin 1999 (within-participant) authors report P = 0.02 in favour of azelaic acid
Proportion of participants with adverse event	See comment	See comment	Not estimable	491 (3 studies[1])	⊕⊕◯◯ **low**[2,4]	RR 3.64, 95% CI 1.81 to 7.31; P = 0.0003 (Elewski 2003), RR 0.74, 95% CI 0.52 to 1.07 (Wolf 2006). In Maddin 1999 1 participant reported stinging on azelaic acid treated site
Physician-assessed improvement in rosacea severity	See comment	See comment	Not estimable	491 (3 studies[1])	⊕⊕◯◯ **low**[2,5]	RR 1.26, 95% CI 1.03 to 1.53; P = 0.02 (Elewski 2003), RR 1.05, 95% CI 0.79 to 1.39 (Wolf 2006)

						, Maddin 1999 score 2.7 (SD 1.0) versus 3.1 (SD 1. 0) (higher is worse)
Assessment of erythema or telangiectasia	See comment	See comment	Not estimable	491 (3 studies)	⊕⊕◯◯ **low**[2,6]	RR 1.35, 95% CI 1.05 to 1.75; P = 0.02 (Elewski 2003), RR 0.99, 95% CI 0.69 to 1.42 (Wolf 2006), in Maddin 1999 the participants and physicians had contradictory judgements
Lesion counts	See comment	See comment	Not estimable	491 (3 studies[1])	⊕⊕⊕◯ **moderate**[2]	No SDs were reported, all three studies demonstrated a clinically important reduction in lesion count in both treatment arms
Time needed until improvement of the skin lesions	See comment	See comment	Not estimable	491 (3 studies[1])	See comment	Improvement for both arms was seen after four to six weeks in all three studies
Duration of remission - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Elewski 2003, Maddin 1999, Wolf 2006
[2] Downgraded one level due to serious risk of bias (all three studies stated to be double-blind, but method of blinding was not described)

[3] Downgraded one level due to serious inconsistency (Elewski 2003 and Wolf 2006 no statistically significant difference (severe heterogeneity unexplained (I^2 >60%), and the 95% CIs do overlap but lead to different interpretation of the effect estimate, but in Maddin 1999 azelaic was more effective)

[4] Downgraded one level due to serious inconsistency (statistically significant difference in participants reporting adverse events in Elewski 2003 (in favour of metronidazole), not confirmed in Wolf 2006 (severe heterogeneity unexplained (I^2 >60% and the 95% CIs did not overlap))

[5] Downgraded one level due to serious inconsistency (no statistically significant difference in Wolf 2006, but in Elewski 2003 and Maddin 1999 azelaic acid is more effective, severe heterogeneity unexplained and the 95% CI do overlap but lead to different interpretation of the effect estimate)

[6] Downgraded one level due to inconsistency (no statistically significant difference in Wolf 2006, but in Elewski 2003 and Maddin 1999 azelaic acid is more effective according to physicians (but metronidazole is more effective according to participants in Maddin 1999)

Summary of findings 6: *Topical ivermectin compared to topical metronidazole for rosacea*

Topical ivermectin compared to topical metronidazole for rosacea						
Patient or population: Participants with rosacea **Intervention:** Topical ivermectin **Comparison:** Topical metronidazole						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Topical metronidazole	**Topical ivermectin**				
HRQOL DLQI, proportion of participants that reported at end of study that rosacea had no impact on QoL	**640 per 1000**	**711 per 1000** (647 to 775)	**RR 1.11** (1.01 to 1.21)	962 (1 study[1])	⊕⊕⊕⊕ **high**	Reduction in DLQI was 5.18 in ivermectin group and 3.92 in metronidazole group (both meeting minimal important difference)
Participant-assessed improvement in rosacea severity Likert scale - good to excellent improvement	**748 per 1000**	**853 per 1000** (800 to 912)	**RR 1.14** (1.07 to 1.22)	962 (1 study[1])	⊕⊕⊕⊕ **high**	This is a statistically significant difference and in concordance with the results on number of participants that experienced no deleterious effect on their quality of life
Proportion of participants with adverse event	**8 per 1000**	**19 per 1000** (6 to 61)	**RR 2.28** (0.71 to 7.35)	962 (1 study[1])	⊕⊕⊕◯ **moderate**[2]	
Physician-assessed improvement in rosacea severity	**754 per 1000**	**852 per 1000** (799 to 905)	**RR 1.13** (1.06 to 1.20)	962 (1 study[1])	⊕⊕⊕⊕ **high**	These assessments are consistent with the assessments of the participants

Assessment of erythema or telangiectasia - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Lesion count	The mean lesion count in the control groups was **-23.60 inflammatory lesions**	The mean lesion count in the intervention groups was **4.10 lower** (5.18 to 3.02 lower)		962 (1 study[1])	⊕⊕⊕⊕ **high**	Both treatments showed clinically important reductions in lesion counts
Time needed until improvement of the skin lesions	See comment	See comment	Not estimable	962 (1 study[1])	⊕⊕⊕⊕ **high**	This was not a predefined outcome, but clear improvement could be seen for both treatment arms around six weeks
Duration of remission - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Taieb 2015
[2] Downgraded one level due to serious imprecision (wide confidence interval due to low occurrence of events)

Summary of findings 7: *Ciclosporin ophthalmic emulsion 0.05% compared to artificial tears for ocular rosacea*

Ciclosporin ophthalmic emulsion 0.05% compared to artificial tears for ocular rosacea						
Patient or population: Participants with ocular rosacea **Intervention:** Ciclosporin ophthalmic emulsion 0.05% **Comparison:** Artificial tears						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Artificial tears	**Ciclosporinophthalmic emulsion 0.05%**				
HRQOL Ocular Surface Disease Index (scale 0 to 100, 100 worst)	The mean OSDI in the control group was **16.9**	The mean OSDI in the intervention group was **8.6 lower** (15.42 to 1.78 lower)		37 (1 study[1])	⊕⊕◯◯ **low**[2]	The difference between change scores at end of study equates to a moderate improvement in quality of life in favour of ciclosporin ophthalmic emulsion
Participant-assessed improvement in rosacea severity - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Proportion of participants with adverse event			**RR 2.32** (0.10 to 53.42)	37 (1 study[1])	⊕⊕◯◯ **low**[2]	
Physician-assessed improvement in rosacea severity Schirmer score	The mean physician-assessed improvement in rosacea severity in the control group was **-1.4**	The mean physician-assessed improvement in rosacea severity in the intervention group was **4.1 higher** (1.66 to 6.54 higher)		37 (1 study[1])	⊕⊕◯◯ **low**[2]	

Assessment of erythema or telangiectasia - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Lesion count - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Time needed until improvement of the skin lesions - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Duration of remission - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Schechter 2009
[2] Downgraded two levels due to very serious imprecision (very wide confidence interval due to low sample size, optimal information size is not met)

Summary of findings 8: *Clindamycin phosphate 1.2% + tretinoin 0.025% gel compared to placebo for rosacea*

Clindamycin phosphate 1.2% + tretinoin 0.025% gel compared to placebo for rosacea						
Patient or population: Participants with rosacea **Intervention:** Clindamycin phosphate 1.2% + tretinoin 0.025% gel **Comparison:** Placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo	**Clindamycin phosphate 1.2% + tretinoin 0.025% gel**				
HRQOL RosaQoL	See comment	See comment	Not estimable	83 (1 study[1])	⊕⊕⊕◯ **moderate**[2]	No mean scores were provided, only percentages of participants that had improved per item on the 21 survey items, no statistically significant difference for any item
Participant-assessed improvement in rosacea severity - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Proportion of participants with adverse event	**275 per 1000**	**674 per 1000** (390 to 1000)	**RR 2.45** (1.42 to 4.23)	83 (1 study[1])	⊕⊕⊕◯ **moderate**[3]	Worsening of rosacea, facial scaling, as well as dry skin were reported most often in the active treatment group

Physician-assessed improvement in rosacea severity PGA as defined by Wilkin 2004	See comment	See comment	Not estimable	83 (1 study[1])	⊕⊕⊕○ **moderate**[2]	None of the primary features of the PGA showed statistically significant differences between the treatment groups except for oedema in favour of placebo
Assessment of erythema or telangiectasia	**150 per 1000**	**257 per 1000** (105 to 627)	**RR 1.71** (0.70 to 4.18)	83 (1 study[1])	⊕⊕⊕○ **moderate**[3]	RR 1.71 (95% CI 0.70 to 4.18) refers to erythema. Telangiectasia RR 2.42, 95% CI 0.95 to 6.17
Lesion count	The mean lesion count in the control group was **-3.13 inflammatory lesions**	The mean lesion count in the intervention group was **3.96 higher** (1.28 lower to 9.20 higher)		83 (1 study)	⊕⊕⊕○ **moderate**[3]	
Time needed until improvement of the skin lesions - not measured	See comment	See comment	Not estimable	-	See comment	There was no improvement
Duration of remission - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Chang 2012

[2] Downgraded one level due to serious imprecision (low sample size, optimal sample size is not met)

[3] Downgraded one level due to serious imprecision (wide confidence interval due to low sample size, optimal sample size is not met)

Summary of findings 9: *Tetracycline compared to placebo for rosacea*

Tetracycline compared to placebo for rosacea						
Patient or population: Participants with rosacea **Intervention:** Tetracycline **Comparison:** Placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo	**Tetracycline**				
HRQOL - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Participant-assessed improvement in rosacea severity	**474 per 1000**	**701 per 1000** (403 to 1000)	**RR 1.48** (0.85 to 2.57)	39 (1 study[1])	⊕⊕⊕◯ **moderate**[2]	
Proportion of participants with adverse event	**53 per 1000**	**50 per 1000** (3 to 744)	**RR 0.95** (0.06 to 14.13)	39 (1 study[1])	⊕⊕⊕◯ **moderate**[2]	Only one adverse event was reported in each group, diarrhoea in the tetracycline group, maculopapular rash in the placebo group
Physician-assessed improvement in rosacea severity	See comment	See comment	Not estimable	107 (2 studies[3])	⊕⊕⊕◯ **moderate**[2]	RR 4.04, 95% CI 1.66 to 9.83; P = 0.002 (Marks 1971) and RR 1.72, 95% CI 1.18 to 2.50; P = 0.005 (Sneddon 1966)
Assessment of erythema or telangiectasia	See comment	See comment	Not estimable	39 (1 study[1])	⊕⊕⊕◯ **moderate**[4]	There were no significant changes in erythema (Marks 1971)

Lesion count	The mean lesion count in the control group was **1.41 inflammatory lesions**	The mean lesion count in the intervention group was **14.64 lower**		39 (1 study[1])	⊕⊕⊕◯ **moderate**[5]	Crude MD -14.64 but skewed data (Marks 1971)
Time needed until improvement of the skin lesions - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Duration of remission - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Marks 1971
[2] Downgraded one level due to serious imprecision (wide confidence interval due to low sample size, optimal sample size is not met)
[3] Marks 1971 and Sneddon 1966
[4] Downgraded one level due to serious imprecision (low sample size, optimal sample size is not met)
[5] Downgraded one level due to serious imprecision (skewed data and low sample size, optimal sample size is not met)

Summary of findings 10: *Doxycycline 40 mg compared to placebo for rosacea*

Doxycycline 40 mg compared to placebo for rosacea						
Patient or population: Participants with rosacea **Intervention:** Doxycycline 40 mg **Comparison:** Placebo						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Placebo	**Doxycycline 40 mg**				
HRQOL - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Participant-assessed improvement in rosacea severity - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Proportion of participants with adverse event	See comment	See comment	Not estimable	537 (2 studies[1])	⊕⊕⊕⊕ **high**	RR 1.14, 95% CI 0.85 to 1.53 (Del Rosso 2007a) and RR 1.27, 95% CI 1.04 to 1.55 (Del Rosso 2007b)
Physician-assessed improvement in rosacea severity Investigator's Global Assessment, two point improvement	See comment	See comment	Not estimable	537 (2 studies[1])	⊕⊕⊕⊕ **high**	RR 1.77, 95% CI 1.24 to 2.52; P = 0.002 (Del Rosso 2007a) and RR 1.41, 95% CI 0.87 to 2.29 (Del Rosso 2007b) and IGA score of 0 or 1 RR 1.59, 95% CI 1.02 to 2.47; P = 0.04 (Del Rosso 2007a) and RR 2.37, 95% CI 1.12 to 4.99; P = 0.02 (Del Rosso 2007b)

Assessment of erythema or telangiectasia Clinician's Erythema Assessments scale 0 to 4	See comment	See comment	Not estimable	537 (2 studies[1])	⊕⊕⊕⊕ **high**	Mean change in CEA -2.7 (doxycycline group) versus -1.8 (placebo group), investigators report P = 0.017 (Del Rosso 2007a); and -1.4 and -1.2 respectively (Del Rosso 2007b)
Lesion counts Scale from: -4.3 to -11.8	See comment	See comment	Not estimable	537 (2 studies[1])	⊕⊕⊕◯ **moderate**[2]	MD -5.90, 95% CI -9.37 to -2.43; P = 0.0009 (Del Rosso 2007a) and MD -5.20, 95% CI -8.27 to -2.13; P = 0.0009 (Del Rosso 2007b)
Time needed until improvement of the skin lesions	See comment	See comment	Not estimable	537 (2 studies[1])	⊕⊕⊕⊕ **high**	The steepest changes in graph plots occurred within three weeks in the doxycycline group
Duration of remission - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Del Rosso 2007a and Del Rosso 2007b
[2] Downgraded one level due to serious imprecision (wide confidence interval)

Summary of findings 11: *Azithromycin compared to doxycycline 100 mg for rosacea*

Azithromycin compared to doxycycline 100 mg for rosacea						
Patient or population: Participants with rosacea **Intervention:** Azithromycin **Comparison:** Doxycycline 100 mg						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Doxycycline 100 mg	**Azithromycin**				
HRQOL - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Participant-assessed improvement in rosacea severity	**800 per 1000**	**784 per 1000** (616 to 1000)	**RR 0.98** (0.77 to 1.25)	67 (1 study[1])	⊕◯◯◯ **very low**[2,3]	There was no statistically significant difference between the groups, but in both treatment arms the majority of participants considered themselves improved
Proportion of participants with adverse event	**67 per 1000**	**108 per 1000** (21 to 551)	**RR 1.62** (0.32 to 8.26)	67 (1 study[1])	⊕◯◯◯ **very low**[2,4]	
Physician-assessed improvement in rosacea severity - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Assessment of erythema or telangiectasia - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

Lesion counts	The mean lesions count in the control group was **2.34 inflammatory lesions**	The mean lesions count in the intervention group was **0 higher**		67 (1 study[1])	⊕◯◯◯ **very low**[2,5]	Lesion count decreased in azithromycin group from 19.24 (SD 9.67) to 1.90 (SD 3.28) at 3 months and for doxycycline from 18.86 (SD 8.95) to 2.34 (SD 3.47). Skewed data
Time needed until improvement of the skin lesions - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Duration of remission	See comment	See comment	Not estimable	67 (1 study[1])	⊕◯◯◯ **very low**[2,3]	No data on duration of remission, but both groups showed no statistically significant change between the third month of treatment and the second month post-treatment in the mean inflammatory lesion counts

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Akhyani 2008
[2] Downgraded two levels due to very serious risk of bias (allocation concealment was at high risk of bias, no blinding)
[3] Downgraded one level due to serious imprecision (low sample size, optimal sample size is not met, optimal sample size is not met)
[4] Downgraded one level due to serious imprecision (wide confidence interval due to low sample size, optimal sample size is not met)
[5] Downgraded one level due to serious imprecision (large SDs and skewed data, low sample size, optimal sample size is not met)

Summary of findings 12: *Doxycycline 40 mg + metronidazole 1% gel compared to doxycycline 100 mg + metronidazole 1% gel for rosacea*

Doxycycline 40 mg + metronidazole 1% gel compared to doxycycline 100 mg + metronidazole 1% gel for rosacea						
Patient or population: Participants with rosacea **Intervention:** Doxycycline 40 mg + metronidazole 1% gel **Comparison:** Doxycycline 100 mg + metronidazole 1% gel						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Doxycycline 100 mg + metronidazole 1% gel	**Doxycycline 40 mg + metronidazole 1% gel**				
HRQOL - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Participant-assessed improvement in rosacea severity - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Proportion of participants with adverse event	**553 per 1000**	**138 per 1000** (61 to 299)	**RR 0.25** (0.11 to 0.54)	91 (1 study[1])	⊕⊕◯◯ **low**[2,3]	The majority of these adverse events were gastrointestinal complaints
Physician-assessed improvement in rosacea severity Reduction in Investigator's Global Assessment	The mean physician-assessed improvement in rosacea severity in the control group was **-1.6**	The mean physician-assessed improvement in rosacea severity in the intervention group was **0.00 higher** (0.11 lower to 0.11 higher)		91 (1 study[1])	⊕⊕◯◯ **low**[2,4]	

Assessment of erythema or telangiectasia Clinician's Erythema Assessment	The mean assessment of erythema or telangiectasia in the control group was **-4.0**	The mean assessment of erythema or telangiectasia in the intervention group was **0 higher**		91 (1 study)	⊕⊕◯◯ **low**[2,4]	Reduction in CEA 4.2 in doxycycline 40 mg and 4.0 in doxycycline 100 mg group, investigator's state P = 0.50
Lesion count	The mean lesion count in the control group was **-12.2 inflammatory lesions**	The mean lesion count in the intervention group was **0.30 lower** (3.03 lower to 2.43 higher)		91 (1 study[1])	⊕⊕◯◯ **low**[2,3]	
Time needed until improvement of the skin lesions	See comment	See comment	Not estimable	91 (1 study[1])	⊕⊕◯◯ **low**[2,4]	A clear improvement was seen from week four for both groups.
Duration of remission - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Del Rosso 2008
[2] Downgraded one level due to serious risk of selection bias and attrition bias (sequence generation and allocation concealment at unclear risk of bias, high drop-out rate and although ITT analysis judged at unclear risk of bias)
[3] Downgraded one level due to serious imprecision (wide confidence interval due to low sample size, optimal sample size is not met)
[4] Downgraded one level due to serious imprecision (low sample size, optimal sample size is not met)

Summary of findings 13: *Doxycycline 40 mg + azelaic acid gel compared to doxycycline 40 mg + metronidazole gel for rosacea*

Doxycycline 40 mg + azelaic acid gel compared to doxycycline 40 mg + metronidazole gel for rosacea						
Patient or population: Participants with rosacea **Intervention:** Doxycycline 40 mg + azelaic acid gel **Comparison:** Doxycycline 40 mg + metronidazole gel						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Doxycycline 40 mg + metronidazole gel	**Doxycycline 40 mg + azelaic acid gel**				
HRQOL - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Participant-assessed improvement in rosacea severity Excellent improvement on a 4-point Likert scale	**465 per 1000**	**489 per 1000** (368 to 651)	**RR 1.05** (0.79 to 1.40)	207 (1 study[1])	⊕⊕⊕⊕ **high**	Excellent improvement was reported in approximately half of each intervention group
Proportion of participants with adverse event	**69 per 1000**	**19 per 1000** (4 to 89)	**RR 0.27** (0.06 to 1.28)	207 (1 study[1])	⊕⊕⊕⊕ **high**	
Physician-assessed improvement in rosacea severity Investigator's Global Assessment of 0, 1 or 2 (clear to mild)	**723 per 1000**	**781 per 1000** (672 to 918)	**RR 1.08** (0.93 to 1.27)	207 (1 study[1])	⊕⊕⊕⊕ **high**	
Clinician's Erythema Assessment - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

Lesion count	The mean lesion count in the control group was **-9.4 inflammatory lesions**	The mean lesion count in the intervention group was **1.10 lower** (4.91 lower to 2.71 higher)		207 (1 study[1])	⊕⊕⊕◯ **moderate**[2]	
Time needed until improvement	See comment	See comment		207 (1 study[1])	⊕⊕⊕⊕ **high**	From four weeks on improvement could be seen for both treatment arms
Duration of remission - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Del Rosso 2010
[2] Downgraded one level due to serious imprecision (wide confidence interval)

Summary of findings 14: *Minocycline 45mg compared to minocycline 45mg + azelaic acid gel for rosacea*

Minocycline 45 mg compared to minocycline 45 mg + azelaic acid gel for rosacea						
Patient or population: Participants with rosacea **Intervention:** Minocycline 45 mg **Comparison:** Minocycline 45 mg + azelaic acid gel						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Minocycline 45 mg + azelaic acid gel	**Minocycline 45 mg**				
HRQOL - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Participant-assessed improvement in rosacea severity - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Proportion of participants with adverse event	**533 per 1000**	**368 per 1000** (208 to 651)	**RR 0.69** (0.39 to 1.22)	60 (1 study[1])	⊕⊕◯◯ **low**[2,3]	
Physician-assessed improvement in rosacea severity Mean change in Investigator's Global Assessment (Likert scale 0 to 5) . Scale from: 0 to 4	The mean physician-assessed improvement in rosacea severity in the control groups was **-2.0 on IGA**	The mean physician-assessed improvement in rosacea severity in the intervention groups was **0.00 higher** (0.32 lower to 0.32 higher)		60 (1 study[1])	⊕⊕◯◯ **low**[2,3]	
Assessment of erythema or telangiectasia Mean change in CEA scale (Likert scale 0 to 4) . Scale from: 0 to 4	The mean assessment of erythema or telangiectasia in the control group was **-4 on CEA**	The mean assessment of erythema or telangiectasia in the intervention group was **1.00 higher**		60 (1 study[1])	⊕⊕◯◯ **low**[2,3]	

		(0.18 lower to 2.18 higher)				
Lesion count	The mean lesion count in the control group was **-12 inflammatory lesions**	The mean lesion count in the intervention group was **1.00 higher** (0.93 lower to 2.93 higher)		60 (1 study[1])	⊕⊕◯◯ **low**[2,3]	In both groups there was a clinically important reduction in lesion counts of 11.00 (SD 4.49) in the minocycline group and 12.00 (SD 3.00) in the comparator group
Time needed until improvement	See comment	See comment	Not estimable	60 (1 study[1])	⊕⊕◯◯ **low**[2,3]	Improvement was seen in both arms at four weeks
Duration of remission - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Jackson 2013
[2] Downgraded one level due to serious risk of performance and detection bias (blinding was assessed as at unclear risk of bias)
[3] Downgraded one level due to serious imprecision (low sample size, optimal sample size is not met)

Summary of findings 15: *Topical metronidazole compared to oral (oxy)tetracycline for rosacea*

Topical metronidazole compared to oral (oxy)tetracycline for rosacea						
Patient or population: Participants with rosacea **Intervention:** Topical metronidazole **Comparison:** Oral (oxy)tetracycline						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Oral (oxy) tetracycline	**Topical metronidazole**				
HRQOL - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Participant-assessed improvement in rosacea severity	See comment	See comment	Not estimable	182 (3 studies[1])	⊕⊕⊕◯ **moderate**[2]	RR 0.71, 95% CI 0.40 to 1.26 (Monk 1991), RR 0. 96, 95% CI 0.80 to 1.17 (Nielsen 1983b) and in Schachter 1991 no exact data were provided other than that ' ' both groups considered their condition much improved"
Proportion of participants with adverse event	See comment	See comment	Not estimable	258 (4 studies[3])	⊕⊕⊕◯ **moderate**[4]	No adverse event (Nielsen 1983b), RR 1.06, 95% CI 0.32 to 3.55 (Monk 1991), 12 adverse events reported in metronidazole group and 9 in tetracycline group (Schachter 1991), RR 0.70, 95% CI 0.30 to 1.65 (Veien 1986)

Physician-assessed improvement in rosacea severity	See comment	See comment	Not estimable	81 (2 studies[5])	⊕⊕⊕◯ **moderate**[2]	RR 0.80, 95% CI 0.47 to 1.35 (Monk 1991), RR 1.00, 95% 0.89 to 1.13 (Nielsen 1983b)
Assessment of erythema or telangiectasia	See comment	See comment	Not estimable	258 (4 studies[3])	⊕⊕◯◯ **low**[2,6]	Erythema score -1.4 versus -1.3 (Monk 1991), ' ' the reduction of erythema was the same in both groups, and the number and extent of telangiectases were unchanged" (Nielsen 1983b) , in Schachter 1991 no differences in erythema nor telangiectasia were seen in either group. In Veien 1986 the percentage of no improvement was 11.1 in the metronidazole group versus 12.5 in the tetracycline group
Lesion count	See comment	See comment		258 (4 studies[3])	⊕⊕⊕◯ **moderate**[2]	Complete clearance in 75% versus 66% of participants (Monk 1991) , ' ' the reduction of papules and pustules was the same in both groups" (Nielsen 1983b), decrease of 68% versus 77% in papule count and of 53% and 61% in pustule count (Schachter 1991). In Veien 1986 only medians were provided with 11.1 lesions

						in the metronidazole group and 0 in the tetracycline group
Time needed until improvement - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Duration of remission - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Monk 1991, Nielsen 1983b, Schachter 1991 (number of participants randomised in Schachter 1991 was unclear)
[2] Downgraded one level due to serious imprecision (low sample sizes)
[3] Monk 1991, Nielsen 1983b, Schachter 1991, Veien 1986 (number of participants randomised in Schachter 1991 was unclear)
[4] Downgraded one level due to serious imprecision (wide confidence intervals due to low sample sizes)
[5] Monk 1991, Nielsen 1983b
[6] Downgraded one level due to serious heterogeneity (in contrast to the other three studies, Schachter 1991 did not show any improvement in erythema and telangiectasia

Summary of findings 16: *Low dose isotretinoin 0.3 mg/kg compared to doxycycline 50-100 mg for rosacea*

Low dose isotretinoin 0.3 mg/kg compared to doxycycline 100 mg for rosacea						
Patient or population: Participants with rosacea **Intervention:** Low dose isotretinoin 0.3 mg/kg **Comparison:** Doxycycline 100 mg after 14 days tapered to 50 mg						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Doxycycline 100 mg	**Low dose isotretinoin 0.3 mg/kg**				
HRQOL - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Participant-assessed improvement in rosacea severity[1] Good to excellent improvement on 5-point Likert scale	**644 per 1000**	**792 per 1000** (676 to 921)	**RR 1.23** (1.05 to 1.43)	261 (1 study[2])	⊕⊕⊕⊕ **high**	Low dose isotretinoin is considered by the participants to be slightly more effective than doxycycline 100 mg
Proportion of participants with adverse event	**171 per 1000**	**204 per 1000** (127 to 328)	**RR 1.19** (0.74 to 1.92)	299 (1 study[2])	⊕⊕⊕⊕ **high**	
Physician-assessed improvement in rosacea severity[1] Complete remission or marked improvement on a 6-point Likert scale)	**689 per 1000**	**813 per 1000** (710 to 938)	**RR 1.18** (1.03 to 1.36)	261 (1 study[2])	⊕⊕⊕⊕ **high**	In agreement with the participant-assessed changes

Assessment of erythema or telangiectasia Improved or healed	**783 per 1000**	**736 per 1000** (650 to 846)	**RR 0.94** (0.83 to 1.08)	285 (1 study[2])	⊕⊕⊕⊕ **high**	Telangiectasia were improved or ‘ ‘ healed” RR 1.03, 95% CI 0.77 to 1. 37
Lesion count[1]	The mean lesion count in the control group was **-13 inflammatory lesions**	The mean lesion count in the intervention group was **3 lower**		261 (1 study[2])	⊕⊕⊕⊕ **high**	
Time needed until improvement - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Duration of remission - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Per-protocol analysis
[2] Gollnick 2010

Summary of findings 17: *Pulsed dye laser compared to Nd:YAG laser for rosacea*

Pulsed dye laser compared to Nd:YAG laser for rosacea						
Patient or population: Participants with rosacea **Intervention:** Pulsed dye laser **Comparison:** Nd:YAG laser						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Nd: YAG laser	**Pulsed dye laser**				
HRQOL - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Participant-assessed improvement in rosacea severity[1]	The mean participant-assessed improvement in rosacea severity in the control group was **34 percent**	The mean participant-assessed improvement in rosacea severity in the intervention group was **16.33 higher** (1.94 to 34.6 higher)		14 (1 study[2])	⊕⊕◯◯ **low**[3]	
Proportion of participants with adverse event[1] Pain as assessed by VAS (0 to 10; higher score is worse)	See comment	See comment	Not estimable	14 (1 study[2])	⊕⊕◯◯ **low**[4]	Pain was assessed on the PDL treated side 3.87 and 3.07 on the Nd:YAG side, the investigators state P = 0.0028
Physician-assessed improvement in rosacea severity - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

Assessment of erythema or telangiectasia[1] Spectrophotometer to assess facial redness	The mean assessment of erythema or telangiectasia in the control group was **-2.5 percent**	The mean assessment of erythema or telangiectasia in the intervention group was **6.4 lower** (11.6 to 1.2 lower)		14 (1 study[2])	⊕⊕◯◯ **low**[3]	
Lesion count - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Time until improvement - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Duration of remission - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval; **RR:** Risk ratio

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Within-participant
[2] Alam 2013
[3] Downgraded two levels due to very serious imprecision (very wide confidence interval due to low sample size, optimal sample size is not met)
[4] Downgraded two levels due to very serious imprecision (very low sample size, optimal sample size is not met)

Summary of findings 18: *Pulsed dye laser compared to intense pulsed light therapy for rosacea*

Pulsed dye laser compared to intense pulsed light therapy for rosacea						
Patient or population: Participants with rosacea **Intervention:** Pulsed dye laser (PDL) **Comparison:** Intense pulsed light therapy						
Outcomes	**Illustrative comparative risks* (95% CI)**		**Relative effect (95% CI)**	**No of Participants (studies)**	**Quality of the evidence (GRADE)**	**Comments**
	Assumed risk	**Corresponding risk**				
	Intense Pulsed Light Therapy	**Pulsed Dye Laser**				
HRQOL - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Participant-assessed improvement in rosacea severity[1] VAS. Scale from: 0 to 10 (0 being a poor and 10 an excellent result)	The mean participant-assessed improvement in rosacea severity in the control group was **7**	The mean participant-assessed improvement in rosacea severity in the intervention group was **1 higher**		40 (1 study[2])	⊕⊕◯◯ **low**[3,4]	Median was 8 (range 2 to 10) for PDL group and 7 (range 2 to 10) for IPL group (10% and 90% percentiles)
Proportion of participants with adverse event Pain as assessed with a VAS scale. Scale from: 0 to 10	Pain assessed on a VAS scale in the control group was **7**	Pain assessed on a VAS scale in the intervention group was **3 lower**		40 (1 study[2])	⊕⊕◯◯ **low**[3,4]	Median was 4 (range 2 to 6) for PDL group and 7 (range 2 to 10) for IPL group (10% and 90% percentiles)
Physician-assessed improvement in rosacea severity - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

Assessment of erythema or telangiectasia 5-point Likert scale	See comment	See comment		40 (1 study[2])	⊕⊕⊕◯ **moderate**[4,5]	On the PDL treated side 18 had an excellent (75% to 100% vessel clearance) response and 12 a good response (50% to 74% clearance) and on the IPL treated sides 11 had an excellent response and 19 a good response
Lesion count - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Time until improvement - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome
Duration of remission - not measured	See comment	See comment	Not estimable	-	See comment	No study addressed this outcome

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).
CI: Confidence interval

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

[1] Within-participant design
[2] Nymann 2010
[3] Downgraded one level due to serious performance and detection bias (investigators and participants were not blinded)
[4] Downgraded one level due to serious imprecision (low sample size, optimal sample size is not met)
[5] ' ' Clinical efficacy was evaluated by one blinded trained physician"

Gemeinsamer Bundesausschuss

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2. **van Zuuren EJ, Kramer SF, Carter BR, Graber MA, Fedorowicz Z**. Effective and evidence-based management strategies for rosacea: summary of a Cochrane systematic review. Br J Dermatol 2011; 165 (4): 760-81.

3. **van Zuuren EJ, Fedorowicz Z, Carter B, van der Linden MM, Charland L**. Interventions for rosacea. Cochrane Database of Systematic Reviews 2015; (4): CD003262.